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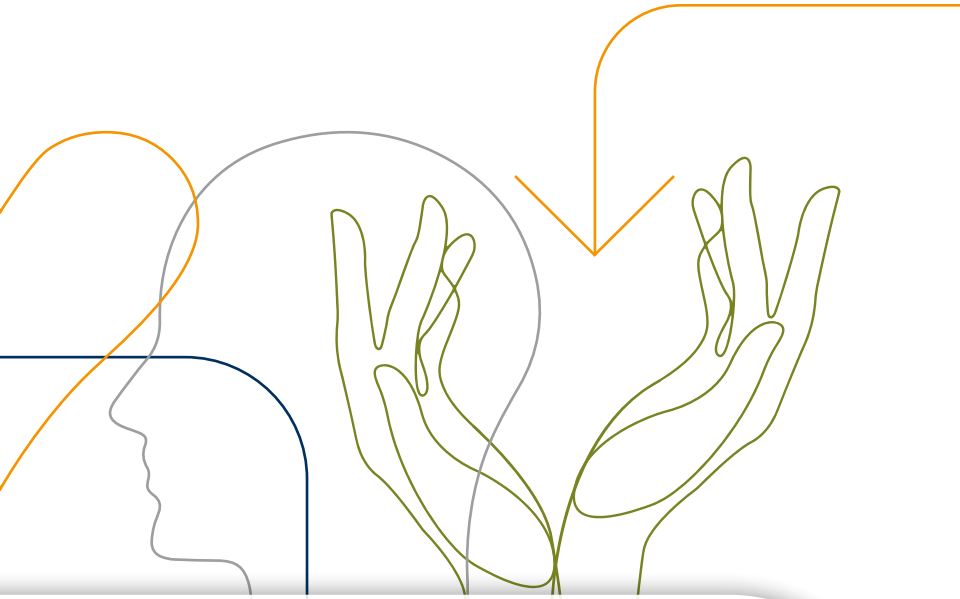

ESMO HANDBOOK OF SUPPORTIVE & PALLIATIVE CARE

Edited by Snežana M Bošnjak, Ivana Bozovic-Spasojevic, Giannis Mountzios and Jayne Wood

ESMO Handbook Series

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Edited by

Snežana M. Bošnjak
Institute for Oncology and Radiology of Serbia, Department of Supportive Oncology and Palliative Care, Belgrade, Serbia

Ivana Bozovic-Spasojevic
Institute for Oncology and Radiology of Serbia, National Cancer Research Centre, Belgrade, Serbia

Giannis Mountzios
4th Oncology Department and Clinical Trials Unit, Henry Dunant Hospital Center, ONCOLIFE Institute Founder, Athens, Greece

Jayne Wood
Palliative Care Team, The Royal Marsden NHS Foundation Trust, London, UK

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www.esmo.org

Contents

Editors

Snežana M. Bošnjak

Institute for Oncology and Radiology of Serbia, Department of Supportive Oncology and Palliative Care, Belgrade, Serbia

Professor Snežana Bošnjak is the Head of the Department of Supportive Oncology/Palliative Care at the Institute for Oncology and Radiology of Serbia (a European Society for Medical Oncology [ESMO] Designated Centre). She is a Clinical Pharmacologist with an expertise in the pharmacotherapy of cancer-related symptoms and anticancer treatment-induced toxicities.

She has been actively involved in the care of cancer patients for a long time, in supportive and palliative care education and research, as well as in efforts to improve the availability of essential medications and the national Serbian policy regarding supportive and palliative care. Professor Bošnjak has been assisting the government of Serbia to integrate supportive and palliative care into the country's healthcare system, including serving as a President of the National Palliative Care Commission of Serbia.

Professor Bošnjak was selected to be a member of the ESMO Faculty, in the Supportive and Palliative Care Group. Professor Bošnjak has authored more than 50 publications in international and national journals in the area of supportive and palliative care.

Ivana Bozovic-Spasojevic

Institute for Oncology and Radiology of Serbia,
National Cancer Research Centre, Belgrade, Serbia

Ivana Bozovic-Spasojevic is the Head of the Daily Chemotherapy Hospital at the Institute for Oncology and Radiology in Belgrade, Serbia. Dr Bozovic-Spasojevic is a specialist in Internal Medicine, subspecialist in Medical Oncology, and has received additional training through the Certificate of Competence in Breast Cancer organised by the European School of Oncology. Her main field of interest is clinical and translational research in breast and gynaecological cancers.

Dr Bozovic-Spasojevic completed a Translational Research Fellowship at the Breast International Group (TransBIG Fellow, 2009-2010) and was Medical Advisor (Clinical Research Fellow, 2010-2012) at the Jules Bordet Institute in Brussels, Belgium.

Since 2015 she has been a member of the National Expert Commission for Oncology at the Ministry of Health, Serbia; she is also a member of the Serbian Central Ethical Committee for Clinical Research and serves as an oncology expert for the Serbian National Drug Agency regarding oncology drug registration.

Dr Bozovic-Spasojevic graduated from the European Society for Medical Oncology (ESMO) Leaders Generation Programme in 2018.

Giannis Mountzios

4th Oncology Department and Clinical Trials Unit, Henry Dunant Hospital Center, ONCOLIFE Institute Founder, Athens, Greece

Dr Giannis Mountzios is the Director of the 4th Department of Medical Oncology and Clinical Trials Unit at the Henry Dunant Hospital Center in Athens, Greece.

Dr Mountzios obtained his Medical Degree from the Aristotle University of Thessaloniki, Greece, in 1998 and from the military medical academy the same year. He completed his residency in Medical Oncology at the University of Athens School of Medicine. In 2007, he obtained a Master's Degree (MSc) in Translational and Clinical Research in Oncology from the Institut Gustave-Roussy and the University Paris XI, France, and became board-certified in Medical Oncology in 2009. In 2010, he obtained his PhD in Thoracic Oncology.

He is active in the field of clinical research in thoracic malignancies and has (co)-authored more than 100 pertinent publications.

He has served as a chair/member of several committees of the European Society for Medical Oncology (ESMO). Since 2019, he has been a member of the ESMO Educational Publications Working Group.

Jayne Wood

Palliative Care Team, The Royal Marsden NHS Foundation Trust, London, UK

Dr Jayne Wood is a Consultant in Palliative Medicine at The Royal Marsden Hospital (RM), London, UK, holding the position of Head of Unit 2013–2021, and provides Consultant support to the Specialist Supportive and Palliative Care Team at the Royal Brompton Hospital (RBH), London, UK.

She also holds the position of Divisional Medical Director for Cancer Services at The Royal Marsden Hospital (NHS Foundation Trust) and is a member of both the European Society for Medical Oncology (ESMO) Supportive and Palliative Care Faculty and the ESMO Designated Centres Working Group.

Over the past 13 years, Dr Wood has worked closely with the teams at RM and RBH to support early integration of specialist palliative care for patients with a diagnosis of cancer, heart and lung disease.

She has a particular interest in education and the integration of palliative care with oncology and has spoken nationally and internationally on the subject; she has authored publications in peer-reviewed international journals.

Contributors

Aapro M. Genolier Cancer Centre, Clinique de Genolier, Genolier, Switzerland

Afshar M. Department of Medical Oncology, St George's University Hospitals NHS Foundation Trust, London, UK

Ahmedzai S.H. Medical School, University of Sheffield, Sheffield; National Institute for Health Research, University of Leeds, Leeds, UK

Anderson R. Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London, London, UK

Angellier E. Institut Curie, Saint Cloud, France

Arends J. Department of Medicine I, Medical Center - University of Freiburg; Faculty of Medicine, University of Freiburg, Freiburg, Germany

Boukovinas I. Bioclinic Thessaloniki, Thessaloniki, Greece

Boutros C. Gustave Roussy, Dermatology Unit, Outpatient Clinic, Villejuif, France

Carbonnel F. Gastroenterology Unit, University Hospital Bicêtre, APHP; Paris Saclay University, Paris, France

Centeno C. Palliative Medicine Department, Clinica Universidad de Navarra; ATLANTES Global Palliative Care Observatory, University of Navarra, Pamplona, Spain

Cherny N.I. Department of Medical Oncology, Shaare Zedek Medical Center, Jerusalem, Israel

Chu C. Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London, London, UK

de Vries F.E. Department of Supportive Care, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Department of Psychiatry and Center for Quality of Life, Netherlands Cancer Institute, Amsterdam, Netherlands

Di Pede P. Oncology-Supportive Care in Cancer Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy

Die Trill M. President Emeritus, International Psycho-Oncology Society

Dirix P. Iridium Kankernetwerk, Antwerp; University of Antwerp, Antwerp, Belgium

Fallon M. Edinburgh Cancer Research Centre, Institute of Cancer Genetics, University of Edinburgh, Edinburgh, UK

Fatigoni S. Medical Oncology, Santa Maria della Misericordia Hospital, Perugia, Italy

Fernando A. Departments of Medical Oncology, Liaison Psychiatry and Cancer Psychological Support, St George's University Hospitals NHS Foundation Trust, London, UK

Giusti R. Medical Oncology Unit, Sant'Andrea Hospital of Rome, Rome, Italy

Guglielmo M. Oncology-Supportive Care in Cancer Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy

Hart N.H. Caring Futures Institute, College of Nursing and Health Sciences, Flinders University, Adelaide, SA; Cancer and Palliative Care Outcomes Centre, Queensland University of Technology, Brisbane, QLD; School of Medical and Health Sciences, Edith Cowan University, Perth, WA; Institute for Health Research, University of Notre Dame Australia, Perth, WA, Australia

Herrstedt J. Department of Clinical Oncology and Palliative Care Units, Zealand University Hospital Roskilde and Naestved, Roskilde; Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Höller U. Radiation Oncology, MVZ Charité-Vivantes, Berlin, Germany

Iyengar N.M. Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Medicine, Weill Cornell Medical College, New York, NY, USA

Jordan K. Department of Hematology, Oncology and Palliative Care, Klinikum Ernst von Bergmann Potsdam, Potsdam; Department of Medicine V, Hematology, Oncology and Rheumatology, University of Heidelberg, Heidelberg, Germany

Kaasa S. European Palliative Care Research Centre (PRC), Department of Oncology, Oslo University Hospital, and Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Keefe D.M.K. Cancer Australia, Sydney, NSW; Adelaide Medical School, The University of Adelaide, Adelaide, SA, Australia

Kefala G. Department of Medical Oncology, Bank of Cyprus Oncology Centre, Cyprus

Kuten-Shorrer M. Department of Oral Medicine, Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, NY; Division of Oral Medicine, Department of Diagnostic Sciences, Tufts University School of Dental Medicine, Boston, MA, USA

Lambertini M. Department of Medical Oncology, Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova; Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genova, Italy

Legeay K. Medical Oncology and Supportive Care Department, Foch Hospital, Suresnes, France

Li M. Department of Supportive Care, Princess Margaret Cancer Centre, University Health Network, Toronto, ON; Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Massarotti C. Physiopathology of Human Reproduction Unit, IRCCS Ospedale Policlinico San Martino, Genova; Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health (DINOGMI), School of Medicine, University of Genova, Genova, Italy

Mountzios G. 4th Oncology Department and Clinical Trials Unit, Henry Dunant Hospital Center, ONCOLIFE Institute Founder, Athens, Greece

Oostendorp L. Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London, London, UK

Papamichael D. Department of Medical Oncology, Bank of Cyprus Oncology Centre, Cyprus

Pentsova E. Memorial Sloan Kettering Cancer Center, New York, NY, USA

Popescu G. Tumor Center Aarau and Hirslanden Clinic Aarau, Aarau, Switzerland

Popescu R.A. Tumor Center Aarau and Hirslanden Clinic Aarau, Aarau, Switzerland

Preusser M. Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

Rajer M. University Medical Center Ljubljana, Ljubljana, Slovenia

Ripamonti C.I. Oncology-Supportive Care in Cancer Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy

Rodin G. Department of Supportive Care, Princess Margaret Cancer Centre, University Health Network, Toronto, ON; Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Roila F. Medical Oncology, Santa Maria della Misericordia Hospital, Perugia, Italy

Ruhlmann C.H. Department of Oncology, Odense University Hospital, Odense; Department of Clinical Research, University of Southern Denmark, Odense, Denmark

Schapira L. Division of Medical Oncology, Department of Medicine, Stanford University School of Medicine, Stanford Cancer Institute, Stanford, CA, USA

Scotté F. Interdisciplinary Patient Pathway Department, Gustave Roussy, Villejuif, France

Smith S. Department of Psychology, Guy's and St Thomas' NHS Foundation Trust, London, UK

Smith S.M. Division of Hematology/Oncology, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, USA

Stone P. Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London, London, UK

Strijbos M. GZA Ziekenhuizen Sint-Augustinus, Antwerp, Belgium

Thillai K. Department of Medical Oncology, Guy's and St Thomas' NHS Foundation Trust, London, UK

Toffolatti L. Oncology-Supportive Care in Cancer Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy

Treister N.S. Division of Oral Medicine and Dentistry, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA; Department of Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, Boston, MA, USA

Tsoukalas N. Oncology Department, 401 General Military Hospital, Henry Dunant Hospital Center, Athens, Greece

White N. Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London, London, UK

Yri O.E. European Palliative Care Research Centre (PRC), Department of Oncology, Oslo University Hospital, and Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Reviewers

The editors and authors wish to thank the following reviewers.

Giuseppe Banna, Interdisciplinary Group for Translational Research and Clinical Trials, Thoracic Tumours, Candiolo Cancer Institute, FPO-IRCCS, Turin, Italy

Giovanni Boniolo, Department of Neuroscience & Rehabilitation, University of Ferrara, Ferrara, Italy

Antonio Calles, Thoracic Oncology, Head & Neck and Sarcoma Unit, Early Drug Development and Phase I Unit, Division of Medical Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Manuela Eicher, Département d'Oncologie, Université de Lausanne, Centre Hospitalier Universitaire Vaudois, Faculté de Biologie et de Médecine, Institut Universitaire de Formation et de Recherche en Soins, Lausanne, Switzerland

Magnus Ekstrom, Respiratory Medicine, Allergology and Palliative Medicine, Lund University, Lund, Sweden; Department of Medicine, Blekinge Hospital, Karlskrona, Sweden; Faculty of Health, University of Technology, Sydney, Australia

Ioannis Georgakopoulos, National and Kapodistrian University of Athens School of Medicine, Athens, Greece

Luigi Grassi, Psychiatry Department, Department of Neuroscience and Rehabilitation, University of Ferrara; Hospital University Psychiatry Unit, S. Anna Hospital, Ferrara; Local Health Trust, Ferrara, Italy

Gudrun Kreye, Department of Internal Medicine II, Clinical Division of Palliative Medicine, University Hospital Krems, Krems, Austria

Jon Martin, Camden, Islington ELiPSe and UCLH & HCA Palliative Care Service, Central and North West London NHS Foundation Trust; National Hospital for Neurology & Neurosurgery, University College London Hospitals NHS Foundation Trust, London, UK

Alexios Matikas, Department of Oncology, Karolinska Institutet; Department of Breast Oncology, Karolinska University Hospital, Stockholm, Sweden

Mila Petrova, MHAT Nadezhda, Sofia, Bulgaria

Evangelia Razis, 3rd Oncology Department and Contemporary Oncology Team, Hygeia Hospital, Athens, Greece

Jordi Remon, Medical Oncology Department, HM CIOCC BARCELONA (Centro Integral Oncológico Clara Campal), Hospital HM Nou Delfos, HM Hospitales, Barcelona, Spain

Florian Strasser, Cancer Survivor & Fatigue Clinic, c/o Onkologie Schaffhausen, Schaffhausen; Centre Integrative Medicine, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

Siva Subramanian, Department of Palliative Care, Goulburn Valley Health, Victoria; University of Melbourne, Victoria, Australia

Ros Taylor, Harlington Hospice and Michael Sobell Hospice, Mount Vernon Hospital, Northwood, Hillingdon, UK

Evangelos Terpos, Department of Hematology, Stem Cell Transplantation Unit, Plasma Cell Dyscrasias Unit, Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Alexandra General Hospital, Athens, Greece

Benedikt Westphalen, Comprehensive Cancer Center Munich & Department of Medicine III, Ludwig Maximilian University of Munich, Munich, Germany

James Woolley, Adult Psychological Support Service, The Royal Marsden NHS Foundation Trust, London, UK

Holly Yang, Scripps Health, San Diego, California, USA

Camilla Zimmermann, Department of Supportive Care, Princess Margaret Cancer Centre, Toronto; Division of Palliative Care, University Health Network, Toronto; Department of Medicine, University of Toronto, Toronto, ON, Canada

Abbreviations

[^{18}F]FET	O-(2-[^{18}F]fluoroethyl)-L-tyrosine
1,25-(OH)$_2$D	1,25-dihydroxyvitamin D
25-(OH)D	25-hydroxyvitamin D
5-ASA	5-aminosalicylic acid
5-FU	5-fluorouracil
5-HT$_3$	5-hydroxytryptamine type 3
ACE	Addenbrooke's Cognitive Exam
ACSM	American College of Sports Medicine
ACTH	Adrenocorticotropic hormone
ADH	Antidiuretic hormone
ADL	Activities of daily living
AE	Adverse event
AED	Antiepileptic drug
AFC	Antral follicular count
ALK	Anaplastic lymphoma kinase
AMH	Anti-Müllerian hormone
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASD	Acute stress disorder
BMI	Body mass index
BOOP	Bronchiolitis obliterans with organising pneumonia
BW	Body weight
CALM	Managing Cancer and Living Meaningfully
CAM	Confusion Assessment Method
CAR	Chimeric antigen receptor
CARTOX	CAR T-cell therapy-associated toxicity
CAT	Cancer-associated thrombosis
CBT	Cognitive behavioural therapy
cfDNA	Cell-free DNA
CINV	Chemotherapy-induced nausea and vomiting

CIPN	Chemotherapy-induced peripheral neurotoxicity
CMV	Cytomegalovirus
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COSA	Clinical Oncology Society of Australia
CRF	Cancer-related fatigue
CRO	Clinician-reported outcome
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
CTC	Circulating tumour cell
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
DHD	Desire for hastened death
DIC	Disseminated intravascular coagulation
DOAC	Direct oral anticoagulant
DSM	Diagnostic and Statistical Manual of Mental Disorders
DVT	Deep vein thrombosis
E_V_E protocol	Explore, Validate or Empathise
ECAS	European Cancer Anaemia Survey
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire
EPAAC	European Partnership for Action Against Cancer
EPCAM	Epithelial cell adhesion molecule
ESA	Erythropoiesis-stimulating agent
ESAS	Edmonton Symptom Assessment System
ESMO	European Society for Medical Oncology
ESMO-MCBS	European Society for Medical Oncology Magnitude of Clinical Benefit Scale
ESPEN	European Society for Clinical Nutrition and Metabolism
ESSA	Exercise and Sport Science Australia

EU-REFER	EUropean REcommendations for female FERtility
FDA	Food and Drug Administration
FFP	Fresh frozen plasma
FLAIR	Fluid-attenuated inversion recovery
FN	Febrile neutropaenia
FXa	Factor Xa
GAD-7	Generalized Anxiety Disorder-7
G-CSF	Granulocyte-colony stimulating factor
GI	Gastrointestinal
GIM	GI mucositis
GnRH	Gonadotropin-releasing hormone
HADS	Hospital Anxiety and Depression Scale
Hb	Haemoglobin
HBV	Hepatitis B virus
HCP	Healthcare professional
HER2	Human epidermal growth factor receptor 2
HFS	Hand-foot syndrome
HIPEC	Hyperthermic intraperitoneal chemotherapy
HIV	Human immunodeficiency virus
HLA-1	Human leukocyte antigen-1
H&N	Head and neck
HNA	Holistic Needs Assessment
HRT	Hormone replacement therapy
HSCT	Haematopoietic stem cell transplantation
HTB	High thrombotic burden
IBMEWG	International Bone Metastases and Exercise Working Group
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICI	Immune checkpoint inhibitor
ILAE	International League Against Epilepsy
i.m.	Intramuscular
irAE	Immune-related adverse event
ISOO	International Society of Oral Oncology
ISTH	International Society on Thrombosis and Haemostasis
i.t.	Intrathecal
i.v.	Intravenous
LARS	Low anterior rectal resection syndrome

LM	Leptomeningeal metastasis
LMWH	Low-molecular-weight heparin
mAb	Monoclonal antibody
MASCC	Multinational Association of Supportive Care in Cancer
MAT	MASCC Antiemesis Tool
MBO	Malignant bowel obstruction
mCRC	Metastatic colorectal cancer
MDT	Multidisciplinary team
MEK	Mitogen-activated protein kinase
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
MSAS	Memorial Symptom Assessment Scale
MST	Malnutrition Screening Tool
mTOR	Mammalian target of rapamycin
MUST	Malnutrition Universal Screening Tool
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCSE	Non-convulsive status epilepticus
NEST	Needs at the End-of-Life Screening Tool
NET	Neuroendocrine tumour
NIV	Non-invasive ventilation
NRS	Numerical rating scale
NRS-2002	Nutrition Risk Screening 2002
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
OM	Oral mucositis
OPG	Osteoprotegerin
OS	Overall survival
PaP	Palliative Prognostic Score
PARP	Poly(ADP-ribose) polymerase
PBT	Primary brain tumour
PCC	Prothrombin complex concentrate
PCR	Polymerase chain reaction
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PE	Pulmonary embolism
PEG	Polyethylene glycol

PET-CT	Positron emission tomography-computed tomography
PGT-M	Pre-implantation genetic testing
PHQ-2	Patient Health Questionnaire-2
PHQ-9	Patient Health Questionnaire-9
PIM	Potential inappropriate medication
PiPS	Prognosis in Palliative care Study
p.o.	Oral administration
POS	Palliative care Outcome Scale
PPI	Palliative Prognostic Index
PPS	Palliative Performance Scale
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient-reported outcome
PRO-CTCAE	Patient-reported outcomes version of CTCAE system
PROM	Patient-reported outcome measure
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone-related protein
PTSD	Post-traumatic stress disorder
q4h	Every 4 hours
QoL	Quality of life
RANK	Receptor activator of nuclear factor kappa-B
RANKL	RANK ligand
RBC	Red blood cell
RCCT	Rare cell capture technology
RINV	Radiotherapy-induced nausea and vomiting
RSCL	Rotterdam Symptom Checklist
s.c.	Subcutaneous
SAAG	Serum ascites albumin gradient
SaO_2	Oxygen saturation
SCP	Survivor care plan
SIADH	Syndrome of inappropriate antidiuretic hormone
SIBO	Small intestinal bacteria overgrowth syndrome
SMI	Severe mental illness
SMR	Standardised mortality ratio
SNAQ	Short Nutritional Assessment Questionnaire
SPEED	Screen for Palliative and End-of-Life Care Needs in the Emergency Department
SSRI	Selective serotonin reuptake inhibitor
TENS	Transcutaneous electrical nerve stimulation

TF	Tissue factor
TKI	Tyrosine kinase inhibitor
TNFα	Tumour necrosis factor-alpha
UFH	Unfractionated heparin
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
VTE	Venous thromboembolism
WHO	World Health Organization

Acknowledgements

The present handbook is the rewarding outcome of the long-lasting fruitful collaboration, passion and huge efforts of many people working within the ESMO family. The idea of revising and combining the two older ESMO handbooks dedicated to supportive and palliative care was born 4 years ago within the nest of the ESMO Educational Publishing Working Group (EPWG). We would like to express our gratitude to the EPWG members, but also to the ESMO Executive Board and the ESMO Educational Committee for their support and their trust in us to lead this much-needed publication. Our deepest thank you goes to all the authors and reviewers for their constant efforts and dedication in making this handbook a reality. Last but not least, this accomplishment would have not been possible without the tireless efforts, dedication, professionalism and perseverance of three unique ladies, Ms Aude Galli, Ms Claire Bramley and Ms Nicki Peters from the ESMO Publishing Team. We thank them especially for their patience and expertise in guiding us through this adventurous scientific endeavour. Finally, above all, this handbook is dedicated to the real heroes, our patients, with the noble wish that this effort will contribute to their comfort and wellbeing through their cancer journey.

Dr Ivana Bozovic-Spasojevic and Dr Giannis Mountzios,
on behalf of all the Editors

Preface

Oncology is not just about treating cancer with the best available antineoplastic therapies, it is about making the lives of our patients better. As oncologists, we have an ethical duty to not only "deliver the best quality anticancer treatment but also to consider the impact of the disease and treatment on each patient's life", as clearly stated in the ESMO position paper on supportive and palliative care published in *Annals of Oncology* in 2018. In this context, educating oncologists on all aspects of a patient's cancer journey, including symptom control, physical, mental, social and emotional wellbeing, as well as end-of-life care, becomes a core value and an absolute priority.

This handbook aims to serve this exact purpose. Written by experienced healthcare professionals, it covers all aspects of patient care, from formal assessment and effective management of symptoms to cancer-related psychological, spiritual and cultural issues; and from the optimal management of disease- and treatment-related side effects to rehabilitation, survivorship and care of the dying patient. Readers will learn how to effectively communicate with cancer patients, to detect and address their unique unmet needs and to provide state-of-the-art holistic care to those living with and beyond cancer. I strongly believe that enhancing skills in supportive and palliative care is fundamental, from both a scientific and an ethical viewpoint, for all oncologists and has the potential to transform the lives of our patients.

Solange Peters, MD, PhD
ESMO President

Integration of Supportive and Palliative Care into Oncology

1

O.E. Yri[1]

K. Jordan[2,3]

S. Kaasa[1]

[1]*European Palliative Care Research Centre (PRC), Department of Oncology, Oslo University Hospital, and Institute of Clinical Medicine, University of Oslo, Oslo, Norway*

[2]*Department of Hematology, Oncology and Palliative Care, Klinikum Ernst von Bergmann Potsdam, Potsdam, Germany*

[3]*Department of Medicine V, Hematology, Oncology and Rheumatology, University of Heidelberg, Heidelberg, Germany*

Introduction

The goal of integration of supportive and palliative care with oncology is to unite two treatment aims: optimal treatment of the tumour – 'the tumour-directed approach' – and optimal treatment of the patient who has the tumour – 'the patient-directed approach'. There is now a growing body of evidence that integration of these two modes of care will provide the optimum patient-centred care. It benefits patients in terms of improved symptom relief, quality of life (QoL), coping, social functioning and also survival. It is time to stop debating *if* integration should be sought and to focus on *how* best to accomplish integration of supportive and palliative care with oncology. All oncologists should strive to implement this new organisation into every individual patient care pathway.

The European Society for Medical Oncology (ESMO) position paper on supportive and palliative care states that, besides anticancer treatments, most cancer patients need help to prevent and alleviate side effects related to such treatment, and to cope with symptoms and needs related to the disease itself. Most patients wish to live as long as possible but

also as well as possible. Physical, psychological, social, existential and spiritual support is therefore needed at every stage of the cancer pathway and not only if the cancer is incurable.

In a patient-centred care approach, any intervention is introduced both at the appropriate time and according to the patient's needs. To facilitate integration, steps must be taken in several areas, as described below. One major challenge is how to systematically implement supportive and palliative care in routine oncology care. In this regard, the multidisciplinary team (MDT) plays a vital role.

What Do We Mean by Integration?

The term 'early integration' facilitates a departure from the common belief that palliative care is only about end-of-life care or only to be provided when anticancer treatment is no longer an option. However, palliative care should not be dichotomised as 'early' or 'late' – its introduction must be timely and needs-based. Integration in healthcare can be seen as a process designed to overcome the various barriers obstructing delivery of optimal care. These barriers may exist on multiple levels – organisational, financial, professional and/or personal. In cancer treatment, many medical professions are involved, and coordination of timely and appropriate interventions is critical for the optimal treatment outcome. This patient-centred care (including both supportive and palliative care) should be integrated using a multidisciplinary approach for discussions about the best possible treatment for the individual patient throughout the continuum of care – from primary diagnosis to end-of-life care. The patient-centred focus is just as important for patients who are at follow-up after curative treatment. The benefits of coordinating medical specialists in MDTs coming from radiology, pathology, surgery, medical oncology and radiotherapy are no longer questioned.

Integration of anticancer- and patient-directed interventions are proposed as an effort to bridge the gap between oncology and palliative and supportive care. In the presence of metastatic disease, surgery, anticancer agents and radiotherapy are, with some exceptions, delivered with the goal to prolong life and/or to treat symptoms. It may be called palliative

treatment by oncologists, but the majority of people associate palliative care with end-of-life care. Therefore, 'supportive care' has been suggested by some experts as a term for any patient-directed measures taken to optimise patient care in earlier phases of the disease, in an effort to lower the threshold for referral, both for oncologists and patients. While definitions are important but also arguable, efforts must be focused on alleviating patients' physical, psychological, social and existential concerns in all stages of disease, from survivorship to end of life.

New developments in anticancer treatments have prolonged life expectancy for many patients, redefining cancer as a chronic illness. This implies that living with cancer rather than dying from cancer has become a more frequent challenge in oncology care. Living with cancer is a new dimension and challenge for most patients and their caregivers. As mentioned earlier, 'to live as long and as well as possible' is the ambitious goal for most patients. It means that healthcare can contribute somewhat, but the lives are lived by each person in their home environment. A balance should be reached between our effort to prolong life, relieve symptoms, improve functions and support patients and their caregivers to live their lives.

How to guide and support the optimal life for patients and caregivers is a 'complex intervention' that requires the competence of different healthcare providers. This benefit should be made visible, understandable and balanced for each individual. As mentioned earlier, an MDT approach is needed, therefore supportive and palliative care is always teamwork. The team must also be balanced with the right contribution from the oncologists, and the patients and their caregivers should be considered as members of the MDTs.

Clinical resources, both community-based and in hospitals, are limited. This must be reflected to ensure a level of care appropriate to the complexity of indicated interventions. Structured systematic cooperation between different specialities and between different levels of care may ensure continuity of care when shifting between hospital departments and between hospital-based and community-based settings. Early referrals to palliative care consultations may be obstructed by limited

palliative resources. Different levels of palliative care based on complexity must therefore be outlined, where hospital and primary care/family medicine specialists also work together. Most patients wish to remain at home as much as possible and for as long as possible, and (some) will die at home. In the home environment, families can live and act differently than in most institutions. Well-functioning, community-based care is crucial to achieve this. If the conditions of the patient worsen and specialist care is needed, early access will facilitate better home care and patient care in general. A dynamic organisation is needed where primary care/family medicine specialists and homecare nurses collaborate in an integrated way with specialist oncological and palliative care.

Randomised studies on integration of oncology and palliative care in various cancers were summarised in the 2018 *Lancet Oncology* Commission article (Kaasa et al). Although different designs and endpoints were used, the studies consistently found that integrated care improved survival and symptom control, and led to less anxiety and depression, reduced use of futile chemotherapy at the end of life, and improved family satisfaction, QoL and use of healthcare resources. So, how can we achieve integration?

To facilitate integration, steps must be taken in several areas, including, but not limited to, the following: organisational infrastructures, education, communication skills, systematic assessments of patients' symptoms and needs (including systematic follow-up of the palliative care interventions implemented in response to the assessment) and research.

Organisational Infrastructures

Healthcare services are often organised in 'silos' – administratively, financially, professionally and culturally (Figure 1).

In integrated care, different specialists can provide their services regardless of these silos. Standardised care pathways are one methodology that may facilitate integrated care. In standardised care pathways, the patient course is planned individually based upon a common template. Interactions and critical events may be depicted. Standardised care pathways represent

a means to overcome dependency on the individual physician's practice for referral or intervention. However, standardised care pathways may also become a barrier to integration if they are perceived to limit the physician's evaluations and adjustments.

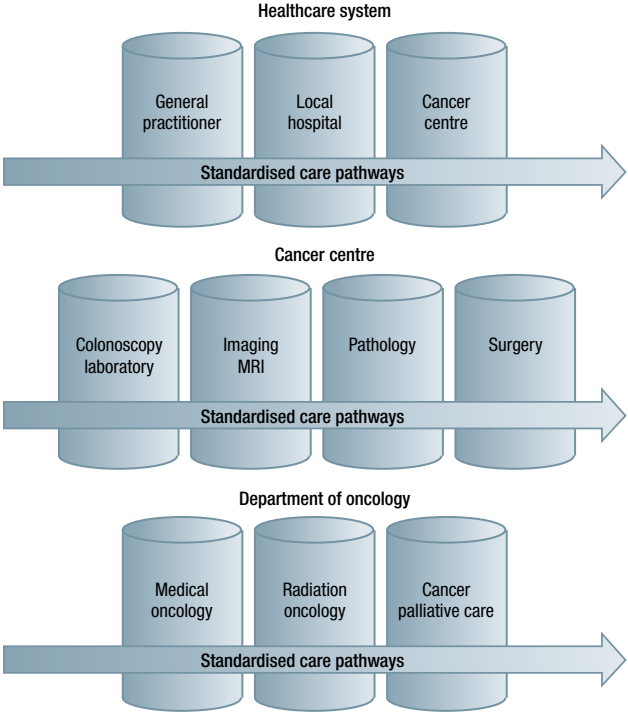

Figure 1 Healthcare includes silos at different levels.
From: Kaasa S, Loge JH, Aapro M, et al. Integration of oncology and palliative care: a Lancet Oncology Commission. Lancet Oncol 2018; 19: e588-e653.

Abbreviation: MRI, magnetic resonance imaging.

Co-localisation of services facilitates contact and referral/communication between departments and individuals. Defining which services can be offered as out-patient and which must be in-patient can reduce hospitalisation,

and technology for communication through electronic patient records, or other low-threshold mechanisms for contact between different levels of care (i.e. primary care, hospitals, nursing homes), should be established.

MDTs are organisational structures that coordinate healthcare by bringing together the many specialists involved, improving the quality of the provided care. The composition of MDTs in oncology often varies according to primary cancer type and the situation of the individual patient. Typically, oncology MDT representatives are surgeons, medical and radiation oncologists, radiologists and pathologists; it is uncommon to include palliative care specialists. For a patient-centred approach, palliative care specialists should be included in oncology MDTs. Also, palliative care MDTs should be implemented, further breaking down organisational silos by inviting relevant specialists from the oncology MDTs in addition to other pivotal professions in palliative care, such as physiotherapists, social workers, psychologists, occupational therapists, dieticians and chaplains. Potentially controversial, the patients and their caregivers could also be considered as members of the MDTs. Referral to palliative care MDTs should be based on predefined unacceptable symptom levels from systematic assessments, but appropriate time points for referral should also be defined in the standardised care pathways.

Education

As a rough rule, oncologists have limited postgraduate education in palliative care, and palliative care specialists (who may have postgraduate training varying from country to country) are not consistently required to have oncology training. As a consequence, misconceptions and differences in opinions as to what is defined as appropriate care for the individual patient may impede patient-centred care. Similarly, lack of knowledge and insight into oncology (the tumour-directed treatment) among palliative care specialists and lack of understanding of palliative and supportive care among oncologists may hinder optimal collaboration. We propose that rotations to palliative care units or teams should be compulsory during oncology training, and that oncology rotations should be compulsory during palliative care training. Doctors trained in both oncology and palliative care (palliative oncologists) may serve as

facilitators for optimal integrated care, advocating supportive and palliative care for their oncology colleagues and *vice versa*. Continued medical education in 'palliative/supportive oncology' – or indeed patient-centred care – for both specialties should be encouraged. Research in palliation provides oncologists with the opportunity of 'evidence-based' best practice and the cooperation between oncologists and palliative care specialists in common research projects should also be encouraged. An international common curriculum in palliative care training, describing mandatory learning goals in essential features of palliative care, should be developed. Such a curriculum could include compulsory rotations in oncology.

Communication Skills

Communication is essential for all clinicians and even more so for oncologists, who are often confronted with breaking bad news during consultations. Continuous training in communication skills must be provided. Appropriate communication skills promote patient-centred care, prognostic awareness and also lower a physician's risk of burnout. In addition to breaking bad news, oncologists provide information on prognosis and treatment alternatives to the patient and their caregivers. Patients are expected to be actively involved in the decisions about their anticancer treatment (tumour-centred) and planning of care, how to optimise QoL, etc. (patient-centred care). This process of shared decision-making may often be conducted in collaboration between the oncologist, palliative care specialist, home care personnel and the family practitioner.

Systematic Assessments of Patient Symptoms, Needs, Interventions and Follow-up

During routine consultations, many symptoms are missed or unaddressed. Systematic symptom assessments using a set of standardised tools to ask the patient for his/her needs, symptoms, toxicities and current challenges in everyday life make doctors aware of symptoms and unmet needs otherwise not detected. A selected set of patient-reported outcome measures (PROMs) should be defined as a part of the standard patient assessment in any oncology and/or palliative care unit and utilised at

regular intervals, the timing of which should be defined in standardised care pathways (see above). Rather than the traditional individual physician-dependent assessment and referral, this will increase the likelihood of referral and facilitate timely patient-centred interventions based on needs and not only on prognosis. The scores must be documented on demand in the patient's records. Symptom scores above predefined levels should then always prompt interventions and/or referral to MDTs or palliative care specialists. Adequate, evidence-based interventions according to supportive/palliative care guidelines must follow such assessments, and the effects of the interventions implemented in response to the assessments must again be followed up and assessed systematically.

Research

The financial resources allotted to palliative care research are usually low. The developments in tumour-directed treatment approaches lead to cancer being considered more as a chronic disease and give opportunity to incorporate supportive and palliative care research into oncology research programmes. National healthcare authorities must prioritise integrated research programmes and projects specifically. Research areas could be concentrated on three levels:

1. System-oriented studies on the implementation of models of care, integration and how to implement evidence-based knowledge;

2. Patient-oriented studies to examine symptoms, communication and decision-making; and

3. Public health-oriented studies on the external validity of research findings and implementation strategies.

ESMO Designated Centres of Integrated Oncology and Palliative Care

Since 2003, ESMO has awarded the 'ESMO Designated Centres of Integrated Oncology and Palliative Care' accreditation. The overall aim of this programme is to promote the integration of palliative care services into existing cancer care programmes (https://esmo.org/designated-centres).

This fast-growing community consists of cancer centres which provide comprehensive services in supportive and palliative care. Centres self-nominate and are then reviewed via a rigorous anonymous process by members of the ESMO Designated Centres Working Group, to ensure that they fulfil the 13 criteria related to advanced programme development, consistent with the established international standards. These criteria are based on recommendations from the World Health Organization guidelines on the provision of palliative care for patients with cancer regarding integration, credentialing, service provision, research and education. The ESMO Designated Centres have a great potential for collaboration between centres for service development and implementation, education and research. The ESMO Designated Centres Working Group has the ambition to contribute to improvement in all of these areas in the coming years. We will need your contributions today and in the future. For any input or active contributions to the programme, contact: designatedcentres@esmo.org for more information.

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Dr Yri has reported no potential conflicts of interest.

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Assessment of Symptoms and Needs

2

R.A. Popescu

G. Popescu

Tumor Center Aarau and Hirslanden Clinic Aarau, Aarau, Switzerland

Symptoms Prevalence and Intensity Depend on How They Are Assessed

Patients with cancer frequently suffer from physical and psychological symptoms. Meticulous assessment of symptoms and needs is thus a prerequisite to establish appropriate treatment goals and evaluate success in reducing suffering.

A comprehensive review of symptom prevalence in over 25 000 patients with incurable cancer published in 2007 by Teunissen et al showed that fatigue, lack of energy, weakness, pain and appetite loss were present in over 50% of this population; most patients complained of more than one symptom. **The number of symptoms recorded in the 44 studies included in this review was highest if a formal questionnaire was used, lower when recorded following a formalised interview and lowest when extracted *post hoc* from patient records**. That questionnaires elicit more symptoms and higher severity has been confirmed by numerous publications. Homsi et al (2006) asked 200 patients referred to their palliative medicine programme open-ended questions about symptoms and their severity, immediately followed by a 48-item symptom checklist. The median number of symptoms volunteered by patients was 1 (range 0-6), 83% of which were moderate or severe and 91% distressing, but a median of 10 symptoms (0-25) were elicited using a symptom checklist, of which 52% were moderate to severe. Seventy-nine percent of distressing symptoms were not volunteered during the preceding interview.

More Accurate Information Through Patient-reported Outcomes

Even when symptoms are recorded, their intensity is underestimated when evaluated by healthcare professionals (HCPs) compared with patients' reports. In 2009, Basch et al published **a comparison of adverse events reported by clinicians** (clinician-reported outcomes [**CROs**]) and patients, and demonstrated that symptoms reported by clinicians were noticed later and perceived as less severe than by the patients themselves. Because symptoms are inherently subjective, the most accurate information is obtained from the patient herself/himself and is often referred to as **patient-reported outcome (PRO)**.

The U.S. Food and Drug Administration (FDA) has defined PROs as "a report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else". A patient-reported outcome measure (PROM) is the instrument or tool, typically a questionnaire or diary, used to gather the health status of the patient. PROs have been incorporated in clinical trial designs, and licensing bodies and learned societies use PROs to rate the benefit of therapies, as incorporated, for example, in the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS).

Validated Questionnaires Can Screen for Multiple Symptoms

PROMs were initially developed to evaluate symptoms and to measure 'quality of life'. PROMs can elaborately measure single symptoms (e.g. pain, fatigue, anorexia/cachexia, etc.) or can be instruments for assessment of multiple symptoms. Such commonly used and extensively validated questionnaires for multiple symptoms include the Edmonton Symptom Assessment System (ESAS), the Rotterdam Symptom Checklist (RSCL) and the Memorial Symptom Assessment System (MSAS).

The **ESAS**, one of the first rapid assessment questionnaires developed, was translated into many languages and extensively used in palliative

care and oncology for symptom screening and monitoring. It evaluates on an 11-point numerical rating scale the severity of nine common symptoms (a tenth can be volunteered) ranging from 0 (no symptoms) to 10 (worst possible) and can be completed rapidly. It is ideally suited for longitudinal monitoring of symptoms and the effects of interventions to alleviate them. It can also be a helpful tool in focusing on the symptoms that need to be addressed with priority. One can ask patients what represents an uncomfortable symptom value for them or set a personal symptom treatment goal: "Using the same symptom scale, at what level would you be comfortable with symptom X?".

The **RSCL** is a more extensive PROM consisting of 30 questions relating to physical and psychological symptoms and 8 further questions exploring the impact of symptoms on activities of daily living. It differs from the ESAS also because it uses patients 'being bothered by symptoms' rather than severity as a measure of symptom impact. Similarly, the **MSAS** evaluates 32 physical and psychological symptoms for the three dimensions of frequency, severity and distress ("How much did it distress or bother you?"); shorter versions have been equally validated.

For psychological symptoms, the Hospital Anxiety and Depression Scale (**HADS**) was generated for use in a hospital medical outpatient clinic. It contains two 7-items subscales, one for depression, the other for anxiety, and was validated extensively in oncology and palliative care patients. Other routinely used questionnaires are the Patient Health Questionnaire-9 (PHQ-9) to assess depressive symptoms, and the Generalized Anxiety Disorder-7 (GAD-7) for anxiety.

PROMs Can More Accurately Measure Severity of Symptoms and Toxicity Grade

As detailed so far, PROs are very helpful in identifying symptoms and measuring the distress they cause. However, the subjective nature of suffering does not always lend itself to quantitative assessments (grading) as used, for example, by the Common Terminology Criteria for Adverse Events (CTCAE). An initiative of the National Cancer Institute (NCI) has translated the subjective items of the CTCAE – those adverse events

that can be directly observed and interpreted by patients – into patient-appropriate language for grading symptoms and toxicity by patients themselves. These so-called **PRO-CTCAEs** have been validated and translated into many languages and are being incorporated in routine clinical practice. PROMs can be submitted for completion on paper in the waiting area of oncology clinics, but access to the internet on computers, tablets or smartphones allows distribution of questionnaires even between clinic visits. Answers are often directly integrated into electronic health records.

Routine Electronic PROMs Can Assess Symptom Burden Between Clinic Visits

Benefits of routine PROM use include better patient awareness of symptoms as they are elicited by questionnaires, leading to more streamlined discussions between HCPs and patients, better understanding of the patient perspective on treatment and care outcomes and higher satisfaction with care. Recent evidence suggests that beside capturing the 'patient experience', one main benefit of PROs is early and systematic identification of new problems, often reported as emerging important symptoms between clinic visits, allowing targeted, rapid intervention. Two recent trials illustrate this:

In 2017, Basch et al showed that systematic monitoring of patients' symptoms using electronic PROMs helped to detect problems earlier in patients receiving palliative chemotherapy. Appropriate timely interventions led to improved quality of life, fewer hospitalisations or emergency room visits and more time on anticancer therapy, with increased survival. In France meanwhile, Denis et al randomised patients with lung cancer who just finished initial treatment to routine follow-up with clinical and computed tomography (CT) scan or web-mediated symptom-monitoring via PROMs with less frequent CT imaging. Patient-scored symptoms triggered an alert when predefined criteria were met, leading to earlier treatment of adverse events or to diagnosis of disease progression in patients with maintained performance status 0-1 able to receive optimal treatment. Survival was improved in the symptom-reporting group by

7 months. Crucial for the good results of these trials were previously agreed triggers for early intervention to address the reported symptoms.

Beyond Symptoms – Assessment of Needs

Published in 2018, the ESMO position paper on supportive and palliative care emphasises the importance of patient-centred care in oncology. By quoting the definitions of supportive care by the Multinational Association of Supportive Care in Cancer (MASCC) and palliative care by the World Health Organization (WHO), it sets a broad remit for the responsibilities of HCPs treating cancer patients: "Along with antitumour treatment, most patients need help to prevent and alleviate side effects and toxicities, and to cope with the disease itself. Furthermore—at any stage of the cancer pathway—physical, psychological, social, existential and spiritual support and rehabilitation, are often needed. Individual cancer patients will express different physical, psychological, social, existential and spiritual needs at different stages of the disease that will often evolve over time."

Thus, an appropriate response to patients' needs requires repeated assessment of these domains in a formal interaction with the patients and their families. Interventions documenting benefit from early palliative care integration on the overall symptom burden, quality of life and, frequently, survival, nearly uniformly included time spent with the patient-family unit every month. Beyond addressing symptoms, coping strategy, family and financial issues, existential and spiritual concerns were a frequent component of these consultations. Available PROMs can be used as screening tools prior to consultations and include quality-of-life questionnaires, measurements of disease burden, functional status, cognitive and psychosocial questionnaires as well as a subjective scoring system of treatment side effects and patient experience of care. Sometimes multiple PROMs are used concomitantly, for example, PRO-CTCAE questions (for assessing adverse effects of anticancer treatment) or ESAS (for symptoms in advanced cancer in-between therapies) plus EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire, for quality of life assessment) plus, for example, HADS.

When Time is Short – Brief Multidimensional Screening Tools

Frequently, in clinical practice **shorter screening tools** including various domains are preferred. The Palliative care Outcome Scale (**POS**) is a 10-item questionnaire for use in advanced cancer patients, widely translated and validated across various populations (including all stages of cancer). POS is broadly accepted and takes a very short time for patients, carers or staff (second version) to complete, making it very useful for incorporation in routine clinical practice.

The Needs at the End-of-Life Screening Tool (**NEST**) was developed to provide clinicians with a sensitive and reliable set of bedside questions to assess and screen individual palliative patients' overall care. It includes four core themes covered by 13 questions corresponding, for mnemonic purposes, to each letter of NEST: for Needs (social), Existential matters, Symptoms and Therapeutic matters.

Based on the NEST, the Screen for Palliative and End-of-Life Care Needs in the Emergency Department (**SPEED**) tool was developed, to identify the need for palliative care in cancer patients being admitted to emergency units. It relies on another set of 13 questions for HCP assessment of social, therapeutic, physical, psychological and spiritual palliative care needs. In 2011, Glare and colleagues published a **five-item Palliative Care Screening Tool**, a practical set of criteria to identify oncology outpatients for whom HCPs should consider specialist palliative care referral. These short multidimensional PROMs highlight the importance of acting upon needs, not merely perceived prognosis, when referring patients to other professionals (e.g. palliative care teams, psycho-oncologists, nutritionists, physiotherapists, spiritual care specialists or social workers).

Valuable Screening Questions

In some settings, even these short tools are not practical or cannot be routinely used. Fortunately, there is extensive literature looking at simple **screening questions** to probe the need for deeper exploration. For

instance, the question "Are you depressed?" correctly identifies about three out of four depressed patients (sensitivity) and correctly excludes the problem in four out of five cancer patients (specificity). Another useful question for depression is 'loss of interest' in things or activities usually enjoyed. If response to both these questions were positive, over 90% of depressed patients would be correctly identified. The two questions of the Patient Health Questionnaire-2 (PHQ-2) are similar and perform equally. The negative predictive value (correctly excluding major depression) is very high, but confirming depression requires further evaluation. Depressed patients are most frequently missed in busy clinics and have a higher-than-average distress level. The regular use of these questions could thus significantly improve 'usual care'. Similarly, the well-known National Comprehensive Cancer Network (NCCN) 'distress thermometer', which includes a one-question numerical rating scale (NRS), does far better than clinicians' own judgement of **distress**, a term describing unpleasant feelings negatively impacting functioning. Distress is present in over one third of cancer patients and includes components of depression, anxiety, anger and adjustment disorders. Patients are asked to answer the question "How distressed have you been during the past week on a scale of 0 to 10?". Values of 4 or 5 indicate mild distress, 6 or 7 moderate distress, 8 or higher severe distress. Combining this with a second question about the impact of the distress for the patients in their daily lives in the two-item 'distress and impact thermometer' offers a very short screening tool, easily included in daily clinical practice, which collects relevant information about the emotional response of patients by including interference of distress in daily life.

Assessing Coping, Social and Spiritual Resources is Paramount

In patients confronted with a life-threatening illness such as cancer, **assessment of coping strategies and spiritual resources** is crucial. A global consensus defined spirituality as a "dynamic and intrinsic aspect of humanity through which persons seek ultimate meaning, purpose and transcendence, and experience relationship to self, family, others, community, society, nature, and the significant or sacred. Spirituality

is expressed through beliefs, values, traditions and practices." Knowing sources of strength and meaning/purpose in life of cancer patients is essential to supporting them – irrespective of the personal and religious convictions of HCPs. Frequent existential issues for patients with advanced cancer are disappointment, hopelessness, meaningless, broken relationships, remorse, guilt and loss of self. A recent very helpful review of spiritual care in oncology, including various screening elements and their interpretation, has been published by Puchalski et al in 2019 in *ESMO Open*; the full text is freely available.

Assessment of psychological and spiritual needs is thus mandatory for appropriate care in cancer patients. Similarly, screening questions about the need for help, financial concerns, overall burden of the disease for families, satisfaction with therapy in terms of effectiveness and toxicity, etc., need to be woven into routine consultations.

Assessments Must Lead to Action

All meticulous eliciting of symptoms and assessment of needs in relevant domains of care is worthless if these symptoms and needs are not acknowledged and addressed by adequate supportive or palliative care interventions. It is therefore imperative that PROMs and screening questions lead to adaptations of care, goals of treatment, and support for family and patients in accordance with their values and priorities.

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Dr R.A. Popescu has reported consulting or advisory roles for Roche, Novartis, Merck Sharp & Dohme, Merck, Lilly, Bristol-Myers Squibb, AstraZeneca, Vifor Pharma, Nutricia, Janssen-Cilag, Pfizer and Kaiku Health; research funding from Roche, Novartis, Sanofi, Bristol-Myers Squibb, AstraZeneca, Daiichi Sankyo, Lilly, Kaiku Health and Pierre Fabre, all to institution.

Dr G. Popescu has reported consulting or advisory roles for Mundi Pharma and Vifor, all to institution.

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Cancer-related Mental Health, Psychological, Spiritual and Cultural Issues

3

A. Fernando[1]

S. Smith[2]

M. Afshar[3]

K. Thillai[4]

[1]*Departments of Medical Oncology, Liaison Psychiatry and Cancer Psychological Support, St George's University Hospitals NHS Foundation Trust, London, UK*

[2]*Department of Psychology, Guy's and St Thomas' NHS Foundation Trust, London, UK*

[3]*Department of Medical Oncology, St George's University Hospitals NHS Foundation Trust, London, UK*

[4]*Department of Medical Oncology, Guy's and St Thomas' NHS Foundation Trust, London, UK*

Mental Health, Psychological and Emotional Issues Related to Cancer – Treating the Patient in an Integrated and Holistic Manner

There is a clear, unmet need in the provision of the mental health, psychological and emotional support for cancer patients. Recognising, assessing and appropriately managing these needs is likely to improve adherence to cancer treatments with resultant improvements in prognosis, as well as associated improvements in functioning and quality of life (QoL). To date, our inability to fully integrate mental health support in cancer care has resulted in limiting the effectiveness of cancer treatments, significant economic costs for patients, families and services, even culminating in treatment refusal, significant distress and suicide.

The nature and degree of psychiatric and psychological comorbidities vary with tumour type and treatment modality. Surgical, radiotherapeutical and medical anticancer therapies are all associated with negative impacts on functioning and QoL, which are under-recognised and under-treated.

Finally, the mental health and psychological needs of cancer patients vary with disease stage, with depression and suicidality being much more prevalent in patients with advanced cancers. Cancer affects not just patients, but carers, families and support networks.

Spiritual and Cultural Issues Related to Cancer

Several retrospective studies have demonstrated clear survival disparities between different ethnic populations, partly influenced by socioeconomic status and access to healthcare. A review of cancer-specific survival from an American cancer registry reported that Black patients had the lowest survival for all cancer sites. Furthermore, it has been shown that minority groups remain significantly underrepresented in clinical trials and this may have significant implications on survival outcomes.

It is important to distinguish culture from race. Cultural beliefs can strongly influence ideas about cancer and are recognised as an important factor (and sometimes barrier) to participation in cancer screening, interaction with healthcare professionals, acceptance of treatment and subsequent outcomes.

Spirituality and religion can also impact cancer care. Many patients will rely on their spiritual or religious beliefs following a cancer diagnosis (a term called 'spiritual coping') and staff should remain sensitive to patients' wishes and encourage open discussions. Ongoing dialogue between caregivers and patients about an individual's religious and spiritual beliefs has been shown to improve QoL and guide discussions about advance care planning.

Prevalence of Mental Health and Psychological Issues Related to Cancer

Studies globally estimate the prevalence of depression in cancer patients to be 16.3%, and anxiety 10.3%. It is clear that depression in cancer

patients is undertreated and increases with severity of cancer and stage of disease. In advanced-stage disease, the prevalence of depression is as high as 36%.

Ten percent of patients will require formal psychological and mental health support within 1 year of being diagnosed with cancer. There is also an elevated risk of suicidality in the first year after diagnosis. A 2014 UK study demonstrated that up to 73% of depressed cancer patients received no evidence-based treatment for their depression.

Psychosocial Understanding of a Cancer Diagnosis and Treatment

A cancer diagnosis, its treatment and effects, represents a threat to a person's internal and external world. It requires a change for the individual and those involved. For most, it will be accompanied with a thought, "Will I live/die?" and powerful emotion. It is a key emotional event and process, affecting every domain of life.

A cancer diagnosis and its treatment represent a core threat to a person and their significant others, and needs to be understood in the context of power and how this is exercised (e.g. social/economic capital). Brennan's model of adjustment to a cancer diagnosis describes an active process for the individual.

There is a relationship between childhood adversity, homelessness, poverty and the experience of discrimination, with poverty being the strongest predictor of developing mental health problems, and these factors are likely to influence and be connected with how a person manages and responds to a cancer diagnosis and treatment.

Dominant western cultural ideas suggest that certain feelings are 'bad' (e.g. sadness, anger) while others are 'good' (e.g. joy, happiness, positivity). This culturally-mediated dichotomy is perhaps unhelpful and actively repressing so-called 'negative affect' (e.g. anger, sadness), putting cancer centre stage. Over-inflated positivity is correlated with poor outcomes and lower QoL.

The use of Holistic Needs Assessment (HNA) in the UK is an example of how key concerns may be identified across multiple domains of a person's life and experience. It is vital that we consider cancer-related distress and mental health in cancer not just at the level of the individual but also address the systemic social factors at play that are often overlooked.

Special Aspects of Mental Health and Psychosocial Issues in Cancer

Clinical Assessment

Cancer is likely to have an impact on a patient's mood and other elements of mental state, which are then likely to impact upon a patient's experience of cancer and associated treatment. It is important that oncologists can assess the nature and severity of this interaction, gauging when to refer to specialist services.

A key point to recognise is that in cancer patients, a more reliable marker of clinical depression is in the anhedonia or loss of enjoyment in daily activities together with negative symptoms such as hopelessness and uselessness, rather than in biological symptoms such as weight and appetite loss which can be attributed to the cancer or treatment.

An understanding of how a patient's functioning/QoL has been affected by cancer can be elicited by taking a narrative history of the cancer journey, asking specifically how diagnosis and various treatments affected different domains of life (e.g. employment, relationships).

It is also important to consider suicide risk. The risk is greatest in the first year after diagnosis, and after recurrence. Older men with head and neck, lung or upper gastrointestinal cancers pose the highest risk of completed suicide. The standardised mortality ratio (SMR) for people with these cancers is 4 to 6.8 times greater than in an age- and sex-matched population. Suicidal ideation together with suicidal intent form the crux of a risk assessment. The presence of intent warrants psychiatric assessment and is an indication of the extent to which an individual is prepared to act on his/her suicidal thoughts.

Finally, assessment of cognitive function is indicated in patients with brain tumours and lung cancers, as well as in patients with delirium and those suffering from cognitive complications of cancer treatment. Routine bedside screening by an oncologist will use the Mini Mental State Examination, which is a universally used, though by no means comprehensive, screening tool for cognitive impairment, and the Montreal Cognitive Assessment (MoCA). Further and more comprehensive cognitive screening can utilise the Addenbrooke's Cognitive Exam (ACE). The Confusion Assessment Method (CAM) can also be routinely used in delirium screening and has been validated in a number of settings.

Tumour-specific Considerations

It is not just lung cancers and other cancers that metastasise to the brain that cause psychiatric symptoms. Patients with tumour types that secrete hormones or autoimmune antibodies or require hormonal therapy, such as breast and prostate cancer, will also be affected. Women receiving adjuvant therapy for breast cancer, typically expected to be cured of their disease, have been shown to be especially susceptible to adverse changes in their sexual functioning. Men with prostate cancer will experience changes in physical appearance with breast enlargement and reduced penis size, erectile dysfunction and loss of libido, in addition to hot flashes – putting these men through the equivalent of the female menopause. Studies have shown chemotherapy to be independently associated with depression. Additionally, it is postulated that inflammatory cytokines released by pancreatic cancer are associated with depression. Some studies have also shown the role of perceived stigma and depressive symptomatology, which may be a dynamic and fluid phenomenon as treatments and survival rates rapidly change in different cancer types.

Patients with Pre-existing Severe Mental Illness

Patients with severe mental illness (SMI) are likely to have poorer engagement with their cancer treatment and are known to have worse cancer outcomes as a result. As such, it can be potentially life-changing to consider strategies to optimise engagement where possible. It is paramount to involve specialist liaison psychiatry teams, where available,

as early as possible in the patient's care. Patients with SMI may have impaired capacity to understand and retain information, weigh up pros and cons and communicate decisions about treatment. If there is doubt, a formal capacity assessment should be sought in cancer patients with SMI regarding consenting to treatment, with appropriate guidance sought.

Having an awareness of how a cancer may impact on an SMI is important, as well as adapting to increased engagement (e.g text message reminders for appointments). Attention needs to be given to the setting where treatment occurs, with relevant understanding of the provisions of appropriate legal frameworks, pertaining to mental health detention and deprivation of liberty, as well as the staff ability to assess and manage risks such as self-harm/suicide.

The impact of alcohol and drug misuse on engagement and cancer treatment should be recognised, and, where possible, specialised teams involved. The presence of substance misuse disorders poses unique problems nearer the end of life, such as in those who may be alcohol-dependent but unable to swallow.

Pharmacological Considerations

It is important to consider the impact of cancer treatment and associated interactions with psychotropic medication in the palliative care of cancer patients. High doses of corticosteroids prescribed as an adjunct to chemotherapy can cause steroid-induced psychoses and significant behavioural disturbances, which may pose a risk to the patient and others. Antidepressants and antipsychotics can competitively inhibit medical anticancer treatments due to psychotropic drug reliance on the cytochrome P450 enzyme system for metabolism. Consideration of what the drug does to the body (pharmacodynamics) and what the body does to the drug (pharmacokinetics) is particularly true in end-of-life care, as both change.

Living With and Beyond Cancer

Traditionally, medicine views recovery as a linear process. It has not tended to look holistically at the patient's ideas of success, experience

and QoL following treatment. In cancer care there is less of a focus on QoL in recovery. It is unsurprising, given this cultural context of cure, that people often think life will return to how it was before diagnosis. It is worth pointing out that today more patients are living with and beyond cancer than dying from cancer, for the first time in history. This poses different psychological difficulties for patients and families, including stigma and relationship and financial pressures.

Often people will experience grief in relation to multiple losses at the end of treatment (e.g. change in appearance, fertility, etc). In order to recover, it is important that the experiences are noted as common and not extraordinary. Threat of cancer recurrence is one common experience for patients after treatment, which can stop people and families rebuilding their lives.

End of Life Concerns

Confusion, helplessness and frustration can arise for individuals and families at the end of life, with potential conflicts of beliefs in the family unit, for example, about the meaning of talking about death and any past experience of loss. There might be a need to protect self and others from pain and suffering and anticipated endings to relationships. Often poorly controlled pain or agitation can adversely impact on having a good death. Despite it being a natural process, death and dying remain difficult for professionals to deal with, and there can be possible tensions created between our professional and personal beliefs about the end of life which are important to acknowledge, as well as proactively recognising the impact it has on our psychological state and wellbeing.

Desire for Hastened Death

Patients nearing a natural death from a terminal disease can have a desire for hastened death (DHD), which is different to suicidality. As the ethical paradigm shifts towards maximising autonomy at the end of life, the phenomenon of DHD becomes more relevant. Interestingly, depression is also under-recognised in this population. US data highlights that rates of DHD reduce once depression is identified and effectively treated. This is also true of poorly controlled pain.

Conclusion

Integrating optimal mental health and psychological care for cancer patients relies on patient centredness and choice, and holistic, evidence-based and multidisciplinary care. Despite the growing commitment to fully integrated, personalised, dynamic and evidence-based supportive and palliative care in cancer, there is still a clear unmet need in cancer mental health. Integration must occur clinically, but also in training the healthcare workforce to manage comorbidity effectively (see Further Reading). Effective integration must also be underpinned by research and in participation with patients and carers, throughout the cancer pathway.

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Dr Fernando has reported speaker and advisory board roles for Janssen.

Dr Smith has reported speaker roles for Astellas and Ipsen.

Dr Afshar has reported speaker roles for Janssen, Astellas and Pfizer.

Dr Thillai has reported speaker roles for Roche.

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Communication with Cancer Patients

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M. Die Trill

President Emeritus, International Psycho-Oncology Society

The Importance and Benefits of Effective Communication in the Cancer Setting

Communication has historically held a place of honour in the physician's daily work, and, more specifically, in oncology. Cancer is one of the most feared diseases of our time that threatens the quality of life (QoL) and survival of patients. It is for these reasons that effective communication is a core skill for oncologists.

Effective communication has enormous benefits. Understanding and learning how to deal with emotions competently will significantly improve doctor-patient communication and patient-centred care, specifically in the cancer setting, where intense emotions often occur. Skilful communication improves the patient's adherence to treatment and their satisfaction with the care received. It ensures adequate informed consent processes and increases participation in complex medical decision-making, empowering patients. It also improves patients' emotional adjustment to cancer and its treatment and helps to clarify realistic expectations about prognosis and disease management. In addition to these well-documented benefits for patients, effective communication is also important and beneficial for healthcare professionals. It helps build positive relationships with patients and families and may help buffer the occurrence of emotional exhaustion.

The basis of all types of effective communication is EMPATHY. Empathy is the ability to identify and understand the patient's feelings and experiences from their perspective. It implies active listening and a focus

on the whole person. Empathic relationships in the clinical context can improve patient outcomes by leading to self-disclosure of the patient's concerns, which may lead to a more accurate diagnosis and more understanding of the patient's and their family's needs. In addition, empathic relationships cause a sense of being listened to and valued as an individual. Reduced depression, lower distress, higher patient satisfaction and improved QoL have been associated with empathic responses in the cancer setting. Sometimes healthcare professionals avoid being empathic out of fear of having to experience the same feelings as their patients. This is a common myth. One does not have to experience pain in his/her right iliac crest to diagnose appendicitis, in the same way that one does not need to experience sadness to be empathic with a patient's sadness. One does not even have to agree with the patient's feelings to be empathic.

Expressing empathy consists of acknowledging the patient's feelings and is a technique (as such, it can be learned) that involves three major steps:

- Identifying the patient's emotions
- Trying to determine what is causing these emotions
- Responding to the patient by showing that you, the clinician, have made the connection between the emotion and its cause

"That must have felt scary when you heard about your recurrence" is a good example of an empathic response, where fear is the emotion expressed (verbally or non-verbally) by the patient, and hearing about a cancer recurrence is the identified cause of the expressed emotion. Expressing understanding through this sort of feedback to the patient is one way to convey empathy.

Doctor: *"Unfortunately Mrs Henry, your test results show that the breast cancer has recurred."*

Mrs Henry: *"Oh my … my mother died of breast cancer, doctor."*

Doctor: *"So you fear that you will also die of cancer because your mother died?"*

In this case, the doctor's empathic response will lead to further discussion with the patient about her feelings, her fear of dying, giving the

clinician the opportunity to clarify the differences between the patient and her mother, and to convey realistic hope.

The BUSTER protocol can guide physicians in their discussions with patients around sensitive issues:

- **B**e prepared: Expect emotion, have a plan for how to hold the discussion, especially if you have to give bad news, and practice self-regulation.
- **U**se non-judgemental listening: Make eye contact, do not try to make things better if they are bad.
- **S**ix-second rule: Avoid escalation of the conversation, for example, wait six seconds before responding to anger or blame; avoid being defensive or blaming.
- *'**T**ell me more'* statements: *"Tell me more about how you are feeling"*.
- **E**mpathise and validate: Acknowledge emotions: *"This is really upsetting news to hear"*.
- Respond with a 'wish' statement: *"I wish we had a more effective treatment"*.

Challenging Situations

Oncologists confront challenging communication situations with their patients thousands of times over the course of their careers, since delivering bad news is a daily task. In addition, if a patient is already in some emotional distress, which cancer patients frequently are, it can be even more difficult for the physician to share negative information with them.

Delivering Bad News

Bad news is any type of information that adversely and seriously affects an individual's view of their future. Delivering bad news in the oncology setting frequently follows the SPIKES protocol, which consists of six steps:

- **S**etting: This makes reference to securing an appropriate area for discussion and includes having a conversation in a quiet and undisturbed area; preparing for what to say and anticipating the patient's and the

family's potential reaction; having key people in the room (who does the patient want in there?); seating the patient close to the clinician; making eye contact and trying to remain calm throughout the discussion.

- **P**erception: Assess the patient's understanding of the seriousness of their condition, observing possible discrepancies between their understanding and what is actually true of their condition, and watching for signs of denial. We do this by asking the patient and their family what they already know: *"Please tell me what you understand is happening with your disease at this time,"* or *"What information have the doctors given you?"*
- **I**nvitation: This refers to obtaining permission before having the discussion with the patient about the disease/treatment, that is: 'ask before you tell'. This step implies setting goals for the discussion (i.e. asking the patient whether they want to know the details of their medical condition or treatment), accepting the patient's right to know and offering to answer all questions the patient and their family may have: *"Is it okay if we discuss the test results today?"*
- **K**nowledge: This step relates to explaining the facts while avoiding medical jargon and explaining them in a way that the patient will understand. Presenting the information in small chunks, and making sure he/she has understood after each piece of information is given, help in this endeavour. Statements such as *"You have a nuclear grade 1 ER/PR-positive spiculated four-centimetre lesion"* should be avoided and substituted with *"Unfortunately, the tests show that you have breast cancer"*.
- **E**motions: This step should start with allowing quiet space for the patient to process the information. Once the patient starts to speak, deal with emotions as they occur. Clinicians may respond to the emotion and explore the patient's feelings with open-ended questions (*"How did that make you feel?"*), avoiding responses with false reassurance, trying to keep our own emotions under control, and responding with empathetic and affirming statements (*"I understand you were not expecting this"*). Often, using *"Tell me more"* helps gain a better understanding of the patient's perspective.

Patient: *"I worry about my husband's reaction to the progression of my disease."*

Doctor: *"Please, tell me more about this."*

- **S**trategy & **S**ummary: The last step in the SPIKES protocol consists of discussing the next steps, defining and agreeing on a plan, asking the patient to repeat their understanding of the information provided and the plan and providing a written summary, if appropriate. Summarising the conversation and offering to respond to questions is the final task.

Patient: *"Does this mean I will die?"*

Doctor: *"Tell me more about what worries you."*

Patient: *"Will I be cured?"*

Doctor: *"I am sorry that a cure is unlikely to happen. Our goal is to keep the disease under control."*

Patient: *"How long will I live?"*

Doctor: *"We can discuss this if you like, but first let me know why you ask?"*

Dealing with Patient Emotions

Emotions are often the underlying source of challenging doctor-patient communication. The E_V_E protocol (Explore, Validate or Empathise) has been described in response to patients' emotions.

- When EXPLORING, the patient feels the oncologist has an interest in him/her: *"Can you please tell me how you feel about this?"*
- VALIDATING implies normalising the patient's feelings: *"Other patients tell me they feel the same way"*.
- EMPATHISING with the patient makes the patient feel connected with the clinician: *"I can understand you feel sad because of your recent recurrence"*.

Discussing Prognosis and Recurrence

Although cancer survival has significantly improved since the mid-1970s for the most common cancers, discussing prognosis remains a challenging task as it is often another piece of difficult news for a patient.

- Avoid giving a specific number ("*You have 6 months"*), which is likely to be inaccurate, or saying *"I don't know how much time you have left"*, which avoids the question and only discredits physician knowledge and expertise.
- Ask the patient exactly why they would like to know. Many patients have specific plans, such as travelling, and want to know if they can go ahead with them; others want to plan for their future and prepare themselves and their families for their death.
- Addressing prognosis is best done by giving a range of possible times: *"We may be talking about a few months to possibly a year"*.
- After giving the information, pause to allow the patient to process and respond to the emotion and/or any questions that arise.

Dealing with recurrence implies addressing chronic disease management and continuity of care and using the strategy of 'hoping for the best while preparing for the worst'. The physician should offer what they can do while remaining grounded in the medical situation: *"I cannot cure your cancer, but I will work with you to slow down your cancer and give you the best possible care"*.

Denial

Denial helps patients deal with frightening situations. Denial may be adaptive in cancer patients when it does not interfere with the patient's ability to make adequate decisions about care or treatment. Denial may help patients deal with their illness in a hopeful way, focusing them on the things that they have control over and ignoring those they do not. It may encourage problem-solving approaches to illness and help expectations that something positive may result from the patient's efforts. In this case, it should not be challenged. Only maladaptive denial, which interferes with the patient's wellbeing or receiving treatment (i.e. when it causes patients to delay their search for medical consultation when symptoms appear, or if it leads them to insist on continuing treatments that have proven to be ineffective in curing or controlling their illness), should be confronted very gently: *"It must be very difficult to hear that your disease is progressing"* is a good way to start.

Responding to Difficult Questions

We may think of difficult questions as those about diagnosis, prognosis or treatment efficacy that are emotionally charged, such as: *"Doctor, am I going to die?"* They become more complex if the patient raises them with subtlety: *"I have seen the patient next door died. Why did he die?"* instead of directly asking whether he/she is going to die. In order to respond:

- Identify what the patient is asking: *"Help me understand your question"*.
- Identify why he/she is asking: *"Tell me more about why you are asking?"*
- Identify the real desire to know the exact response
- Inquire about the patient's perception of his/her situation
- Answer the question/clarify information
- Identify and respond to the patient's emotions
- Respond by returning the question: *"What worries you most about dying at this time?"*
- Convey realistic hope: *"Even though there are no treatments to cure your cancer, we will try to slow it down and focus on a good quality of life"*.

Supporting Patients Approaching the End of Life

Unfortunately, despite medical advances in cancer treatment, a large proportion of cancer patients still eventually die from their disease. It is at this point that the goals of cancer care can change from curative to palliative, or they may even be palliative from the time of diagnosis when patients present initially with advanced disease. The general objective is to guide the patient in understanding that he/she has a life-limiting disease and to establish the appropriate goals of care focusing on QoL and emphasising what can be done, medically.

Provide the information by going through the SPIKES protocol, after responding to emotion (E):

- Ask open-ended questions to elicit the patient's concerns, personal goals and values

- Negotiate new goals of care based on the patient's QoL expectations: contrast 'cure' with 'care', introducing the concept of a palliative approach as one where something can always be done
- Provide space for expressions of grief (i.e. tearfulness) that are responses to the loss of health and living
- Focus on what can be done
- Reinforce the availability of continued support

Maintaining Realistic Hope

Maintaining realistic hope is a difficult task at specific times in the cancer setting.

- Explore and facilitate QoL goals: *"What things would you like to do in the time that you have?"*
- Do not provide misleading information to positively influence hope: *"What are your expectations about the future?"*
- Describe elements of good symptom control: "*We will do anything we can to actively treat and relieve your symptoms"*.
- Emphasise living over dying: *"Sometimes it helps to try to maintain a sense of normalcy or have a daily routine"*.

Even in the most advanced cases of cancer, even when the tumour is no longer treatable, we can always treat the patient: *"Even though there is no treatment available at this moment to treat your disease, we have efficient ways of controlling your symptoms and optimising the quality of your life"*.

Cultural Competence

Living in multicultural, multi-ethnic and multireligious communities, as we currently do, forces us to be sensitive to cultural issues that enhance trust with our patients. Learning about the beliefs and practices of groups most frequently treated in our institutions allows us to get a better understanding of the meaning that life, death, disease, suffering and caregiving have for our patients. The clinician needs to be aware of cultural norms that define the dynamics of medical decision-making processes

in families, in order to provide the best care possible, while avoiding stereotyping individuals. Direct inquiry about how a patient and/or family prefer to hear information and how they prefer to make medical decisions allows the clinician to tailor their communication to each situation.

Declaration of Interest:

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Predicting Prognosis

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N. White
C. Chu
L. Oostendorp
R. Anderson
P. Stone
Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London, London, UK

The Importance of Predicting Prognosis

Making an accurate prognosis, or predicting how long someone will live, is a complex clinical skill. The difficulty is compounded by factors such as the nature and stage of the cancer, patient characteristics and the responsiveness of the disease to treatment. Many clinicians, aware of the inherent uncertainty accompanying their predictions, feel inhibited about sharing their survival estimates with patients, relatives or even with their own clinical colleagues. However, in a palliative care context, a patient's prognosis can be as, if not more, important than their diagnosis.

Some patients and relatives want as much information as possible about what to expect as their disease progresses, whereas others would rather not know anything at all about it. Most patients and relatives fall somewhere in between, caught between wanting and not wanting to know and between desiring more specific or vaguer predictions.

Prognostic information can be important to patients for several reasons. On a practical level, knowing that one has only a short time left to live can enable patients to prepare for their impending death. This may include tasks such as writing a will, preparing an advance statement of wishes, organising lasting powers of attorney, arranging (and

possibly paying for) one's own funeral, mending relationships and saying goodbye to loved ones. Of course, none of these tasks are solely dependent on knowing one's prognosis. Nonetheless, it remains the case that until one understands that time is short, there is a temptation to indefinitely postpone such planning. Having a realistic understanding of one's prognosis is also important if patients are to engage in informed shared decision-making with their clinical teams. Unrealistic prognostic appraisals can lead patients to accept burdensome therapies, which can be time-consuming and require many hospital visits, with little chance of success (i.e. prolonging life). Patients may choose to forego such treatments if they have a better understanding of their prognosis. In some circumstances, knowing one's prognosis can facilitate access to certain financial benefits. In the UK, for example, having a prognosis of less than 6 months entitles one to a higher rate of certain state benefits. Some insurance policies will pay out as soon as the policyholder is deemed to have a terminal illness.

Although access to palliative care services should not solely be determined by prognosis, it remains the case that prognostic information is extremely helpful for prioritisation and planning of services. For instance, hospices (inpatient palliative care units) in the UK offer admissions for terminal care to patients who are imminently dying (usually taken to mean the final days or weeks of life), but do not routinely offer longer-term inpatient care.

Even in the final days of life, knowing a patient's prognosis can be useful. At this late stage of the illness, patients themselves are seldom able to engage in prognostic talk. However, for relatives and friends around the deathbed, being informed that the patient is likely to die in the coming hours or days can help relatives feel prepared for the death and make decisions about care. Relatives can then make informed decisions about whether to stay at the bedside overnight, summon friends or arrange for religious practices to be observed. If a death is unexpected, this can negatively affect families and their long-term adjustment to the bereavement.

Predicting Prognosis in the Era of Immunotherapy

In general, clinicians' predictions about length of survival correlate with actual survival but tend to be over-optimistic, that is, they estimate that the patient has longer to live than they actually do. Many of the studies undertaken in this area were conducted in an era of 'traditional' cancer therapies (surgery, chemotherapy and radiotherapy) or among patients no longer receiving disease-directed treatment. The advent of newer therapies (immunotherapies and targeted therapies) has made the process of prognostication for certain cancers more complex. For example, until recently, metastatic melanoma had a dire prognosis. One of the few available treatments was dacarbazine chemotherapy, which was largely ineffective. The median survival of patients was around 6 months and virtually no patients went into remission. However, since the advent of immunotherapies the prognosis of patients with stage 4 disease has been transformed, with many patients now surviving for years and others going into complete remission. Unfortunately, the efficacy of immunotherapies is not consistent and a sizeable number of patients derive no benefits or experience unpleasant adverse effects. Research identifying biomarkers to predict response to immunotherapy and risks of developing treatment-related toxicity is increasing. Improved clinical outcomes are associated with features of tumour biology (for example, increased tumour mutation burden) and certain patient characteristics (for example, higher levels of human leukocyte antigen-1 [HLA-1] diversity or presence of specific commensal organisms in the gut).

For patients with certain advanced cancers, who were previously given no hope of longer-term survival, some of the reported responses with immunotherapy have been so dramatic that it has made it difficult for patients to accept their poor prognosis (even if their own particular cancer is not amenable to immunotherapy). Others, looking at the recent improvements in survival for certain tumours, may believe that a new miracle cure is just around the corner. Nonetheless, for all of the reasons previously described, it is important for clinicians to try to give as honest and accurate an appraisal of expected prognosis as possible, while at the same time acknowledging and (if possible) quantifying the level of uncertainty that accompanies any prediction.

The Reasons Why Some Clinicians are Better Prognosticators Than Others

There is a wide variation in reported prognostic accuracy among clinicians, and the reasons for this are much debated. Research has investigated the prognostic accuracy of different types of clinicians from the same professional group (e.g. oncologists versus general practitioners), across two or more professions (e.g. doctors versus nurses), and between individual prognosticators versus multidisciplinary teams. Across the board, the evidence is highly variable, due to methodological issues such as small sample sizes or inconsistent comparisons (e.g. different doctors giving different estimates on different patients), with no clear evidence in favour of any profession or type of individual being superior to another. There is however some support for the notion that a prognosis provided by a multidisciplinary team may be more accurate than one that comes from a solitary professional (either doctor or nurse).

Several (sometimes mutually contradictory) explanations for differences in prognostic abilities between individuals have been offered. More experienced or senior clinicians may be better prognosticators by virtue of having accumulated a greater wealth of clinical experiences from which to draw their clinical intuition. Conversely, simply being more senior may not correlate with prognostic accuracy because expertise is honed by practice and more junior staff may make prognostic estimates more frequently than their senior colleagues. There is mixed evidence about whether staff who know the patient better (e.g. care workers or nursing staff) or staff who are less intimately involved in the patient's day-to-day care (e.g. doctors providing a second opinion) are better prognosticators.

Recent research has suggested that prognostication may be a skill that can be taught. The intuitive factors that were used by palliative care doctors (who had previously performed well on a test of their prognostic abilities) were taught to medical students using an online training platform. Following the training, the medical students' prognostic skills more closely mirrored the experts' performance than a control group of students who did not receive the training.

Tools to Support Predicting Prognosis

Several prognostic tools have been developed and validated to support clinicians when predicting survival. Some of the more frequently used tools for patients with advanced disease are described in this section and in Table 1.

Palliative Performance Scale (PPS)

This tool provides an overall indicator of the patient's functional ability (see Anderson et al, 1996). It requires information obtainable from observation at the patient's bedside, without the need for additional tests. Although the PPS is well able to discriminate between patients with differing survival prospects, the scale itself was not specifically developed as a prognostic tool and therefore lacks some face-validity as a stand-alone measure. Nonetheless, it provides a useful 'shorthand' for describing the extent of a patient's physical decline and, therefore, their prognosis.

Palliative Prognostic Score (PaP)

The PaP is calculated using a combination of laboratory measures, clinical features and clinical prediction (see Pirovano et al, 1999). The PaP has been well-validated and is widely used. There are, however, some conceptual and practical limitations with the PaP. First, the calculation of the score is heavily reliant on the clinical prediction of survival and so it does not represent a completely objective appraisal of prognosis. Second, the prognostic categories are framed in terms of quite broad ranges and it is not clear how useful patients, relatives or clinicians actually find it to know that the probability of 30-day survival is (for instance) between 30% and 70%. Nonetheless, using the same broad categories, the PaP is at least as accurate as a clinical prediction of survival.

Palliative Prognostic Index (PPI)

The PPI (see Morita et al, 1999) is similar to the PPS, in that it requires information about the patient that is readily available without the need for additional testing. The PPI produces a score which categorises survival as less than 3 weeks, less than 6 weeks, or greater than 6 weeks.

Table I Characteristics of Selected Prognostic Tools.

Palliative Performance Scale (PPS)		Palliative Prognostic Score (PaP)		Palliative Prognostic Index (PPI)		Prognosis in Palliative care Study (PiPS)	
Domain	**%**	**Domain**	**Score**	**Domain**	**Score**	**PiPS-A**	
Ambulation		Total white cell count		PPS		ECOG performance status	
Full	100-80	Normal [4.8-8.5]	0	10-20	4	General health status	
Reduced	70-60	High [8.5-11.0]	0.5	30-50	2.5	Abbreviated Mental Test Score >3	
Mainly sit/lie	50	Very high [>11]	1.5	≥60	0	Primary breast cancer	
Mainly bed	40	Lymphocyte percentage		Level of oral intake		Primary prostate cancer	
Totally bed bound	30-10	Normal [20.0-40.0]	0	Mouthfuls or less	2.5	Distant metastases (any)	
Activity level and Evidence of disease		Low [12.0-19.9]	1	Reduced but more	1	Liver metastases	
Normal activity & work; No evidence	100	Very low [0-11.9]	2.5	than mouthfuls		Bone metastases	
Normal activity & work; Some evidence	90	Dyspnoea		Normal	0	Anorexia	
Normal activity with effort; Some evidence	80	Yes	1	Peripheral oedema		Dysphagia	
Unable normal job/work; Significant disease	70	No	0	Yes	1	Dyspnoea	
Unable hobby/housework; Significant disease	60	Anorexia		No	0	Weight loss in last month	
Unable to do any work; Extensive disease	50	Yes	1	Delirium		Pulse rate	
Unable to do most activity; Extensive disease	40	No	0	Yes	4	**PiPS-B**	
Unable to do any activity; Extensive disease	30-10	KPS		No	0	ECOG performance status	
Self-care		>50	0	Dyspnoea at rest		General health status	
Full	100-70	30-40	0	Yes	3.5	Abbreviated Mental Test Score >3	
Occasional assistance necessary	60	10-20	2.5	No	0	Primary prostate cancer	
Considerable assistance required	50	CPS (in weeks)				Distant metastases (any)	
Mainly assistance	40	>12	0			Bone metastases	
Total care	30-10	11-12	2			Anorexia	
Intake (food & fluid)		9-10	2.5			Pulse rate	
Normal	100-90	7-8	2.5			Fatigue	
Normal or reduced	80-30	5-6	4.5			White blood count	
Minimal to sips	20	3-4	6			Lymphocyte count	
Mouth care only	10	1-2	8.5			Neutrophil count	
						Platelet count	

Table 1 Characteristics of Selected Prognostic Tools. (Continued)

Palliative Performance Scale (PPS)	Palliative Prognostic Score (PaP)	Palliative Prognostic Index (PPI)	Prognosis in Palliative care Study (PiPS)
Conscious level Full 100-70 Full or confusion 60-50 Full or drowsy +/- confusion 40-20 Drowsy or coma +/- confusion 10			Urea Albumin Alkaline phosphatase Alanine transaminase C-Reactive protein
Outcomes			
Total percentage is calculated from the 'best fit' across all domains, starting from the top. Score in deciles ranging from: 10% (the patient cannot move from bed, has full care needs and only tolerating mouth care) up to 100% (the patient is alert and fully independent)	The total score is calculated. Categorises (probability of surviving 30 days): Group A (score: 0-5.5) >70% probability. Group B (score: 5.6-11.0) 30%-70% probability. Group C (score: 11.1-17.5) <30% probability	The total score is calculated. Score range: 6.5-15 = <3 weeks survival 4-6 = <6 weeks survival <4 = >6 weeks survival	The PiPS algorithm categorises patients into three risk groups, with expected survival of: Days (0-13 days) Weeks (14-55 days) Months (>55 days)

Abbreviations: CPS, Clinical Prediction of Survival; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status.
General health status = recording of the presence or the absence of ascites, peripheral oedema, delirium and decreased oral intake; pulse rate/minute.

One of the theoretical advantages of PPI over PaP is that it does not rely on clinical predictions of survival; however, it is less well-validated, and some studies have found it to be less accurate than clinical predictions.

Prognosis in Palliative care Study (PiPS-A / PiPS-B)

The PiPS predictor models (see Stone et al, 2021a, 2021b) use a combination of clinical and laboratory measures to make a survival prediction about whether patients will survive for 'days' (fewer than 14 days); 'weeks' (between 14 and 55 days); or 'months+' (greater than 55 days). There are two different scales: PiPS-A can be used in all patients and only requires information about observed clinical characteristics and PiPS-B requires additional information obtained from blood results. PiPS-B has been shown to be at least as accurate as a combined multi-professional estimate of survival, but PiPS-A is less accurate.

Most prognostic tools have shown acceptable levels of discrimination and are well calibrated for a palliative care population. However, relatively few have been directly compared against the accuracy of clinicians' predictions. Thus, prognostic tools should currently only be considered as complementary (rather than alternatives) to clinical judgement.

The Importance of Communication

Most patients and their families wish to receive prognostic information even when there is significant uncertainty. Acknowledging the uncertainty but explaining how a prognostic estimate was reached can help patients to understand their prognosis. Overly precise estimates are unlikely to be accurate and so should be avoided in conversations with patients and relatives, but less specific estimates can still provide useful prognostic information and may be preferred. Further research is required to identify areas of good practice and to develop training resources for clinicians.

Key Messages

1. In a palliative care context, a patient's prognosis can be as, if not more, important than their diagnosis.

2. The advent of newer therapies (immunotherapies and targeted therapies) has made the process of prognostication for certain cancers more complex. The response to therapies is inconsistent and can lead to unrealistic treatment expectations.
3. There are several validated tools to predict survival; however, it is unclear how accurate these tools are in comparison to clinical prediction alone.
4. Multidisciplinary teams might provide a more accurate prognosis than individual clinicians.
5. Less specific estimates (such as "weeks", or "months"), rather than specific timeframes, can provide useful information and a framework for prognostic discussions.

Declaration of Interest:

Dr White developed the ORaClES online training for medical students.

Dr Chu has reported no potential conflicts of interest.

Dr Oostendorp developed the ORaClES online training for medical students.

Dr Anderson has reported no potential conflicts of interest.

Professor Stone was the lead applicant on the development of the PiPS prognostic model and the ORaClES online training.

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Cancer- and Treatment-related Symptoms

6

Toxicities of Immunotherapy and Targeted Therapy

6.1

C. Boutros[1]

F. Carbonnel[2]

[1]*Gustave Roussy, Dermatology Unit, Outpatient Clinic, Villejuif, France.*
[2]*Gastroenterology Unit, University Hospital Bicêtre, APHP; Paris Saclay University, Paris, France*

During the past decade, advances in the understanding of the signalling pathways involved in tumour progression have led to the emergence of more selective, mechanism-based therapies including targeted therapies and immune checkpoint inhibitors (ICIs). These new therapies have dramatically improved the treatment landscape for many tumours. This chapter focuses on the dermatological, endocrine and digestive adverse events (AEs) that may be associated with these new cancer therapies, based on their mechanisms of action, and provides general guidelines for the appropriate management of these AEs. Although not detailed in this chapter, other relevant AEs may occur and require awareness to avoid a serious outcome, such as respiratory AEs in fragile patients with pulmonary tumours. In this subpopulation of patients, AEs may be potentially severe due to the sequential use of ICIs and targeted therapies. It is important to follow five steps with the aim to reduce the impact of toxicity related to these new therapeutic strategies: prevent, anticipate, detect, treat and monitor.

The Mechanism of Action of Immune Checkpoints

The cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) modulate the T-cell immune response at different levels. CTLA-4 regulates the amplitude of the early stages of T-cell activation in the secondary lymphoid organs.

Anti-CTLA-4 antibodies, such as ipilimumab and tremelimumab, activate a wide range of T cells throughout the body, leading to a broad spectrum of immune-related AEs (irAEs).

In contrast to CTLA-4, which primarily regulates T-cell activation at early stages in the lymphoid organs and may lead to a broad spectrum of irAEs, PD-1 interacts with its ligands PD-L1 (programmed death-ligand 1) and/or PD-L2 primarily within the peripheral tissue and the tumour microenvironment. Hence, the anti-PD-1 antibodies pembrolizumab, nivolumab and cemiplimab, and the anti-PD-L1 antibodies atezolizumab, durvalumab and avelumab induce T-cell reactivation specifically within the tumour microenvironment and tissue, which may explain their restricted spectrum of irAEs. PD-L1 is often overexpressed in different tumours, and its interaction with PD-1 on T cells enables cancer cells to evade T-cell-mediated immune responses. Thus, blocking the PD-1/PD-L1 interaction can restore T-cell activation and anti-tumour responses. The success of antibody-based PD-1/PD-L1 blockade therapies has provided a major breakthrough in the fight against cancer.

The Mechanisms of Action of Targeted Therapies

The signalling pathways that regulate apoptosis and cell proliferation are deregulated in cancer cells. The altered components of these signalling pathways represent selective targets for anticancer therapies.

Targeting the ligands before they can associate with their receptors has been validated with bevacizumab, a humanised monoclonal antibody (mAb) targeting circulating vascular endothelial growth factor (VEGF). Similarly, targeting the cell receptor prevents the binding of growth factors to their receptors, as is the case with the mAbs cetuximab and panitumumab that bind specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR).

Another approach consists of inhibiting oncogenic drivers such as EGFR, anaplastic lymphoma kinase (ALK) translocations, *ROS* gene rearrangements, *MET* deregulations, *BRAF* mutations and VEGF receptors (VEGFRs) with small molecules. An example of this approach is the use of EGFR inhibitors such as erlotinib, gefitinib, afatinib and

osimertinib, ALK and ROS inhibitors such as crizotinib, and VEGF receptors such as imatinib, dasatinib, sunitinib or sorafenib.

Toxicities of ICIs and Their Management

ICIs may induce variable irAEs; almost any organ may be affected. IrAEs attributed to anti-PD-1/PD-L1 appear to be less frequent and less severe when compared with anti-CTLA-4. Indeed, grade 3-4 irAEs range from 7% to 12% in patients receiving anti-PD-1/PD-L1 and reach 10%-18% in patients receiving anti-CTLA-4. For the combination of anti-PD(L)-1 and anti-CTLA-4, the risk of grade 3-4 irAEs is 33%. Table 1 summarises the global management guidelines of irAEs attributed to ICIs.

Table 1 General Management of irAEs (Not Including Endocrine Toxicities).

Grade	Management	Monitoring
1	• Continue ICI • Symptomatic treatment	• Close follow-up • If worsening: treat as grade 2 or 3-4
2	• Withhold ICI • Symptomatic treatment	• Close follow-up • Resume ICI when symptoms regress to grade 1 • Consider prednisolone 0.5-1 mg/kg per day if the symptoms persist more than 5-7 days • If worsening: treat as grade 3-4 • Consider pneumocystis prophylaxis depending on the clinical context: cotrimoxazole 480 mg twice daily Monday/Wednesday/Friday or pentamidine if cotrim allergy
3-4	• Withhold ICI • Consider hospitalisation • Initiate prednisolone 1-2 mg/kg per day	• Continue prednisolone until improvement to grade 1 • Consider prednisolone tapering over at least one month • Consider other immunosuppressants if no improvement or worsening after 48 hours

Abbreviations: ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.

Skin Toxicity

Skin irAEs are prevalent among all ICIs. They usually develop early in the course of treatment (within the first few weeks after initiation). Risk of skin toxicity is higher with anti-CTLA-4 compared with anti-PD-1/PD-L1 (in 60% versus 20% of patients, respectively). Skin irAEs are primarily of

grade 1 or 2 (serious skin irAEs are rare and do not usually require dose reductions or treatment discontinuation), including pruritus, rash, erythema and vitiligo. Rash is either asymptomatic or associated with pruritus, and is typically erythematous, oedematous and maculopapular. It generally affects the trunk and extremities. Skin irAEs are commonly managed symptomatically with emollients, antihistamines and topical corticosteroids. In most cases, they do not require treatment discontinuation (Table 1). Vitiligo is more frequently described in patients with melanoma (where it seems to be associated with clinical responses) than with other cancers.

Endocrine Toxicity

The risk of onset of endocrine disorders is within the first 10 weeks on ICI. Hypothyroidism and hyperthyroidism are the most frequent endocrine disorders with anti-PD-1/PD-L1 and do not generally require treatment discontinuation because symptoms are reversible with hormone replacement therapy (HRT). Hypophysitis is more frequent with anti-CTLA-4.

Hypophysitis

Hypophysitis occurs in 1%-6% of patients treated with ipilimumab and in 8% of patients treated with the combination of ipilimumab and nivolumab. Hypophysitis manifests as headache, vertigo, nausea, diplopia or weakness. A complete work-up is necessary to determine pituitary, thyroid, adrenal and gonadal status. When hypophysitis is suspected, a confirmatory blood test is required and HRT should be initiated without delay (at least with hydrocortisone 20-10-10 mg/day).

Thyroid disorders

Thyroid disorders occur in 5%-10% of patients treated with anti-PD-1/PD-L1 and in up to 20% of patients treated with the combination of ipilimumab and nivolumab, whereas the incidence is <5% in those treated with ipilimumab alone. They either present with hypothyroidism or a transient thyrotoxicosis followed by hypothyroidism. Thyrotoxicosis is generally reversible and does not require treatment. Hypothyroidism usually requires long-term HRT using thyroxine 0.5-1.5 µg/kg, monitoring with a thyroid blood test 4-6 weeks later to adapt the HRT doses.

Adrenal insufficiency

Adrenal insufficiency results in a low level of cortisol and a normal to high level of adrenocorticotropic hormone (ACTH). ICIs may be continued with adrenal insufficiency. However, immediate HRT is required, comprising oral hydrocortisone at 20-10-10 mg/day to avoid adrenal crisis, which may be revealed by severe dehydration, electrolyte disturbance or hypotension, requiring urgent hospitalisation to initiate methylprednisolone intravenously.

Gastrointestinal Toxicity

Enterocolitis is the most common form of gastrointestinal (GI) toxicity associated with ICIs. The median onset time is 1 month after the first infusion of an anti-CTLA-4 and 2-4 months after the first infusion of an anti-PD-1.

Incidence rates of all-grade diarrhoea and colitis are approximately 35% and 10% with anti-CTLA-4, 10% and 1% with anti-PD-1, and 32% and 15% with the combination. The main symptoms of ICI-induced enterocolitis are diarrhoea and abdominal pain; haematochezia and fever are less frequent. Severe acute colitis can lead to dehydration, toxic megacolon, colonic perforation (seen in 1%-6.6% of patients) and death, especially in cases of delayed diagnosis.

The main differential diagnoses of ICI-induced enterocolitis are infections, diverticulitis and intestinal metastases. Complete blood count, serum electrolyte, creatinine, albumin and C-reactive protein (CRP), searching for stool enteropathogens and toxin of *Clostridioides difficile*, as well as whole-blood polymerase chain reaction (PCR) cytomegalovirus (CMV) are mandatory. In patients who may require infliximab or vedolizumab, interferon gamma-release assay screening for tuberculosis, hepatitis B virus (HBV) and human immunodeficiency virus (HIV) serology should be carried out. Early flexible rectosigmoidoscopy or ileocolonoscopy with biopsies in patients with suspected enterocolitis of grade >1 is strongly recommended. Endoscopic features include erythema, erosion, ulceration and luminal bleeding, although normal colon mucosa can be present in up to 40% of patients despite grade ≥2 symptoms of colitis. Deep ulcerations

and extensive inflammation above the left colon are predictive of a steroid-refractory disease course and may require immunosuppressant treatment. An abdominal computed tomography (CT) scan is indicated in patients with severe acute colitis with suspected perforation, toxic megacolon or abscess.

Management of grade 1 diarrhoea consists of loperamide, abundant oral fluids and a low-fibre diet. ICI treatment can be continued. Persistent grade 1 diarrhoea with histological inflammation and grade 2 diarrhoea/colitis can be treated with corticosteroids (prednisolone 40 mg/day). Infliximab or vedolizumab should be considered if inadequate response is achieved. ICI treatment can be resumed once GI symptoms resolve. Patients with grade 3 and 4 diarrhoea/colitis should be hospitalised. ICI treatment should be stopped and methylprednisolone 40-60 mg/kg/day intravenously should be started. Responders should be switched to the oral form and tapered over 4-8 weeks. Infliximab (5 mg/kg on days 1, 14 and 42) should be administered to patients with steroid-refractory ICI-induced enterocolitis. Vedolizumab is an alternative option (300 mg on days 1, 14 and 42) and appears to be efficacious although it is associated with a slightly delayed response.

Hepatitis

Hepatitis occurs in 5%-10% of patients treated with ipilimumab, nivolumab and pembrolizumab, and in 25%-30% of patients treated with ipilimumab and nivolumab combined. The onset of hepatitis occurs during the first 2 months. In grade 1 hepatitis, ICIs may be continued. In grade 2 hepatitis, ICIs should be discontinued and serum transaminases and bilirubin monitored twice weekly. Oral prednisone or methylprednisolone should be initiated at 0.5-1 mg/kg/day if transaminases and total bilirubin do not improve within 1-2 weeks. Patients with grade 3 or 4 hepatitis should be evaluated by a hepatology team. Liver biopsy should be considered. ICIs should be permanently discontinued, and corticosteroids (methylprednisolone) initiated at 1-2 mg/kg/day. If there is no response to corticosteroids within 2-3 days, immunosuppressive therapy should be considered, particularly mycophenolate mofetil at 1000 mg twice daily.

Toxicities of Targeted Therapies and Their Management

The doses of targeted therapies may be modified depending on the level of toxicity.

Skin Toxicity

Acneiform rash

Acneiform rash develops in the majority of patients treated with EGFR and MEK inhibitors. The incidence of rash induced by EGFR inhibitors, such as cetuximab or panitumumab, ranges from 25%-85% for all-grade toxicities and from 1%-10% for grade 3. Skin rash appears within 2-4 weeks and is represented by papules and pustules, extreme itchiness and severe pain. The incidence of rash is higher with the MEK inhibitor trametinib than with chemotherapy (57% versus 10%). Prophylactic use of the oral antibiotic doxycycline (100 mg/day), topical corticosteroids, emollients and sunscreen upon the initiation of treatment reduce the incidence of severe skin toxicities (grade ≥2). Patient education comprises wearing light clothing, restricting bath and shower time to less than 10 minutes and using lukewarm water. Cleansers with a high pH or alcohol should be avoided. The same approach is recommended for acneiform rash related to tyrosine kinase inhibitors (TKIs).

Hand-foot syndrome (HFS) and hyperkeratotic lesions

HFS develops frequently in patients treated with multikinase angiogenesis inhibitors such as sunitinib, sorafenib, pazopanib, axitinib and regorafenib. All-grade and high-grade rates of HFS are 4.5%-61% and 1.8%-20%, respectively. The lowest rates are with pazopanib, and the highest rates with regorafenib. Painful, erythematous lesions typically affect the palms and soles and affect daily living activities. Hyperkeratotic, painful thickness on the palms and soles may be associated primarily with regorafenib. In grade 1 and 2 HFS, emollients are recommended regularly. Hot water and constrictive footwear should be avoided. Keratolytics, such as 10%-40% urea or 5%-10% salicylic acid, may be indicated for hyperkeratotic lesions, while topical analgesics (e.g. lidocaine gel) may help to relieve pain.

Endocrine Toxicity

Endocrine disorders, primarily thyroid disorders, diabetes and dyslipidaemia, are generally observed with TKIs, but do not require treatment discontinuation. Thyroid disorders are observed in 10%-80% of patients. In patients with no previous history of endocrine disorder, the incidence of thyroid disorders is 30%-40%, with half being subclinical forms. Thyroid disorders related to TKIs present as either hypothyroidism or a transient thyrotoxicosis followed by hypothyroidism (in 20%-40% of cases). The risk of thyroid disorders is highest with sunitinib, sorafenib and imatinib, and is moderate with axitinib, cabozantinib, erlotinib, pazopanib and vandetanib. Thyrotoxicosis is generally brief and reversible. Subclinical hypothyroidism requires a second blood sample control 2-4 weeks later, as hypothyroidism may be transient. If biological hypothyroidism is confirmed, HRT may be considered in symptomatic patients.

Thyroid disorders are reversible after TKI discontinuation at a rate that is not well determined. At the end of TKI treatment, levothyroxine may be progressively discontinued, under monitoring.

Dyslipidaemia is observed in 50% of patients treated with TKIs and 7%-88% of patients treated with mammalian target of rapamycin (mTOR) inhibitors, and also with lorlatinib (70% all grades, and 15% grade ≥3). Pravastatin, rosuvastatin and pitavastatin should be initially considered to treat hypercholesterolaemia because they are unaffected by inhibition of cytochrome P450.

Diabetes is observed in 15%-40% of patients treated with TKIs and 12%-50% of patients treated with mTOR inhibitors. Therefore, fasting venous glycaemia should be preferentially measured before treatment initiation, 2 weeks later and then monthly until discontinuation of the treatment regimen. Full lipid assessment should also be done before treatment initiation then every 3 months during treatment.

Gastrointestinal Toxicity

Perforation

Bevacizumab may cause GI perforation and fistula. GI perforation has been mostly reported in patients treated with bevacizumab for metastatic

colorectal cancer (mCRC) and renal cell cancer. The risk of perforation is increased in patients treated with bevacizumab for mCRC who have a colonic stent. Other predisposing factors of GI perforations are a history of heavy chemotherapy, diffuse peritoneal carcinomatosis, small bowel disease, bowel obstruction, inflammatory bowel disease and bowel resection. Colonic stenting is contra-indicated in patients who are receiving bevacizumab. Additionally, when possible, 6--8 weeks should elapse between the last dose of bevacizumab and surgery. Perforation may be asymptomatic or associated with abdominal pain. Patients treated with bevacizumab who have a new onset and severe abdominal pain should be investigated for potential GI perforation (physical examination and CT scan). Mortality rate is 22%. Early detection of perforation may reduce morbidity and mortality.

Rates of GI perforations are low and not significantly different from controls in patients treated with aflibercept, ramucirumab and antiangiogenic TKIs.

Diarrhoea

Antiangiogenic TKIs may be associated with nausea and diarrhoea. These symptoms are very frequent in patients who receive these drugs and may affect up to 50% of patients. Severe forms (grade 3 or 4) are uncommon.

Diarrhoea is also common in patients receiving TKIs targeting EGFR, such as erlotinib and gefitinib; it usually appears during the first 4 weeks of treatment. It is generally well managed with loperamide.

Pulmonary Toxicity

TKIs may be associated with pneumonitis, mainly with EGFR and ALK inhibitors in lung cancers. In pooled meta-analyses, the overall incidence of pneumonitis was 2.14% in advanced non-small cell lung cancer patients treated with ALK inhibitors and 1.12% with EGFR inhibitors. The incidence of pneumonitis was significantly higher in the Japanese population. Other aetiologies, mainly disease progression and infectious pneumonitis, should be eliminated, with endoscopic procedures if necessary, and systemic corticosteroids should be initiated.

Conclusion

Over the last decade, novel treatment strategies such as ICIs and targeted therapies have enlarged the therapeutic arsenal in several tumour types. However, these are often accompanied by a unique spectrum of toxicities. Prompt identification and management of these AEs is essential for optimal continuation of treatment and a better quality of life for patients.

Declaration of Interest:

Dr Boutros has acted as a board advisor for Bristol-Myers Squibb, has been speaker for Merck and has received travel fees from Lilly, Amgen and Pfizer.

Dr Carbonnel has received advisory board or lecture fees from Merck Sharp & Dohme, Bristol-Myers Squibb, Janssen, Pfizer, Takeda and Celltrion.

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Radiotherapy-induced Symptoms

6.2

U. Höller

Radiation Oncology, MVZ Charité-Vivantes, Berlin, Germany

This chapter focuses on radiation-induced symptoms that oncologists encounter during combined chemoradiotherapy of frequent cancers. Radiotherapy-induced symptoms are determined by and, importantly, restricted to the irradiated organs and tissues. Beside these specific symptoms, fatigue and/or nausea may occur during radiation of large volumes and/or the abdomen.

Normal tissue effects of radiation are due to cell killing and "to a variety of biologic processes that include oxidative stress, inflammation, depletion of injured cells, senescence and elaboration of pro-inflammatory and pro-fibrogenic cascades" (Citrin et al, 2017).

Acute and late effects are distinguished. Acute effects manifest within 90 days of radiotherapy. They are caused by cell killing and inflammation, present in tissues with a high cell turnover (e.g. mucosa, bone marrow) and result in cell depletion. They usually resolve completely, but in severe cases they transition into consequential late effects. Late effects are expressed with a latency of months to many years. They are due to depletion of stem cells, endothelial lesions and fibrosis. Late effects are usually irreversible.

Severe toxicity has become rare as radiotherapy techniques have improved dramatically (image guidance, intensity/volume-modulated radiotherapy). However, toxicity does occur. Supportive therapy is decisive to prevent treatment breaks. Even a few days off therapy can jeopardise the treatment benefit.

Radiotherapy-induced Nausea and Vomiting

Radiotherapy-induced nausea and vomiting (RINV) is underestimated and occurs in up to 28% of patients after a median of 3 treatment days. The emetic risk is classified as high, moderate, low and minimal and is defined by the treatment site, volume and dose of radiation (Table 1). Individual patient factors that increase the risk are female gender, poor general health, age, concurrent/recent chemotherapy, anxiety, advanced disease stage and prior treatment-related nausea.

Prevention is mandatory for patients at moderate/high risk of RINV and may be considered for low risk (Table 1). For concomitant chemotherapy, the pharmaceutical substance with the highest risk of nausea/vomiting defines the prevention. The duration of prophylaxis during fractionated radiotherapy has not been studied; however, administration during the first week is recommended. Rescue medication for low-risk patients seems effective with 5-hydroxytryptamine type 3 (5-HT_3) receptor or dopamine receptor antagonists.

Table 1 Risk Level and Prophylaxis of Radiation-induced Nausea and Vomiting.

Risk of nausea/emesis	Risk level	Irradiated site	Prophylaxis
High	>90%	Total body	5-HT_3 RA and dexamethasone
Moderate	>60%-90%	Upper abdomen, thoracic/lumbar spine depending on RT technique and RT volume, neuroaxis	5-HT_3 RA, dexamethasone possible
Low	30%-60%	Pelvis, cerebrum, head and neck, thorax	5-HT_3 RA or rescue
Minimal	<30%	Extremities, breast	Rescue

Abbreviations: 5-HT_3, 5-hydroxytryptamine type 3; RA, receptor antagonist; RT, radiotherapy.

Neurotoxicity

Neurotoxicity comprises localised injury, the site of which defines the symptoms: usually, fatigue and neuropsychological and cognitive deficits. It is of major concern for patients and caregivers. However, deficits by the tumour have been shown to exceed therapy-induced toxicity.

Risk factors are hypofractionation (high dose per fraction), large radiation volume, concurrent/previous neurotoxic agents (methotrexate, BRAF inhibitors) and young age.

Acute Toxicity

Brain oedema may occur/be aggravated during radiotherapy. Symptoms are focal deficits, seizures and brain pressure (headache, aspontaneity, psychic disorder, vomiting without nausea and singultus). Dexamethasone is administered at the lowest effective dose, once in the morning (4-8 mg) and tapered as soon as clinically possible.

Early-delayed Toxicity

One to four months after radiotherapy, lethargy, fatigue and loss of appetite may occur. Steroid therapy may reduce symptoms, which resolve or decrease.

Late Toxicity

Neuropsychological dysfunction is characterised by cognitive and memory deficits, dyskinesia and, in rare cases, dementia. It appears months to years after treatment and may progress. Prevention with memantine was studied but data are weak. Management is symptomatic; donepezil was shown to be ineffective.

Brain necrosis develops one to many years after high-dose radiation, i.e. at tumour site, and must be distinguished from tumour recurrence. Unfortunately, magnetic resonance imaging (MRI) is not specific. O-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET) positron emission tomography-computed tomography (PET-CT) increases specificity. Necrosis may resolve, frequently stabilises, or may progress. Dexamethasone is initiated early to mitigate inflammation and/or symptoms. Bevacizumab seems to reduce symptoms and the radiographic extent of radionecroses. Persistent/progressive symptoms require surgical treatment.

Lung Toxicity

Subacute Toxicity

Radiation-induced pneumonitis is an inflammation of the lungs. Radiation triggers a cascade of inflammatory enzymes. Exudative alveolitis, sloughing of type I pneumocytes and endothelial cells appear.

Risk factors are hypofractionation, large irradiated lung volume, chemotherapy with platins/taxanes, older age and female gender. Ongoing smoking seems to suppress these inflammatory reactions. The extent of clinical symptoms is associated with pre-existing pulmonary disease/impaired lung function and smoking history. In order to maintain lung function, patients are advised not to smoke. The incidence of pneumonitis of grade ≥3 has dropped to 4%-7%. It is rarely fatal.

Symptoms are non-productive cough, dyspnoea (breast cancer or oesophageal cancer patients)/worsening of dyspnoea (lung cancer patients), sometimes low-grade fever and pleuritic mild chest pain and malaise. Symptoms appear 1-6 months after the end of therapy.

Radiation-induced pneumonitis must be differentiated from other pulmonary diseases (e.g. infectious pneumonia, exacerbated chronic obstructive pulmonary disease [COPD], tumour progression, obstruction) by high-resolution CT. It presents early on as ground-glass opacity and later as fibrosis, and is always restricted to the radiation volume. The only exception is bronchiolitis obliterans with organising pneumonia (BOOP), a hyperergic lung reaction typical in breast cancer patients. Infiltrations appear in and out of the irradiated volume and migrate during the course of disease. BOOP is completely reversible.

Prevention: amifostine, an organic thiophosphate acting as a scavenger of free-oxygen radicals, does not reduce the incidence/severity of pneumonitis. Inhaled beclomethasone, a suppressor of inflammation, and pentoxifylline, anti-inflammatory by inhibition of interleukin and tumour necrosis factor-alpha (TNFα), is promising.

Management: steroids suppress the inflammation but do not seem to mitigate the extent of pneumonitis or ensuing fibrosis. They are administered according to symptoms, e.g. initially prednisolone given orally 60 mg daily for 4-7 days, reduced stepwise over 6-7 weeks to avoid rebound. Antibiotics are added if infection is suspected or risk is high. If symptoms persist, bronchoalveolar lavage is performed. Long-term ineffective steroid medication may be replaced by azathioprine or cyclosporine A. Pneumonitis either resolves or leads to lung fibrosis.

Late Toxicity

Lung fibrosis manifests many months after radiotherapy, with or without preceding pneumonitis. Its extent relates to the radiation volume and determines the clinical effect (reduced lung function, pulmonary hypertension) that is aggravated by pre-existing impaired lung function. Management is symptomatic.

Gastrointestinal Toxicity

Oesophagitis

Acute oesophagitis

Acute oesophagitis is a frequent side effect of (chemo)radiotherapy for thoracic tumours, i.e. lung/oesophageal cancer. The incidence and severity depend on the irradiated oesophageal volume and the dose, fractionation (hyperfractionated-accelerated radiotherapy, i.e. twice-daily treatment, doubles the risk) and concurrent chemotherapy (grade 3-4 oesophagitis occurs in up to 18% of patients).

Acute oesophagitis is usually transient and mild. Symptoms appear approximately in the second/third week of radiotherapy and resolve within 2-4 weeks after the end of therapy. Patients initially complain of difficulties with swallowing (dysphagia), followed by painful swallowing (odynophagia) and later on pain independent of swallowing. General substernal discomfort, nausea and anorexia may result. Clinical examinations are sufficient and should be done regularly for timely initiation of therapy.

Prevention: amifostine has been shown to reduce the incidence and severity of ≥ grade 2 acute oesophagitis only in phase II/III trials with methodological limitations. Because of its side effects, amifostine is not established.

Management: aims to relieve symptoms and maintain adequate nutrition, to avoid irritating substances (tobacco, alcohol, spicy/hot food), to eat puréed food, to consume liquid meal supplements, and rigorous pain management frequently mandating opioids. Oesophagitis is often linked to a reduced function of the lower oesophageal sphincter.

Proton-pump inhibitors (alternatively, H_2-receptor blockers and antacids) treat the symptoms of reflux and reduce the acidic influence on inflammation.

Late toxicity

Oesophageal stricture/stenosis may occur months/years after radiotherapy and requires repeated endoscopic dilatation. Fistulae are rare.

Enteropathy

Pelvic radiation may cause acute and late enteropathy, also referred to as radiation enteritis/colitis or pelvic radiation disease, a term that comprises a wide range of symptoms. The complex symptoms after multimodality therapy of rectal cancer are summed up as 'low anterior rectal resection syndrome' (LARS).

Enteritis is attributed to radiation-induced depletion of mucosal cells and additional mechanisms, i.e. extensive production of free radicals, activation of inflammatory pathways and vascular endothelial dysfunction, resulting in reduced mucosal surface, endothelial thickening and fibrosis.

Risk factors are large radiation volume (e.g. nodal radiotherapy), altered fractionation, additional chemotherapy (5-fluorouracil [5-FU], capecitabine, irinotecan), previous surgery and risk factors for vascular disease (hypertension, diabetes, collagen vascular disease, smoking).

Acute enteropathy

Acute enteropathy is frequent, usually mild and, in the case of simultaneous chemotherapy, moderate. Symptoms are diarrhoea, sometimes nausea, abdominal pain or cramps and bloating; in severe cases, enteral bleeding, dehydration and malnutrition. Symptoms begin in week 2 to 3 of radiotherapy and resolve within 4 weeks after the end of treatment.

Prevention has been widely studied. Prodrugs of aminosalicylates (balsalazide, olsalazine) or the active compound (mesalazine) and the combination of 5-aminosalicylic acid (5-ASA) with sulfapyridine (sulfasalazine) showed partly reduction, partly aggravation of symptoms because

of diarrhoea as a side effect of the drug itself. Sulfasalazine may be used with great care.

Probiotics (living microorganisms in food/dietary supplements that benefit bacterial growth in the intestine), prebiotics (non-digestible dietary carbohydrates for stimulation of bacterial growth) and synbiotics (a combination of both) are considered promising and safe; however, evidence is inconclusive. A low-fibre diet seems to improve nutrition but does not reduce acute enteritis. Sucralfate, glutamine and octreotide are ineffective.

Management is symptomatic: antidiarrhoeal medication with loperamide, supplemented with 5-HT_3-receptor antagonists against irritable bowel syndrome; cholestyramine against bile acid diarrhoea, probiotics against antibiotic-associated diarrhoea, and spasmolytic and defoaming agents. Patients not responding to loperamide may benefit from octreotide. Adequate nutrition is of utmost importance. Professional counselling of patients early on and timely organisation of enteral/parenteral nutrition are necessary.

Late toxicity

Clinical signs of late side effects are persisting/recurrent symptoms similar to acute toxicity, and are usually mild. If severe, malabsorption and malnutrition may result. In very severe and (fortunately) rare cases, stenosis/strictures, diffuse bleeding and perforation/fistulae occur.

Management is symptomatic and as described above. A comprehensive guideline for this complex condition was authored by Andreyev et al (2015).

Surgery is indicated only in the case of very extensive intestinal obstruction, fistula or perforation and after failure of conservative management. Complication rates and mortality are very high.

Skin Toxicity

Radiodermatitis is an issue only for patients whose tumour/nodal disease is close to or in the skin: cancer of the skin, breast, head and neck, vulva and anus.

Acute Radiodermatitis

Acute radiodermatitis is characterised by faint to brisk erythema, hyperpigmentation, oedema and tenderness of the skin. Scaling and dryness of skin, pruritus and/or pain may develop. Severe radiodermatitis presents as painful moist desquamation, fibrinous exudate/crusting and superficial ulceration. It appears in week 3 of standard fractionated radiotherapy and may peak 1 week after the end of therapy. The skin fully recovers within 3 to 4 weeks after the end of treatment. Severe radiodermatitis leads to pigmentation changes, alopecia and/or dryness of the skin.

Risk factors are hyperfractionation, continued smoking, additional trauma such as exposure to heat/ultraviolet (UV) light or chafing and chemo/immunotherapy.

Radiodermatitis is confined to the treatment field and its severity related to the applied dose. It should be discerned from erysipelas, contact dermatitis, tinea and bullous impetigo (*Staphylococcus aureus* infection). The radiation oncologist should always be consulted.

For prevention, daily gentle washing or showering with mild soap or syndet, emollient cream containing 3%-5% urea (if comfortable), and avoidance of tight-fitting garments, extensive sun exposure, bathing, perfume/makeup and sauna/solarium are recommended. The only effective prevention is potent steroid cream. The benefit of calendula cream is controversial; it carries the risk of allergic reaction. Other substances are either ineffective (trolamine, aloe vera, sucralfate) or data are insufficient.

Management: moderate symptoms are relieved with cooling, non-traumatic pads and disinfectant solutions; pain is reduced by semi-permeable dressings. Moist desquamation is treated with non-adherent hydrocolloid dressings or moisture vapour permeable dressings, and wound infection with rinsing with disinfectant solutions. Silver coated dressings may be considered for their antibacterial properties. Antimicrobials are initiated at infection but not as prophylaxis. The benefit of sucralfate cream, hydrocortisone 1%, honey and trolamine is unclear.

Late Toxicity

Dermal thinning, oedema and hypo- or hyperpigmentation, xerosis and scaling may occur after radiation. Patients complain of tenderness, vulnerability of skin and/or itching. Many years after radiotherapy, telangiectasis (multiple, prominent thin-walled small vessels) may impair cosmesis. (Sub)cutaneous fibrosis may occur and, in severe cases, the skin and underlying soft tissue is retracted, joint movement is limited and/or skin breakdown results in a chronic ulcer.

Management includes skin care as described above. Bothersome or bleeding telangiectasias are treated with long-pulsed dye laser. Fibrosis has long been considered irreversible. There is limited evidence that fibrosis may be mitigated by pentoxifylline plus alpha-tocopherol.

Chronic skin ulcers are a rare late effect of radiotherapy. Tumour recurrence has to be excluded, then rigorous topical and systemic antimicrobial treatments are initiated because of frequent infections. Pentoxifylline plus alpha-tocopherol should be taken orally for a couple of months. A small study showed long-lasting remission of fibrosis and ulcer. Hyperbaric oxygen may be considered.

Declaration of Interest:

Dr Höller has reported no potential conflicts of interest.

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Gastrointestinal Problems

6.3

Introduction: The Prevalence of Gastrointestinal Complications in Cancer Patients and the Impact on their Quality of Life

Cancer survival rates have significantly improved over the years due to advances in multidisciplinary and multimodality cancer therapies.

However, many therapies come with significant adverse effects that may result in decreased quality of life (QoL) and early treatment cessation, which can impact clinical outcome.

Twenty to twenty-five percent of patients treated for cancer will experience some kind of adverse event or sequelae following treatment, of which gastrointestinal (GI) symptoms are the most common and have the greatest impact on daily activities.

This chapter discusses the assessment and management of the main GI side effects seen with anticancer therapies and cancer-related GI symptoms.

Adequately managing symptoms is crucial to improving patients' QoL and their compliance with cancer therapies. Interdisciplinary working groups for managing GI symptoms should include members with expertise in palliative and supportive care in order to optimise clinical outcomes.

Ivana Bozovic-Spasojevic (Ed.)

Malignant Bowel Obstruction

6.3.1

C.I. Ripamonti

M. Guglielmo

Oncology-Supportive Care in Cancer Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy

Incidence

Malignant bowel obstruction (MBO) is a frequent complication in advanced cancer patients with abdominal cancer: MBO is present in 5.5%-51% of patients with gynaecological malignancies (especially ovarian cancer) and in 10%-28% of colorectal cancer patients. The small bowel is more frequently involved than the large bowel (61% versus 33%).

Causes

Several pathophysiological mechanisms may be involved, such as extrinsic, intraluminal or intramural occlusion of the lumen, that induce a cascade of events producing a vicious circle of secretion-distension-secretion and definitive MBO (Figure 1).

Clinical Features

GI symptoms occur in different combinations and intensities depending on the site of obstruction. Vomiting, nausea, pain (both colicky and/or continuous), xerostomia, somnolence, dyspnoea and even sensation of hunger may be present and can be evaluated with validated assessment tools.

Diagnosis

Diagnosis is established or suspected on clinical grounds and usually confirmed with abdominal radiographs demonstrating air-fluid levels.

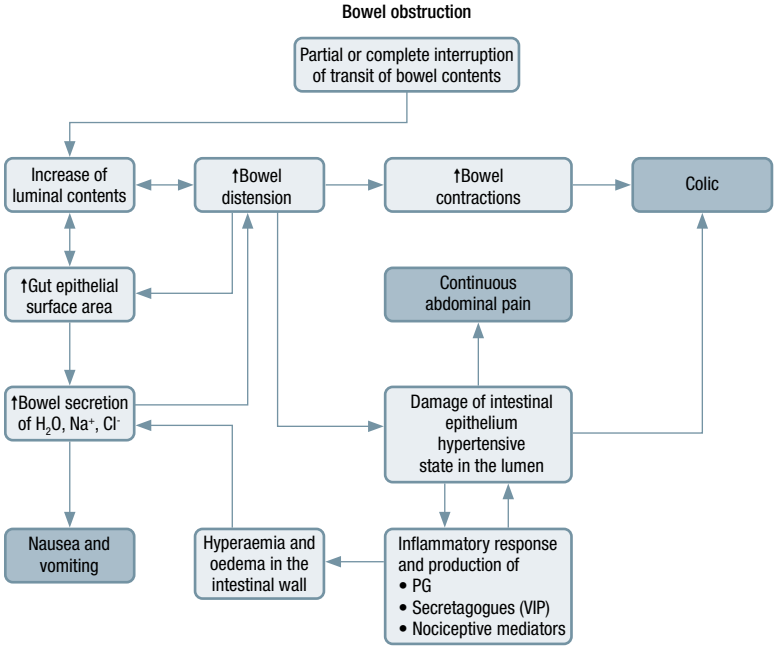

Figure 1 Definitive bowel obstruction.
From: Ripamonti CI, Easson AM, Gerders H. Malignant bowel obstruction. In: Bruera E, Higginson I, von Gunten CF, Morita T (Eds). Textbook of Palliative Medicine and Supportive Care, 3rd edition, 2021. London: CRC Press Taylor& Francis Group, Chapter 62, 587-601.

Abbreviations: PG, prostaglandins; VIP, vasointestinal polypeptides.

Computed tomography (CT) combined with intravenous and oral ± rectal contrast provides a better global assessment of the abdomen and pelvis and can help identify the transition point(s) in bowel obstruction, thereby determining the site, cause and severity of obstruction.

Principles of Treatment

The management of MBO must be highly personalised according to stage of illness, prognosis, the possibility of further antineoplastic therapies, general status, performance status and the patient's choices. Treatment

options including surgery, endoscopy (stenting, venting procedures), interventional radiotherapy and aggressive medical management should be discussed, along with the complication rates and the expected success of each intervention. In clearly incurable situations, significant patient discomfort and suffering must be balanced with the need to simplify the care of those patients with a short time to live to maintain a good QoL (Figure 2).

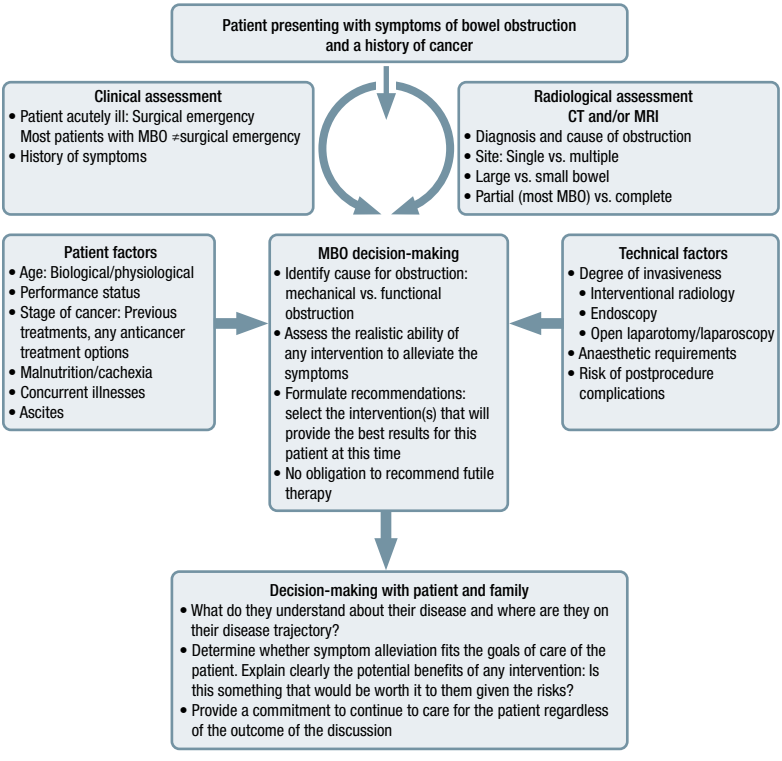

Figure 2 Algorithm for assessing and managing a patient with MBO.
From: Helyer L, Easson AM. Surgical approaches to malignant bowel obstruction. J Support Oncol 2008; 6:105-113.

Abbreviations: CT, computed tomography; MBO, malignant bowel obstruction; MRI, magnetic resonance imaging.

Parenteral nutrition should be considered in selected patients who benefit from standard palliative treatment of malignant obstruction and are obliged to maintain a total bowel rest for weeks or months.

Drug therapy comprising analgesics, antisecretory drugs and antiemetics, without using a nasogastric tube, can be administered via continuous parenteral infusion. Figure 3 shows the pharmacological approach well validated by prospective and randomised trials.

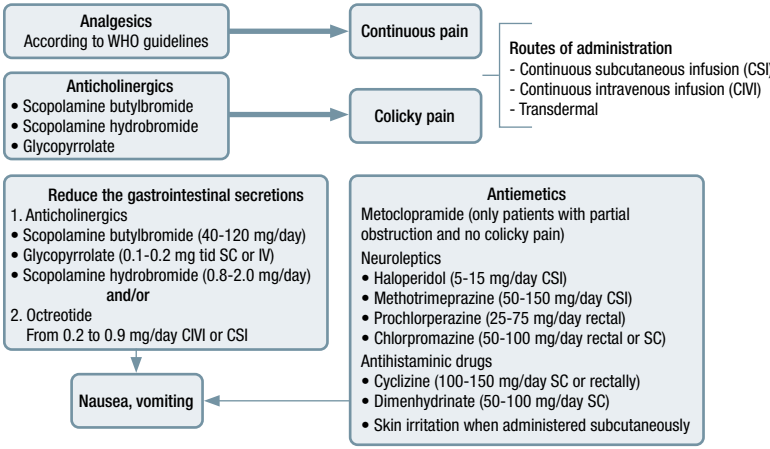

Figure 3 Symptomatic pharmacological approach.
From: Ripamonti CI, Easson AM, Gerders H. Malignant bowel obstruction. In: Bruera E, Higginson I, von Gunten CF, Morita T (Eds). Textbook of Palliative Medicine and Supportive Care, 3rd edition, 2021. London: CRC Press Taylor & Francis Group, Chapter 62, 587-601.

Abbreviations: IV, intravenous; SC, subcutaneous; tid, three times/day; WHO, World Health Organization.

Vomiting can be managed using two different pharmacological approaches: anticholinergics (scopolamine butylbromide, glycopyrrolate) and/or octreotide (as recommended by the European Society for Medical Oncology [ESMO] and Multinational Association of Supportive Care in Cancer [MASCC]), which reduce GI secretions, and/or antiemetics acting on the central nervous system, alone or in association with drugs to reduce GI secretions (Figure 3). Olanzapine may also be useful.

Declaration of Interest:

Dr Ripamonti has reported no potential conflicts of interest.

Dr Guglielmo has reported no potential conflicts of interest.

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Constipation

6.3.2

F. Scotté[1]

K. Legeay[2]

[1]*Interdisciplinary Patient Pathway Department, Gustave Roussy, Villejuif, France*

[2]*Medical Oncology and Supportive Care Department, Foch Hospital, Suresnes, France*

Constipation is a widespread, subjectively experienced symptom and a source of major morbidity and distress, prevalent with the use of opioids. It is poorly anticipated, recognised and treated. It is defined as the slow movement of faeces through the intestine, resulting in infrequent irregular bowel movements, and difficult passage of dry, hard stools. As it is subjective, constipation is variously expressed according to the individual patient's experience (frequency, stool characteristics, pain, etc.).

Incidence

Between 40% and 90% in advanced cancer patients. More prevalent in the elderly.

Causes

Organic factors: Medication (opioid analgesics, antacids, antitussives, anticholinergics, antidepressants, antiemetics, neuroleptics, iron, diuretics, chemotherapeutic agents), metabolic disorders (dehydration, hypercalcaemia, hypokalaemia, uraemia, diabetes, hypothyroidism), neuromuscular dysfunction, structural issues (abdominal or pelvic mass or carcinomatosis, post-surgery, radiation fibrosis) and pain.

Functional factors: Age, diet (poor food and fluid intake), lack of activity, environment.

Grading

- Grade 1: Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification or enemas
- Grade 2: Persistent symptoms with regular use of laxatives or enemas; limiting instrumental activities of daily living (ADL)
- Grade 3: Obstipation with manual evacuation indicated; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated

Prevention, Diagnosis and Management

- Assess in all cancer patients, specifically with patient-reported outcomes measures (PROMs)
- Prevent in situations at risk (opioids, loss of mobility)
- Ensure access to toilets, especially in all cases of decreased mobility
- Mobilise patient and increase walking and adapted physical activities
- Dietetic support: hydration with adequate water intake, diet rich in fibres (vegetables, fruits, etc.)
- Manage known decrease in food intake (anorexia of ageing, chewing difficulties), which negatively influence stool volume and consistency and bowel movements
- Optimise toileting by educating patients to attempt defaecation at least twice a day, usually 30 minutes after meals and to strain no more than 5 minutes
- Abdominal massages can be useful
- Laxatives may be required:
  - ✓ Osmotic laxatives (polyethylene glycol [PEG], lactulose or magnesium and sulphate salts)
  - ✓ Stimulant laxatives (senna, cascara, bisacodyl and sodium picosulphate)
- Suppositories and enemas are preferred in cases of faecal impaction (caution with contraindications)

- Non-absorbable, soluble dietary fibre or bulk agents should be avoided in non-ambulatory patients with low fluid intake because of the increased risk of mechanical obstruction
- Stimulant laxatives can be used, with awareness of risk for pain and cramps
- Combined opiate/naloxone medications can reduce the risk of opioid-induced constipation. The recent development of mu-opioid receptor antagonists enables the optimisation of pain control and reduces the impact of adverse events.

Declaration of Interest:

Dr Scotté has reported honoraria/consultation fees from Roche, Amgen, Helsinn, Vifor Pharma, Merck Sharp & Dohme, GlaxoSmithKline, Pfizer, Bristol-Myers Squibb, Arrow, Alliance Healthcare, Leo Pharma, Pierre Fabre Oncology, Viatris, Sanofi and Sandoz.

Ms Legeay has reported no potential conflicts of interest.

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Diarrhoea

6.3.3

C.I. Ripamonti

P. Di Pede

Oncology-Supportive Care in Cancer Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy

Diarrhoea is defined as the frequent passage of loose stools (more than three in 24 hours) with urgency. It impacts the QoL of cancer patients.

Most Frequent Causes and Incidence

- Chemotherapy with incidence of grade 4 toxicities up to 20% or more
- Targeted therapies (incidence varies depending on the class of the drug)
- Immunotherapeutic approaches
- Other drugs (hormonal therapy, antibiotics, laxatives, antacids, non-steroidal anti-inflammatory drugs [NSAIDs], iron)
- Diet: bran, fruits, hot spices, alcohol
- Radiotherapy: up to 60% of patients will have temporary mild diarrhoea during pelvic radiotherapy
- Surgical procedures, coeliac plexus block
- Neutropaenic enterocolitis; ischaemic colitis (from non-neutropaenic enterocolitis)
- Cancer associated with diarrhoea as a symptom (carcinoid syndrome from neuroendocrine tumours [NETs], colon cancer, intestinal lymphoma, medullary carcinoma of the thyroid, pancreatic tumours [particularly islet cell tumours (Zollinger-Ellison syndrome)])
- Pancreatic disease-related bile malabsorption
- Phaeochromocytoma

- Infections (e.g. *Clostridium difficile*)
- Enteral feeding
- Diarrhoea is less common than constipation in palliative care due to abuse of laxatives, malabsorption and altered fluid absorption in the bowel

Grading

The Common Terminology Criteria for Adverse Events (CTCAE) is the most frequently used grading system, although it does not take into account volume and duration of symptoms, subjective complaints and patients' perceptions of severity. The implementation of the patient-reported outcomes (PROs) version of the CTCAE system (PRO-CTCAE) will allow a clearer pattern of symptoms to be collected.

Principles of Treatment

Management approaches are shown in Figure 1 and in Table 1.

- Uridine triacetate (10 g orally every 6 hours for 20 doses) is recommended for the management of early-onset, severe or life-threatening diarrhoea and/or neutropaenia within 96 hours of completion of 5-FU (5-fluorouracil) or capecitabine treatment
- Oral budesonide has shown efficacy in chemotherapy-induced diarrhoea refractory to loperamide; prophylactic use is not recommended
- Antibiotics are indicated only in cases of fever, hypotension, peritoneal signs, neutropaenia, small intestinal bacteria overgrowth syndrome (SIBO), perianal sepsis or bloody diarrhoea suggestive of either neutropaenic enterocolitis, *Clostridium difficile* infection or other infective causes
- The combination of a low-fat diet and bile acid sequestrants may be an effective integrated therapy in cases with unabsorbed bile salts
- Colesevelam is the better tolerated of the available agents, which are limited by GI side effects, including bloating, flatulence and abdominal discomfort

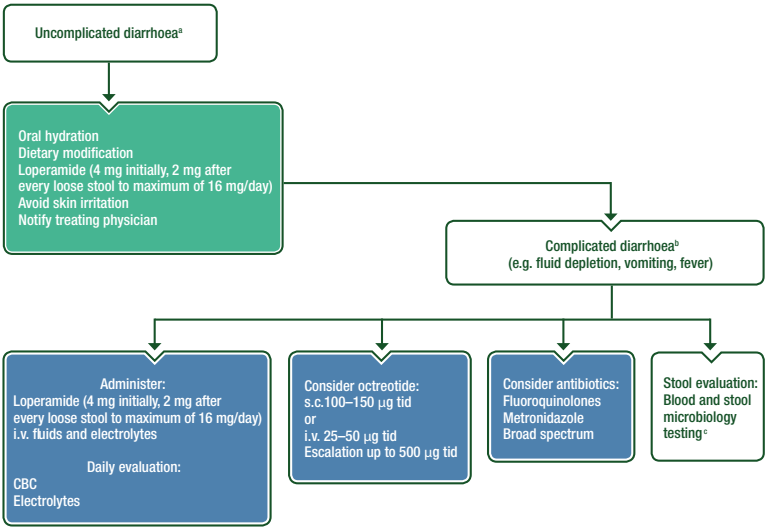

Figure 1 Algorithm for therapeutic approach.
From: Bossi P, Antonuzzo A, Cherny NI, et al; ESMO Guidelines Committee. Diarrhoea in adult cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2018; 29: iv126-iv142.

[a] *Treatment setting: ambulatory and/or outpatient supportive care outpatient unit*
[b] *In-hospital treatment*
[c] *Consider Clostridium difficile, Salmonella, Campylobacter and other causes of infectious colitis*

Abbreviations: CBC, complete blood count; i.v., intravenous; s.c., subcutaneous; tid, three times a day.

Table 1 Diarrhoea in Advanced Care Patients Not Receiving Oncological Therapies.
From: Bossi P, Antonuzzo A, Cherny NI, et al; ESMO Guidelines Committee. Diarrhoea in adult cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2018; 29: iv126-iv142.

Cause	Example	Management
Drugs	Laxatives, antibiotics, antacids, PPIs, NSAIDs, iron, antidiabetics	Adjust medication
Local	Overflow diarrhoea (incomplete obstruction or constipation and impacted stools) Resections, fistulae or manifestations of tumour which reduce absorptive surfaces Exocrine pancreatic insufficiency Late effects of RT	Enema Symptomatic therapy with loperamide Enzyme therapy
Immune	Late effects of immunotherapy GvHD	Immunosuppression

Abbreviations: GvHD, graft-versus-host disease; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; RT, radiotherapy.

Declaration of Interest:

Dr Ripamonti has reported no potential conflicts of interest.

Dr Di Pede has reported no potential conflicts of interest.

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Cachexia and Nutrition

6.3.4

J. Arends

Department of Medicine I, Medical Center - University of Freiburg; Faculty of Medicine, University of Freiburg, Freiburg, Germany

Incidence, Pathophysiology and Clinical Impact of Cachexia

Cachexia remains a largely underdiagnosed and undertreated condition. Approximately half of all patients with advanced cancer experience cachexia, with the prevalence rising in the last weeks of life. The development of cachexia is driven by the presence of the tumour, metabolic reactions of the host and treatment-induced toxicities. Cachexia is a complex syndrome which includes 'objective' components (inadequate food intake, weight loss, physical inactivity, loss of muscle mass, metabolic derangements, especially tumour-associated systemic inflammation inducing catabolism) and 'subjective' components (e.g. anorexia, early satiety, taste alterations, distress, fatigue and loss of concentration and interest in daily activities). The presence of cachexia is associated with a severely compromised QoL and clinical outcome, including tolerance to antineoplastic treatments, response to treatment, complication rates and survival.

Definition of Cachexia

Today, cachexia is understood to be a form of disease-related malnutrition, defined by the combination of (i) either significant weight loss (>5% in 6 months), low body mass index or low muscle mass (by validated body composition measuring techniques) and (ii) activation of systemic inflammation. Early forms, i.e. pre-cachexia (anorexia with weight loss <5%), should be detected and treated comprehensively, while in late

cachexia stages (severe weight loss, unresponsive tumour progression, short expected survival) nutritional care should focus on counselling and relieving distressing symptoms.

Early Detection and Assessment of Cachexia

To improve detection of cachexia, all cancer patients should be screened repeatedly for nutritional risk, nutritional impact symptoms, low muscle mass, psychosocial problems and side effects of cancer and its treatment that impact nutrition. At-risk patients need to be assessed in more detail to diagnose treatable defects and to determine essential parameters of nutritional status for follow-up. The following screening tools are suggested by the 2021 ESMO Clinical Practice Guidelines on cancer cachexia in adult patients: Malnutrition Universal Screening Tool (MUST), Nutrition Risk Screening 2002 (NRS-2002), Short Nutritional Assessment Questionnaire (SNAQ) and the Malnutrition Screening Tool (MST).

Treatment of Cachexia

Comprehensive treatment requires a multi-targeted and multi-specialist approach aimed at managing the objective signs and relieving the associated symptoms. The primary goal is to meet the essential physiological and psychological needs of the patient. This includes providing energy (30 kcal/kg BW [body weight]/day), nutritional substrates (especially protein, 1.2-1.5 g/kg BW/day) and anabolic stimuli (e.g. muscle training) as well as compassionate support addressing the dysfunctions of the psychological (pleasure) and social (communication) aspects of food and eating. Nutritional and metabolic interventions range from dietary counselling to oral nutritional supplements, pharmacological agents, enteral tube feeding and parenteral nutrition, as required. The invasiveness of an intervention needs to be chosen and adapted according to, among other aspects, the cancer prognosis and the preferences of the patient, weighing transparently in each case the benefits and risks together with the patient. Thus, nutritional interventions, including – if required – enteral or parenteral nutrition, should be offered early in patients with a good long-term prognosis. Close to the end of life, efforts should focus primarily on symptom control.

Declaration of Interest:

Dr Arends has received honoraria from Baxter, B. Braun, Fresenius Kabi, Hipp and Nutricia.

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Mucositis

6.3.5

M. Kuten-Shorrer[1,2]
N.S. Treister[3,4]
D.M.K. Keefe[5,6]

[1]*Department of Oral Medicine, Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, NY, USA*
[2]*Division of Oral Medicine, Department of Diagnostic Sciences, Tufts University School of Dental Medicine, Boston, MA, USA*
[3]*Division of Oral Medicine and Dentistry, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA, USA*
[4]*Department of Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, Boston, MA, USA*
[5]*Cancer Australia, Sydney, NSW, Australia*
[6]*Adelaide Medical School, The University of Adelaide, Adelaide, SA, Australia*

Mucositis is an acute toxicity resulting from direct and indirect damage to the GI tract mucosa, secondary to cancer therapy. Severe mucositis is a potentially dose-limiting toxicity, directly impacting cancer treatment outcomes. Complications of mucositis, such as infection and dysphagia, may necessitate hospitalisation, substantially increasing the cost of care and adversely affecting patients' QoL.

Incidence

The incidence, course and clinical presentation of mucositis are site-dependent and vary based on the cancer treatment regimen. Oral mucositis (OM), restricted to the oral cavity and oropharynx, is more frequent than GI mucositis (GIM), occurring distal to the oropharynx. OM occurs in 20%-40% of patients receiving conventional chemotherapy for solid tumours, 80%-100% of patients receiving head and neck (H&N) radiotherapy and approximately 80% of patients undergoing myeloablative

haematopoietic stem cell transplantation (HSCT). Several classes of targeted anticancer therapies are also associated with mucositis.

Clinical Presentation

Mucositis typically begins shortly after the first cycle of chemotherapy with gradual recovery within 14 days after treatment discontinuation. Full-blown radiotherapy-associated OM develops around the third week of treatment, lasting up to 6 weeks following completion. OM is characterised by erythema and painful ulceration of the non-keratinised mucosa. Ulcers are typically extensive and irregular in shape, with a greyish-white pseudo-membrane. While the term 'mucositis' is broadly used in reporting mucosal toxicities associated with targeted anticancer therapies, many of these are well-characterised and must be differentiated from the classic OM. Mammalian target of rapamycin (mTOR) inhibitors are associated with fast onset aphthous-like ulcers. Immune checkpoint inhibitors are associated with lichen planus and erythema multiforme-like changes. Oral reactions related to use of tyrosine kinase inhibitors (TKIs) include dysgeusia, oral sensitivity and pain with or without presence of clinical lesions.

GIM presents with abdominal pain, nausea, vomiting or diarrhoea. Oesophagitis commonly accompanies OM, especially following H&N chemoradiotherapy, enhancing symptoms and further limiting oral intake.

Grading

The World Health Organization (WHO) OM scale and the National Cancer Institute (NCI) CTCAE are straightforward and widely used scoring systems. Both five-point scales combine objective and subjective (degree of symptoms and interference with oral intake) measures of mucositis. Moderate to severe symptoms (grades 3-4) typically drive clinical intervention.

Principles of Treatment

Management strategies focus on prevention and symptomatic relief to improve QoL and ensure the uninterrupted delivery of cancer therapy. The recently updated MASCC/ISOO (International Society of Oral Oncology) guidelines favour the use of standardised oral care protocols, oral cryotherapy, photobiomodulation therapy and benzydamine mouthwash to prevent OM. Pain control for established OM can be achieved with lidocaine-based topical analgesia and mucosal coating agents, with stronger agents, such as topical morphine and patient-controlled analgesics, reserved for severe cases.

Declaration of Interest:

Dr Kuten-Shorrer has reported no potential conflicts of interest.

Dr Treister has reported no potential conflicts of interest.

Dr Keefe has reported no potential conflicts of interest.

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Chemotherapy/Radiotherapy-related Nausea and Vomiting

6.3.6

F. Scotté[1]

K. Legeay[2]

[1]*Interdisciplinary Patient Pathway Department, Gustave Roussy, Villejuif, France*

[2]*Medical Oncology and Supportive Care Department, Foch Hospital, Suresnes, France*

Chemotherapy- and radiotherapy-induced nausea and vomiting (CINV and RINV) are two of the most troubling adverse events. Nausea and vomiting can lead to dehydration, electrolyte imbalances and malnourishment, sometimes resulting in emergency department visits or hospitalisation. Dose reductions or delays in chemotherapy may be necessary as a result of CINV or RINV, which may negatively impact patient outcomes and QoL, and furthermore, increase the overall cost of cancer care. The knowledge and use of regularly updated guidelines improve the efficacy of antiemetics as well as patient outcomes. Recent developments have yielded prediction tools (e.g. the MASCC Antiemesis Tool [MAT]) in order to personalise antiemetic prophylaxis.

Incidence

The emetogenicity of anticancer treatment depends on the type of anticancer drug and site of radiation.

Causes

Two major pathways have been defined:

- Central pathway, predominantly involved in the delayed phase
- Peripheral pathway, predominant in the acute phase

Grading

- High risk emetogenic (>90% of patients experience nausea and vomiting)
- Moderate risk (30%-90%)
- Low risk (10%-30%)
- Minimal risk (<10%)

Principles of Treatment

Antiemetic drugs are used following emetogenic risk and time of the anticancer treatment (anticipatory = before treatment; acute = first 24 hours; delayed = beyond 24 hours) (Table 1).

Table 1 Antiemetic Prophylaxis in CINV and RINV.

From: Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol 2016 Sep;27(suppl 5):v119-v133.

Emetic risk group	Acute phase	Delayed phase
High non-AC	5-HT_3 + DEX + NK_1	DEX or (if APR 125 mg for acute) MCP + DEX or APR
High AC	5-HT_3 + DEX + NK_1	None or (if APR 125 mg for acute) DEX or APR
Carboplatin	5-HT_3 + DEX + NK_1	None or (if APR 125 mg for acute) APR
Moderate (other than carboplatin)	5-HT_3 + DEX	No routine prophylaxis (DEX can be considered for oxaliplatin, anthracycline or cyclophosphamide)
Low	5-HT_3 or DEX or DOP	No routine prophylaxis
Minimal	No routine prophylaxis	No routine prophylaxis
RINV/Area of treatment		**Antiemetic**
High = Total body irradiation		Prophylaxis with a 5-HT_3-RA + DEX
Moderate = Upper abdomen, craniospinal		Prophylaxis with a 5-HT_3-RA + optional DEX
Low	Cranium	Prophylaxis or rescue with DEX
	Head and neck, thorax region, pelvis	Prophylaxis or rescue with DEX, a dopamine RA or a 5-HT_3-RA
Minimal = Extremities, breast		Rescue with DEX, a dopamine RA or a 5-HT_3-RA

Abbreviations: 5-HT_3, serotonin$_3$ receptor antagonist; AC, anthracycline, cyclophosphamide; APR, aprepitant; CINV, chemotherapy-induced nausea and vomiting; DEX, dexamethasone; DOP, dopamine receptor antagonist; MCP, metoclopramide; RA, receptor antagonist; NK_1, neurokinin$_1$ receptor antagonists such as aprepitant or fosaprepitant or rolapitant or nepa; RINV, radiotherapy-induced nausea and vomiting.

Declaration of Interest:

Dr Scotté has reported honoraria/consultation fees from Roche, Amgen, Helsinn, Vifor Pharma, Merck Sharp & Dohme, GlaxoSmithKline, Pfizer, Bristol-Myers Squibb, Arrow, Alliance Healthcare, Leo Pharma, Pierre Fabre Oncology, Viatris, Sanofi and Sandoz.

Ms Legeay has reported no potential conflicts of interest.

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Tumour-related Nausea and Vomiting in Advanced Cancer

6.3.7

C.I. Ripamonti

L. Toffolatti

Oncology-Supportive Care in Cancer Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy

Incidence

In advanced cancer, nausea and vomiting occur more frequently in females. Nausea is most prevalent in gynaecological cancers (42%, with up to 80% in cervical and vaginal cancers) and stomach cancer (36%) and occurs less frequently in H&N cancer (6%) and lung cancer (14%). The prevalence of moderate to severe nausea is 16%; the incidence of nausea and vomiting in patients treated with oral morphine is about 70%. At the end of life, prevalence is reported between 20% and 70%.

Causes

Nausea and vomiting are usually described as a multicausal syndrome. Figure 1 shows the most frequent causes and Figure 2 the emetic pathways and neurotransmitters.

Assessment

The presence and intensity of nausea and vomiting as well as the impact on QoL are dynamic events which can change in respect to both physical and psychological factors. To obtain an adequate follow-up on symptom control, assessment should be carried out frequently during the illness. Nausea and vomiting can occur independently, their severity and duration are separable phenomena and must be evaluated separately and systematically together with all the other physical and emotional symptoms. Nausea

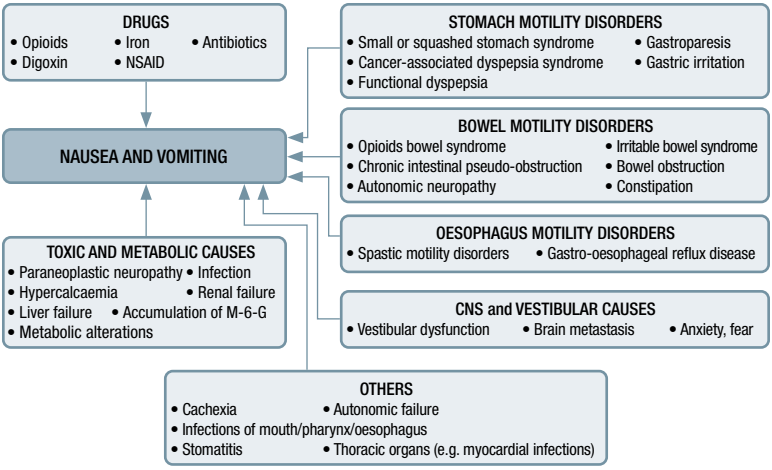

Figure 1 Most frequent causes of tumour-related nausea and vomiting.

Abbreviations: CNS, central nervous system; M-6-G, morphine-6-glucoronide; NSAID, non-steroidal anti-inflammatory drug.

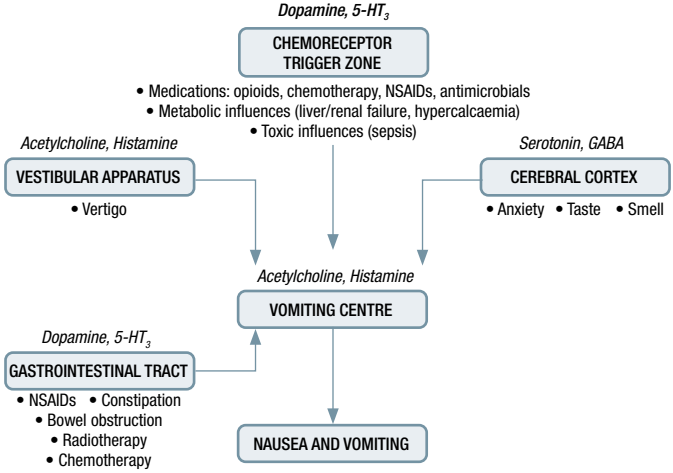

Figure 2 Emetic pathways and neurotransmitters involved in tumour-related nausea and vomiting.

Abbreviations: 5-HT_3, serotonin$_3$; NSAID, non-steroidal anti-inflammatory drug.

is a subjective symptom reported by the patient by means of validated PRO tools (e.g. Edmonton Symptom Assessment System [ESAS] tool, see Chapter 2), while vomiting is an objective clinical sign.

Principles of Treatment

The therapeutic intervention for managing nausea and vomiting foresees careful evaluation of the causes and triggering factors in order to act adequately; the patient's drug regimen should be checked.

In advanced cancer patients, chronic nausea and vomiting have been shown to improve after the administration of prokinetic drugs such as metoclopramide in uncontrolled and controlled studies, particularly for patients with dysmotility-like symptoms, for whom gastroparesis is frequently caused by opioids. Preliminary data suggest that continuous subcutaneous infusion of metoclopramide is superior to intermittent administration for the management of chronic nausea in advanced cancer: metoclopramide is considered an antiemetic drug of choice in advanced cancer by the 2021 MASCC recommendations.

As second-line therapy, potent and sedative antiemetics such as haloperidol, prochlorperazine, dimenhydrinate, phenothiazine and olanzapine are used. Of note, a small randomised pilot study showed olanzapine to be superior to placebo for the treatment of advanced cancer-related chronic nausea and/or vomiting.

Switching the opioid and/or the route of administration is an effective approach to manage opioid-induced emesis.

Corticosteroids are among the most potent antiemetics. These agents are synergistic with metoclopramide and 5-HT_3 antagonist against chemotherapy-induced emesis and chronic nausea. These drugs can be given orally, subcutaneously or intravenously. Corticosteroids are particularly useful in nausea and vomiting induced by intracranial disease and increased intracranial pressure, or bowel obstruction.

Treatment of nausea and GI symptoms should include pharmacological and non-pharmacological approaches and not be limited to the use of drugs alone.

Declaration of Interest:

Dr Ripamonti has reported no potential conflicts of interest.

Dr Toffolatti has reported no potential conflicts of interest.

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Malignant Ascites

6.3.8

G. Kefala

D. Papamichael

Department of Medical Oncology,
Bank of Cyprus Oncology Centre, Cyprus

Definition

Ascites is the abnormal accumulation of fluid into the peritoneal cavity. While the most common cause is liver cirrhosis, malignancies account for about 10% of cases. Less common factors include heart failure, pancreatic disease and nephrotic syndrome. Malignant ascites is the result of peritoneal carcinomatosis, multiple liver metastases and, rarely, Budd-Chiari syndrome. Increased vascular permeability, neovascularisation and portal hypertension are the main underlying pathogenetic mechanisms.

Aetiology

GI and ovarian cancers are the most common cause of malignant ascites due to peritoneal carcinomatosis. Any type of cancer resulting in high-volume liver disease may also be related to ascites.

Clinical Presentation

Clinical presentation varies among patients and includes GI symptoms such as nausea and vomiting, abdominal distention, constipation and anorexia. Manifestations from other systems such as urinary frequency, oedema, weight gain or breathlessness may also be present.

Diagnosis

Diagnosis based on clinical examination and ultrasound has been the preferred diagnostic tool for confirmation. Cytology remains the gold

standard of diagnosis with 100% specificity but 60% sensitivity and is used when other causes should be excluded. Serum ascites albumin gradient (SAAG) score is calculated at first evaluation, as non-malignant causes may co-exist (SAAG <1.1 indicates an exudate and possibly malignancy as the underlying cause). Spontaneous bacterial peritonitis should also be considered in the differential diagnosis of ascites, especially in patients with co-existent hepatic cirrhosis. In this setting, patients are more likely to also present with abdominal pain and, quite often, fever.

Treatment

Treatment is determined by symptoms, ascitic volume, rate of accumulation and chemosensitivity of the underlying cancer. Chemotherapy may be preferred over palliative care in cases of chemosensitive tumours such as ovarian cancer. Hyperthermic intraperitoneal chemotherapy (HIPEC), with or without cytoreduction, has been reported as beneficial in small series but cannot be recommended for routine clinical use.

Palliative care aims to alleviate symptoms and improve QoL. Asymptomatic patients should not be treated proactively. Diuretics are effective in approximately 50% of cases where symptoms are present. If response is inadequate, diuretics combined with paracentesis can achieve symptom relief in more than 90% of cases.

Invasive techniques may be considered in patients with long life expectancy, requiring multiple paracentesis. Intraperitoneal catheters allow serial easy self-drainage, resulting in fewer hospital visits and increased patient autonomy. Complications include risk of infection, tube obstruction and protein loss. Peritoneovenous shunt is another option, preferred when survival is expected to last for months rather than weeks.

Declaration of Interest:

Dr Kefala has reported no potential conflicts of interest.

Dr Papamichael has reported no potential conflicts of interest.

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Respiratory Problems

6.4

M. Rajer[1]

S.H. Ahmedzai[2]

[1]*University Medical Center Ljubljana, Ljubljana, Slovenia*
[2]*Medical School, University of Sheffield, Sheffield; National Institute for Health Research, University of Leeds, Leeds, UK*

Introduction

Supportive and palliative care of respiratory problems in cancer patients need an holistic approach, which considers the underlying malignant disease, comorbidities (such as chronic obstructive pulmonary disease [COPD], other chronic lung diseases and intercurrent infections) as well as the anticancer treatment. Respiratory problems appear with all cancer types, but especially in those affecting the thorax, head and neck.

Dyspnoea

Dyspnoea, or breathlessness, is defined as the subjective experience of breathing discomfort. It arises from physiological, psychological, social and environmental factors, and significantly affects daily activities.

Frequency and Impact

Dyspnoea is a common sensation of everyday life, usually associated with undue exertion. Cancers in which at least 50% of patients report breathlessness include lung, head and neck, genitourinary, breast and lymphoma. Dyspnoea becomes increasingly common and more severe with advancing cancer and near the end of life.

Causes

Solid tumours may cause respiratory problems directly by their presence in the lungs or mediastinum (primary or metastatic disease), or through

pleural or pericardial involvement. Lymphomas and leukaemia can also affect the lungs and airways directly, or through pleural and mediastinal lymphatic involvement. Sarcopaenia occurring naturally in older age may be compounded by cancer cachexia, which affects thoracic and diaphragmatic muscles, contributing to inefficient ventilation. Oncologists should always be aware of non-malignant causes of respiratory symptoms such as anaemia, COPD, cardiac disease, pulmonary thromboembolism and pulmonary hypertension.

Table 1 Causes of Dyspnoea in Cancer Patients.
From: Ahmedzai SH. Breathlessness in advanced disease. Medicine 2020; 48:23-28.

System	Example of pathology	Example of disease
Pulmonary	Airflow obstruction	COPD, asthma, cancer
	Reduced lung compliance	Chemotherapy (bleomycin), immunotherapy, pulmonary (including radiation) fibrosis, emphysema, pulmonary consolidation
	Pleural effusion	Cancer, heart failure
	Chest wall restriction	Mesothelioma, malignant vertebral collapse/compression, neuromuscular disease
	Diaphragmatic restriction	Ascites
	Ventilation-perfusion mismatch	Pulmonary embolism
	Cachexia affecting the respiratory musculature	Cancer, COPD, heart failure
Cardiovascular	Pump failure	Chemotherapy, trastuzumab, acute or chronic heart failure
	Pericardial effusion	Cancer
	Hypovolaemia	Bleeding, too rapid drainage of ascites
Systemic	Anaemia	Chronic disease, cancer
	Biological effects of ageing	Decrease in lung elasticity Decrease in respiratory muscle strength Reduction in forced vital capacity and peak flow rate Increased air trapping Deterioration in gas exchange Reduction in ventilatory response to hypoxia and hypercapnia Increased ventilatory response to exercise Sarcopaenia

Abbreviation: COPD, chronic obstructive pulmonary disease.

There is increasing recognition of dyspnoea arising from several kinds of anticancer treatment including pulmonary toxicity from chemotherapy, targeted therapies and immune checkpoint inhibitors. Although it is relatively uncommon with acute pneumonitis after thoracic radiation, late pulmonary damage and fibrosis can present as dyspnoea many years after treatment completion.

Causes of dyspnoea in cancer patients are summarised in Table 1.

Investigation and Assessment

New-onset dyspnoea should be assessed by clinical history and examination. Simple bedside tests may be useful, including pulse oximetry, blood pressure and electrocardiogram. Key investigations are thoracic imaging (radiograph or computed tomography [CT]), including specific tests to exclude pulmonary thromboembolism, if clinically suspected. Pulmonary function tests usually correlate poorly with dyspnoea levels. Arterial blood gases are rarely justified and may be distressing to a patient with advanced disease near the end of life.

It is useful to ask patients to quantify their dyspnoea verbally (mild, moderate, severe), or numerically on a 0 (none) to 10 (worst) scale. It is important to assess the impact of dyspnoea on the patient's ability to move and carry out daily functions.

Treatment

Managing non-malignant causes

The first step is to treat reversible causes such as airflow obstruction due to asthma or COPD; some patients with these conditions may benefit from a short course of corticosteroids by inhalation or orally. Symptomatic anaemia can be managed by blood transfusion or with erythropoiesis-stimulating agents (ESAs). For further information on anaemia, please refer to Chapter 6.8.1, bearing in mind that in the very advanced stages, transfusion may offer little symptomatic improvement.

Physical methods

Pleural or pericardial effusion should be managed using appropriate

drainage techniques. Repeated episodes or chronic effusions may require surgical intervention, such as long-term tunnelled catheter.

Distressing stridor from acute upper airway obstruction can respond to bronchoscopic placement of an expandable metal stent, or to a single fraction of radiation and a short course of steroids. In some centres, bronchoscopic laser or photodynamic therapy may be offered.

Oxygen

Trial of supplemental oxygen therapy should be reserved for patients with dyspnoea and demonstrated hypoxaemia (i.e. oxygen saturation [SaO_2] <92%) aiming for 92%-96% SaO_2. The target saturation should be 88%-92% in patients with COPD or with hypoventilation, because of the risk of worsening hypercapnic respiratory failure at higher saturation levels.

Non-invasive ventilation (NIV) has a limited place in cancer-related dyspnoea and requires careful selection and assessment.

Non-pharmacological management

There is evidence that increasing cool airflow over the lower part of the face (divisions II and III of the trigeminal nerve) can help to reduce the sensation of dyspnoea. This is easily done with a small handheld fan; patients may also benefit by feeling more in control of exacerbations using this technique. If a fan is not available, opening a window to improve room ventilation can be helpful at low cost.

Studies have shown that teaching patients the principles of breathing control, pacing of activities and using psychological techniques such as cognitive behavioural therapy (CBT) may be helpful for patients in the earlier stages of cancer with dyspnoea who wish to remain more active and lead a social life. Multidisciplinary-, nurse- or physiotherapy-led clinics can be helpful for ambulatory patients.

Pharmacological management

The main classes of medications recommended by the European Society for Medical Oncology (ESMO) guidelines for the management of breathlessness in patients with cancer include:

a. **Bronchodilators.** This class is of value if there is at least partly reversible airflow obstruction (e.g. with asthma or COPD). It will not be helpful for relieving fixed upper airway obstruction, ventilation-perfusion mismatching from major lobar or whole lung collapse or large effusion; used in these situations, the incidental adrenergic tachycardia and anxiety could make patients feel worse.

b. **Opioids.** There is evidence that low doses of opioid can relieve the sensation of dyspnoea as well as the accompanying anxiety in advanced disease. Morphine has been studied most, but other opioids such as hydromorphone or oxycodone could also work. It is not clear if repeated short-acting doses or twice-daily long-acting doses are better: it is recommended to start with the former and move to the latter if the patient tolerates the opioid. The oral route is preferred, but subcutaneous (s.c.) or intravenous (i.v.) injections can be used for more rapid relief. Very short-acting opioids such as buccal or nasal fentanyl are best reserved for acute short episodes. The dose of opioids used for dyspnoea is much lower than for cancer-related pain; most patients will need up to 30-40 mg oral morphine daily or equivalent. For patients already on opioids for pain, the dose can be increased gradually by 20%-30% over the current dose.

   The main limitations of using opioids include constipation, nausea and sedation; and, in patients with severe COPD, obesity-related hypoventilation or sleep apnoea syndrome, there is an increased risk of respiratory depression.

c. **Benzodiazepines.** This class of drugs is helpful in reducing anxiety in acute episodes, or at the end of life, when dyspnoea becomes refractory to other treatments (readers can refer to Chapter 7). Shorter-acting drugs such as oral or sublingual lorazepam are better than diazepam. For s.c. or i.v. use, midazolam is preferred. The combination of an opioid with benzodiazepine is powerful for the relief of severe distress (e.g. in a dying person with major airway obstruction or pericardial tamponade) and this humane benefit should be balanced against the risk of increasing hypoventilation.

d. **Corticosteroids.** Steroids are best reserved for short-term burst use in cases of airflow obstruction (asthma, COPD). They can be helpful

for stridor arising from major upper airway blockage or lymphangitis carcinomatosa.

e. **Balance between pharmacological and non-pharmacological interventions.** In the earlier stages of cancer, and in patients with a longer prognosis, it is recommended to focus on non-pharmacological interventions, such as breathing control, psychological techniques and using a handheld fan for acute episodes. With more advanced disease, the pharmacological interventions will become more prominent, although good psychosocial care and attention to mobility aids can also be used towards the end of life (see Figure 1).

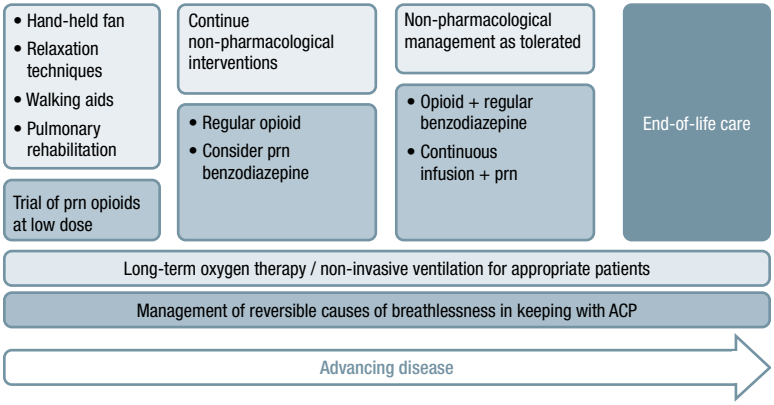

Figure 1 Schematic diagram of therapeutic options for dyspnoea with advancing level of disease in cancer.

From: Keenleyside G, Ahmedzai SH. Breathlessness in advanced disease. Medicine 2008; 36:82-87.
Abbreviations: ACP, advance care plan; prn, as required.

Cough

Frequency and Impact

Cough is a common but often under-recognised symptom. Especially in thoracic malignancies, it may be the most common symptom, equal to pain and dyspnoea. It may be distressing because of the interruption of breathing and sleep, or because it produces pain or vomiting. Persistent cough may significantly impair quality of life and has psychosocial consequences, especially if it is accompanied by dyspnoea.

Causes

There are many causes of cough related to cancer, its treatments and/or comorbid conditions. These causes are shown in Table 2.

Table 2 Common Causes of Cough in Cancer Patients.
Modified from: Bausewein C, Simon ST. Shortness of breath and cough in patients in palliative care. Dtsch Arztebl Int 2013; 34:563-571 and Stover DE, Gulati CM, Geyer AI, Kaner RJ. Pulmonary toxicity. In: DeVita VT, Lawrence TS, Rosenberg SA (Eds). DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, 10th edition. Philadelphia, PA: Lippincott Williams and Wilkins, 2014; 2004-2012.

Non-malignant	Cancer and/or cancer treatment
Acute infection	Respiratory tract obstruction (tumour) Neutropaenic pulmonary infection
Respiratory tract disorders (asthma, COPD)	Causes related to cancer treatment i.e. radiation pneumonitis, or pneumonitis induced by immunotherapy
Irritants (foreign body, cigarette smoke, reflux)	Pleural disease (effusion, mesothelioma)
Cardiovascular (heart failure)	Interstitial disease (lymphangitis, pulmonary metastases, radiation pneumonitis)
Chronic inflammation (cystic fibrosis, bronchiectasias)	
Food aspiration (motor neurone disease, multiple sclerosis)	
Concomitant medication (ACE inhibitors)	

Abbreviations: ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease.

Investigation and Assessment

Troublesome and persistent cough should be investigated by radiography or CT imaging to identify a cause (e.g. infection, pneumonitis from acute anticancer treatments or pulmonary fibrosis as a late effect of earlier thoracic radiation).

Treatment of Cough

The first goal of treatment is to eliminate or alleviate any reversible cause. After managing conditions such as COPD, control of cough depends on the cancer treatment itself. If the cause of the cough cannot be eradicated (e.g. advanced cancer at end of life), then symptomatic treatments aimed at palliation can be used.

Oncological Options

Wherever possible, treatment should be cancer-directed. The fastest acting interventions are external beam radiotherapy, or bronchoscopic laser treatment of intraluminal tumour. Appropriate use of chemotherapy can be considered. It should be noted that intraluminal airway stents placed for dyspnoea may themselves provoke an irritant cough.

Non-pharmacological Treatment Options

Non-pharmacological treatment interventions are often underused but can be effective in treating patient experience. The most effective ones are cough suppression approaches that include education, identifying cough triggers, improvements in laryngeal and vocal hygiene, hydration, breathing exercises and speech pathology training.

Pharmacological Treatment Options

a. Cough suppressants are indicated in dry cough. Simple linctus mixtures, usually containing sugar or honey, can help but should be used with caution in diabetics. Opioids are the most effective cough suppressants, starting with codeine 30-60 mg or pholcodine 10 mL 3-4 times a day; alternatively starting with low-dose morphine (2 mg every 4 hours [q4h]). With a more refractory dry cough, morphine preparations (5 mg single-dose trial, then 5-10 mg q4h or 5-10 mg slow-release morphine twice daily). In patients already receiving opioids, a 20% increase in dose may be helpful. It is very important to consider constipation as a common side effect which needs to, and can be, managed effectively to avoid limiting the use of opioids.

b. Mucolytics, such as acetylcysteine or bromhexine, are agents that thin respiratory tract mucus, making it less thick and sticky and easier to cough up. Inhalations with saline solution can also be given for this purpose. They should not be prescribed in frail patients who cannot cough and expel the mucus, because they can cause accumulation of more mucus and worsening of the patient's dyspnoea. In patients with tracheostomy, good hygiene around the opening and use of humidification and saline nebulisation can be helpful.

Haemoptysis

Haemoptysis is commonly caused by bleeding from a pulmonary tumour invading the adjacent airway and is one of the most distressing symptoms for the patient and the family. It is usually a sign of advanced lung cancer. The estimated prevalence in lung cancer is 25% to 50%. Therapeutic interventions are palliative. The management depends on the volume of blood expectorated.

Low-volume Haemoptysis

Initial medical management consists of stopping any current anticoagulant therapy and starting tranexamic acid 1500 mg orally followed by 1000 mg three times daily. Radiation gives very effective palliation and should be discussed with every patient. Studies have shown that external beam radiotherapy is more effective compared with brachytherapy, which can be considered after external beam radiotherapy failure. Improvement of haemoptysis can be achieved in 80% of patients. Optimal recommended doses of external beam radiotherapy are not defined in this setting. Some authors recommend higher doses in fit patients (e.g. 39 Gy in 13 fractions), while lower doses and fewer fractions should be applied in frail patients (20 Gy in 5 fractions, or 17 Gy in two weekly fractions, or 10 Gy in one fraction). In persistent cases, tranexamic acid could be administered (if not contraindicated) at a dose of 1000 mg i.v. every 6-8 hours.

Massive Haemoptysis

Massive haemoptysis (more than 200 ml of blood) is more likely in patients with centrally located tumours. Severe acute stridor can accompany massive bleeding into the trachea. The main goal of therapeutic interventions is to relieve the symptoms and make the patient as comfortable as possible. If appropriate, patients can be intubated and bronchoscopy performed, although endobronchial stenting is not an option for this indication. If the bleeding source is known, bronchial artery embolisation can be considered.

For the majority of patients with recurrent massive haemoptysis, achieving longer survival is not realistic. It is important to provide psychological

support for the patient and his/her relatives. Place the patient in the most comfortable position (usually lateral, with the bleeding side down, if known). Use dark bedding and containers to hide blood volume, to comfort both patient and family.

Bleeding is usually not painful for the patient, so sedative drugs such as benzodiazepines are used before opioids. The exact dose, route of administration and drug will depend on each case. Midazolam is usually used at a dose of 5 mg i.v. or 5-10 mg s.c. and titrated until complete sedation. For continuous haemoptyses, it is usually best to start an s.c. or i.v. infusion of midazolam.

For information about terminal secretions please refer to Chapter 7.

Declaration of Interest:

Dr Rajer has reported no potential conflicts of interest.

Professor Ahmedzai has reported no potential conflicts of interest.

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Neurological Complications

6.5

Introduction

Neurological complications of any type are prevalent in approximately 50%-70% of patients with cancer and may severely impact their functioning, communication and quality of life.

There is a diverse spectrum of neurological conditions attributed either to malignant disease *per se* or to sequelae from various types of anticancer treatment. Mild to severe cognitive impairment, dementia, encephalopathy, delirium, seizures, stupor and coma are only some of the more common neurological manifestations of advanced cancer.

Malignant tumours can spread to the central nervous system (CNS) and manifest as brain metastases, meningeal carcinomatosis or hydrocephalus, and may be associated with intracranial oedema or spinal cord compression.

Furthermore, various cancer treatments including radiotherapy, CNS surgery, chemotherapy, immunotherapy and molecular targeted therapies can affect neurological function and lead to substantial morbidity and disability.

Due to their impact on cognition and functioning, it is imperative to identify and treat neurological conditions in cancer patients in a timely and efficient manner. In this chapter we summarise the main neurological complications in patients with cancer and provide the principles of early diagnosis and management.

Giannis Mountzios (Ed.)

Delirium

6.5.1

C. Centeno

Palliative Medicine Department, Clinica Universidad de Navarra; ATLANTES Global Palliative Care Observatory, University of Navarra, Pamplona, Spain

Delirium is a neurocognitive syndrome, common in older people and patients with cancer, particularly in those who have advanced disease or are in their last hours or days of life. Cancer and the associated complications predispose patients to delirium. Additionally, many cancer treatments (chemotherapy, immunotherapy, whole brain radiotherapy, etc.) increase the risk of delirium. Delirium is associated with a higher risk of mortality and causes significant physical morbidity. It is often a distressing experience, not only for patients, but also for families and professional caregivers.

Predisposing factors include visual impairment, severity of illness, pre-existing cognitive impairment and dehydration. Frequent contributory precipitants of delirium include medications (predominantly opioids), electrolyte imbalance and infections.

In many patient settings, delirium is often missed, in part due to fluctuation of symptoms and subacute presentation, and to misdiagnosis as another psychiatric disorder. The initial suspicion of delirium can arise from the systematic exploration of the patient's cognition, or also when the family reports recent changes in the patient's behaviour or the patient themself complains of confusion. The reference standard for the diagnosis of delirium is careful clinical assessment of the patient. The DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) specifies a disturbance in attention and awareness as an essential diagnostic feature of delirium.

The management of delirium includes the potential identification and treatment, with investigation according to clinical features and the

expected survival, of possibly reversible precipitating risk factors. This includes polypharmacy, opioid-induced neurotoxicity, dehydration and renal failure, infection, hypercalcaemia and brain metastasis. The provision of support and information by the healthcare team to the patient and their family is an important part of the management. In this sense, it is crucial to use verbal and non-verbal strategies to reassure the patient.

Delirious patients who are distressed by delusions, hallucinations and other perceptual disturbances, have severe agitation or are at risk from harming themselves or others may benefit from the lowest effective dose of antipsychotics. If severe agitation or distress persists, consider the use of a short-acting parenteral benzodiazepine. Refractory agitated delirium in dying patients often requires proportional palliative sedation.

Interprofessional delirium education interventions should be a core component of a unit- or hospital-wide strategy to improve the recognition, assessment and management of delirium by the entire healthcare team.

Declaration of Interest:

Professor Centeno has reported no potential conflicts of interest.

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Seizures

6.5.2

E. Pentsova

Memorial Sloan Kettering Cancer Center, New York, NY, USA

Seizures, either partial or secondary generalised, are commonly encountered in patients with CNS metastases and primary brain tumours (PBTs). Any type of seizures may occur in 10%-50% of patients with CNS metastases: intraparenchymal and/or leptomeningeal, and in 40%-80% of patients with PBT at initial diagnosis. Neuroimaging should always be a part of the work-up for patients with the first onset of seizures, with or without systemic cancers. Patients with CNS metastases tend to have fewer seizures than those with PBTs. Low-grade tumours (oligodendroglioma, dysembryoplastic neuroepithelial tumours, ganglioglioma and astrocytoma) are more common than glioblastoma and are associated with seizures originating from adjacent brain tissue rather than the mass lesions themselves, and are responsible for up to 10% of all epilepsy cases.

While seizures are frequently seen in this category of patients, neither short-term nor long-term prophylaxis are recommended for patients with CNS tumours who have not developed seizures. There is a consensus to start antiepileptic drug (AED) therapy after a first seizure and to avoid enzyme-inducing AEDs, as interaction with chemotherapy agents leads to a reduction of chemotherapy drug concentration and increased toxicity.

It should be noted that metastatic or primary CNS tumours can cause a certain ictal pattern, which transforms into convulsive or non-convulsive status epilepticus (NCSE). NCSE is a highly under-recognised condition, as clinical manifestations of NCSE are nonspecific and often present as a decreased level of alertness. It is important to check for NCSE in any patient with CNS tumours and altered mental status by ordering

an electroencephalogram (EEG) or video/prolonged EEG, as this condition is highly treatable.

Seizures at the end of life, reported in up to 56% of patients with metastatic or PBTs, is another crucial topic. A prior history of seizures increases the risk of seizures at the end of life to more than 50%; up to 12% of patients without any prior seizures develop an onset at the end of life. Aggressive AED management should be considered with either benzodiazepines or subcutaneous levetiracetam at the end of life.

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Encephalopathy

6.5.3

E. Pentsova

Memorial Sloan Kettering Cancer Center, New York, NY, USA

Encephalopathy is common in patients with cancer. Common causes include metabolic dysfunction, structural brain disease and a variety of agents used in cancer treatment including immune checkpoint inhibitors. Patients with acute encephalopathy are often confused, disoriented, delirious, and may be associated with myoclonus, language impairment and insomnia. Here, we focus on a condition known as posterior reversible encephalopathy syndrome (PRES) and encephalopathy related to chimeric antigen receptor (CAR) T-cell therapy.

PRES is a well-described entity of acute changes in mental status, confusion, headache, often seizures and visual abnormalities, and/or cortical blindness. PRES in patients with cancer is classically associated with elevated blood pressure related to either immunosuppressive agents such as tacrolimus, cyclosporine, high-dose steroids or to certain cytotoxic drugs including cisplatin, cytarabine, cyclophosphamide, vincristine, etoposide, gemcitabine or monoclonal antibodies such as bevacizumab. Magnetic resonance imaging (MRI) of the brain shows diffuse hyperintensity on fluid-attenuated inversion recovery (FLAIR) images, predominantly involving parieto-occipital white matter. However, abnormal signalling in the basal ganglia and other parts of the brain have been described. The posterior hemispheres are more susceptible, probably because they have less sympathetic innervation. Treatment includes normalisation of elevated blood pressure if present, discontinuation of drugs related to PRES and best supportive care.

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a well-known side effect of CAR T-cell therapy. Current advances in treatment of haematological malignancies with CAR T-cell therapy

have demonstrated promising results. ICANS was observed in 3%-8% of patients across all the CAR T-cell studies. Its pathophysiology is not completely understood but endothelial activation is characterised by capillary leak and disseminated intravascular coagulation associated with blood-brain barrier dysfunction and passive diffusion of cytokines into the brain. In addition to classical signs of ICANS such as delirium, lethargy, encephalopathy and seizures, expressive aphasia, especially naming difficulty, is the most common feature of early CAR T-cell-related neurotoxicity. It may occur during, or more commonly within 5-7 days following the CAR T-cell infusion or even beyond 5-7 days when cytokine release syndrome resolves. The standard approach to identify neurotoxicity resulting from CAR T-cell therapy at early stages is to perform baseline (prior to infusion) and follow-up neurological examinations, with careful documentation of mental status and language function based on the CAR T-cell therapy-associated toxicity, and manage the condition following CAR T-cell therapy-associated TOXicity (CARTOX) Working Group recommendations. MRI of the brain is usually normal.

Declaration of Interest:

Dr Pentsova has reported no potential conflicts of interest.

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Brain Metastasis

6.5.4

M. Preusser

Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

Brain metastases are a common complication in patients with cancer and are associated with high morbidity and mortality. Incidence is highest in patients with lung cancer, breast cancer and melanoma, and median survival times range from a few weeks to a few years depending on tumour type, extent of disease and clinical patient condition.

Tumour-directed treatment options for patients with brain metastases include neurosurgical resection, radiotherapy (stereotactic radiosurgery or whole brain radiotherapy) and medical treatments. Recent advances in pharmacotherapy of many solid cancers, including documented intracranial activity of several novel drugs, have led to an increased use of targeted therapies and immunotherapies in brain metastasis patients, sometimes before or instead of surgery and radiotherapy. Still, treatment of brain metastasis is not curative, and supportive and palliative measures are regularly needed in the clinical management of affected patients. Particularly, common indications for palliative and supportive measures in brain metastasis patients include brain oedema and seizures.

Brain oedema is ideally diagnosed on T2-weighted FLAIR MRI of the brain. The treatment of choice for brain oedema is dexamethasone, but should only be indicated in patients requiring relief of symptoms. Asymptomatic patients with radiological evidence of brain oedema do not usually require anti-oedema treatment. The dexamethasone dose should be restricted to the lowest level needed for symptom control, to limit steroid-associated adverse effects.

Seizures are found in approximately 20% of patients at diagnosis of brain metastases, most commonly corresponding to focal or focal to bilateral tonic-clonic seizures, according to the latest nomenclature of

the International League Against Epilepsy (ILAE). The main diagnostic procedures in patients with evident or suspected seizures are cranial MRI and EEG. An EEG is particularly important to clarify the differential diagnosis of NCSE in patients with otherwise unexplained worsening of neurological symptoms. Tumour control by effective antineoplastic therapy is an important part of seizure control, where possible. While primary prophylaxis of seizures is not recommended in brain tumour patients, most patients who have experienced epilepsy should be treated with anticonvulsants to prevent further seizure events.

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Leptomeningeal Metastases in Solid Tumours

6.5.5

E. Pentsova

Memorial Sloan Kettering Cancer Center, New York, NY, USA

Leptomeningeal metastasis (LM) is a devastating complication of cancer and is associated with an extremely poor prognosis with a median overall survival (OS) of 3-3.5 months, particularly in solid tumours. LM has been increasingly recognised in patients with solid tumours and otherwise well-controlled systemic disease, such as mutated epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer (NSCLC) controlled with EGFR/ALK inhibitors, breast cancer stable on trastuzumab and melanoma stable on immunotherapy or targeted therapy.

LM is defined by the presence of cancer cells in the cerebrospinal fluid (CSF), whether the cancer cells entered the CSF compartment via choroid plexus or seeded into the CSF from any metastases in contact with CSF. The cancer cells can remain within the meninges, or invade the parenchyma of the brain, spinal cord, or cranial and peripheral nerves (Figure 1). Patients may present with various symptoms: headache, gait instability, seizures, subacute confusion/memory changes, cranial neuropathies, sensory changes, dizziness, back pain or urinary incontinence. Patients with headache would benefit from emergent evaluation with neuroimaging and a lumbar puncture with opening pressure, as they may benefit from ventriculoperitoneal shunt placement and then continue cancer-directed treatment.

LM remains one of the underdiagnosed complications of cancer. LM may be present at the time of brain metastases diagnosis in up to 30% of patients. Establishing the diagnosis of LM based on standard CSF

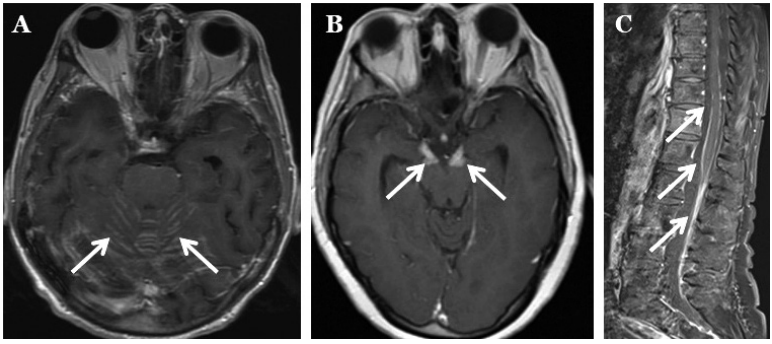

Figure 1 Axial images of post-contrast MRI scans showing leptomeningeal enhancement involving cerebellar folia (A), enhancement of the bilateral oculomotor nerves at the origins from the midbrain (B), and enhancement around spinal cord and the cauda equina (C).

Abbreviation: MRI, magnetic resonance imaging.

cytology analysis or MRI findings is often difficult, particularly at early stages. Brain and spine MRI scans with and without contrast have the advantage of being non-invasive, but their findings may be non-specific and equivocal for LM. CSF cytology examination provides confirmation of LM but has low diagnostic sensitivity of 44%-67% at the first lumbar puncture, often requiring multiple lumbar punctures to establish a diagnosis of LM. New technologies utilising an immunomagnetic circulating tumour cell (CTC) selection method based on a rare cell capture technology (RCCT) and anti-epithelial cell adhesion molecule (EPCAM) antibody conjugated ferroparticles have been used to evaluate CSF CTCs of patients with LM and have demonstrated potential as diagnostic biomarkers. Collection of tumour-derived cell-free DNA (cfDNA) in readily accessible body fluids including CSF, often referred to as 'liquid biopsy', has the potential to make personalised cancer treatment available to a much larger number of patients and allow monitoring of genetic changes in the tumour during therapy. However, to date we have limited knowledge of molecular aberrations in the CNS compartment, especially in the CSF, at the time of LM presentation and during treatment.

Current treatment options for LM are restricted to palliative whole brain radiotherapy, chemotherapy or comfort care only. Previously, patients with LM were excluded from clinical trials. One randomised trial, published more than 20 years ago, tested intrathecal (i.t.) chemotherapy with liposomal cytarabine versus i.t. methotrexate. Results in both arms were disappointing. This lack of efficacy is largely explained by the lack of activity of cytarabine in the major types of cancer that develop LM: breast, NSCLC or melanoma. An ongoing study has shown the efficacy of lapatinib, capecitabine, tucatinib and i.t. herceptin for patients with human epidermal growth factor receptor 2 (*HER2*)-positive breast cancer and high-dose osimertinib and afatinib in EGFR-positive NSCLC. Multiple clinical trials for LM are underway.

Declaration of Interest:

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Spinal Cord Compression

6.5.6

M. Preusser

Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

Spinal cord compression due to metastases is present in up to 10% of cancer patients and is a medical emergency that needs immediate medical attention. Patients with prostate cancer, lung cancer, breast cancer, melanoma, renal cell cancer, lymphoma and myeloma are at highest risk for metastatic spinal cord compression. The prognosis of patients affected by this complication is frequently in the range of a few months and palliative care is often needed. The symptoms of metastatic spinal cord compression may develop sub-acutely over days to weeks or can present acutely. Frequent symptoms include segmental deficits (commonly in the sacral region), hyporeflexia followed by hyperreflexia, extensor plantar responses, loss of sphincter tone and sensory deficits. Pain may also occur. The diagnostic procedure of choice is spinal MRI. The main treatment options include surgery, conventional or stereotactic radiotherapy and supportive measures.

Surgical intervention is indicated for establishing a histological diagnosis: epidural spinal cord compression (especially in the context of new onset or deterioration of symptoms, or radio-resistance) or spinal instability, or if there is a need for immediate decompression. Radiotherapy can be delivered as the sole treatment, or adjuvantly after surgical intervention. Dexamethasone is considered advisable from diagnosis, and, if clinically appropriate, to reduce pain and neurological dysfunction. In addition, bisphosphonates or denosumab should be considered in patients with bone metastases, to reduce the risk of skeletal-related events. The role of antineoplastic pharmacotherapy is not well defined in patients with metastatic spinal cord compression, but may be considered on an individual patient basis, especially when agents with high response rates are available.

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Peripheral Neuropathy

6.5.7

M. Preusser

Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

Peripheral neuropathy is a common and often dose-dependent side effect of antineoplastic therapy. The most common cause is chemotherapy (chemotherapy-induced peripheral neurotoxicity [CIPN]), but novel agents such as immunotherapies may also lead to peripheral iatrogenic neuropathy. Platinum compounds, vinca alkaloids, taxanes and thalidomide have the highest risks for CIPN. However, the risk is dependent on the type of medication, cumulative dose, scheduling and combination with other neurotoxic agents, and the presence of comorbidities such as diabetes, alcohol abuse, renal insufficiency and others. CIPN typically presents as predominantly sensory axonal neuropathy with occasional motor and autonomic involvement.

Symptoms of CIPN usually occur during the first 2 months of treatment, with progression during active antineoplastic treatment, and stabilise soon after treatment completion. Typical symptoms are acral pain, paraesthesia, dysaesthesia, allodynia and hyperalgesia. Sensory loss appears in a 'glove and stocking type' distribution and is associated with numbness in hands and feet, including impaired perception of light touch, vibration sense and proprioception.

Diagnosis is established by clinical neurological examination and neurophysiological methods such as nerve conduction studies. In some cases, somatosensory potentials, electromyography or nerve biopsy may be needed. So far, no effective prevention strategies for CIPN have been identified. Duloxetine is the only agent recommended for treatment of neuropathic pain, based on a clinical trial. Other agents that may be considered include anticonvulsants (pregabalin, gabapentin), tricyclic antidepressants and opioids. The role of vitamin B-complex supplements

has not been established and is not recommended by current guidelines. For patients with sensory nerve damage, leading to impairment in activities of daily living, occupational therapy and assistance measures (e.g. special keyboards, electric toothbrushes, special holders and grips for small household items, etc.) are recommended.

Declaration of Interest:

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Psychiatric Problems in Cancer Patients

6.6

F.E. de Vries[1,2]

M. Li[1,3]

G. Rodin[1,3]

[1]*Department of Supportive Care, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*
[2]*Department of Psychiatry and Center for Quality of Life, Netherlands Cancer Institute, Amsterdam, Netherlands*
[3]*Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, ON, Canada*

This chapter provides a concise overview of the most common psychiatric problems encountered in cancer care and of their management in the cancer setting. These problems may be grouped into three broad categories. These are:

1. Psychiatric symptoms that occur *de novo* during or after cancer diagnosis or treatment, in response to the physical, psychological and practical burden of the disease and the treatment.
2. Psychiatric disorders that predate the onset of cancer, including schizophrenia, mood disorders and personality disorders that may impact treatment.
3. Neuropsychiatric disorders that are a direct result of cancer or cancer treatment.

Prevalence

Clinically significant psychiatric symptoms are present in about one third of cancer patients at any point in the disease trajectory. The most

common psychiatric disorders are depression in 15% to 20% of cancer patients and adjustment and anxiety disorders, each in about 10%. Anxiety disorders tend to be most common at the time of diagnosis, when patients are waiting for or receiving test results, and when there are perceived changes in clinical status. Symptoms of depression and demoralisation more often occur with disease progression and increasing proximity to death. In long-term cancer survivors, clinically significant distress may persist even a decade after the time of onset and active treatment.

Assessment

Because psychological distress is often undetected in cancer clinics, systematic screening for distress has been recommended as a standard of care. Screening and assessment questionnaires that have been validated in cancer patients include the Patient Health Questionnaire-9 (PHQ-9) to assess depressive symptoms, the Generalized Anxiety Disorder-7 (GAD-7) for anxiety, the Hospital Anxiety and Depression Scale (HADS) that assesses both anxiety and depression, and the National Comprehensive Cancer Network (NCCN) Distress Thermometer, which rates nonspecific distress about multiple cancer-related issues. The Edmonton Symptom Assessment Scale (ESAS), which has single items on depression and anxiety, has also been widely used. These questionnaires are valuable to detect and quantify distress, although a clinical interview is required to make a formal diagnosis of a psychiatric disorder. A positive screen should prompt a clinic-based evaluation of the psychological state and social circumstances of the patient, recent life events and perceived changes in their disease status, and the presence of pain and other contributing physical symptoms. Suicidal ideation and intention should also be specifically assessed. Referral for psychiatric assessment is indicated for symptoms that are moderate to severe, prolonged or complex, associated with suicidal intention, or when there is evidence of a major psychiatric disorder that is not well controlled or that may interfere with compliance with cancer treatment. The assessment of distress in family members may also be important, in view of the burden of caregiving that is often substantial.

Management of Specific Psychiatric Disorders

Growing evidence supports the value of collaborative models of care in which clinic-based staff or case managers provide low-intensity evidence-based interventions, monitor symptom severity and collaborate with mental health consultants and/or with community-based mental health teams. Such collaborative care has been considered the optimal model of care for cancer-related psychiatric symptoms. Low-intensity interventions include guided self-management using e-health, problem solving or group-based support; more intensive interventions include psychotherapy and/or pharmacotherapy for more severe or prolonged symptoms (Table 1). Non-pathological stress reactions such as transient worry about the future, sadness or irritability, difficulty concentrating and difficulty sleeping may benefit from low-intensity clinic-based interventions. These include normalisation of distress and reassurance, supportive and empathic communication, acknowledgment and validation of distress, mobilisation of social support and reinforcement of healthy coping behaviours. The last may include physical activity and exercise, social or faith-based support, journalling and relaxation techniques. More severe, persistent or complex psychological or psychiatric disturbances may require more specific or specialised interventions.

Stress- and Trauma-related Disorders

The cancer trajectory typically includes multiple stressful events that may trigger a stress- or trauma-related disorder. Traumatic stress symptoms include the re-experiencing of traumatic events related to cancer diagnosis and its treatment, behavioural or emotional avoidance, dissociation or numbing of emotions, and autonomic hyperarousal, with anxiety, impaired concentration and insomnia. More severe symptoms of traumatic stress that occur within 1 month of the traumatic event may meet criteria for the diagnosis of an acute stress disorder (ASD). Symptoms that persist beyond this time point may meet criteria for post-traumatic stress disorder (PTSD). ASD has been found to occur in up to one third of patients following diagnosis of a life-threatening cancer, and a lifetime diagnosis of PTSD has been made in about 15% of all cancer patients. The most common interventions for ASD and PTSD are trauma-based

Table I Common First-line Psychotherapies and Pharmacotherapy in Cancer.

Psychotherapy	
Modality	**Examples**
Relaxation	• Progressive muscle relaxation, visualisation, box breathing • Music and art therapy
Group peer self-help programmes	• General or disease-specific cancer support groups • Structured exercise programmes
Mindfulness	• Mindfulness-based stress reduction (MBSR) • Mindfulness-based cognitive therapy (MBCT) • Acceptance and commitment therapy (ACT)
Cognitive behavioural	• Cognitive behavioural therapy (CBT) • Behavioural activation therapy (BAT) • Problem solving therapy (PST) • Graded phobia exposure
Psychodynamic	• Interpersonal therapy (IPT) • Supportive-expressive therapy • Core conflictual relationship theme (CCRT)
Existential	• Dignity therapy • Meaning-centred psychotherapy (MCP) • Managing cancer and living meaningfully (CALM) psychotherapy
Pharmacotherapy	
Drug	**Clinical Pearls**
SSRI • Citalopram • Escitalopram • Sertraline	• Least CYP450 interactions of all SSRIs • Escitalopram may have more rapid onset • Sertraline may help with hot flushes • All SSRIs are effective at low dose for pseudobulbar affect
Mixed action • Venlafaxine (SNRI) • Duloxetine (SNRI) • Bupropion (NDRI) • Mirtazapine (NaSSA) • Vortioxetine (SMS) • Amitriptyline (TCA) • Nortriptyline (TCA)	• Consider for prominent hot flushes • Indication for neuropathic and chronic pain • Benefits for fatigue, sexual dysfunction • Benefits for insomnia, anorexia, diarrhoea • Pro-cognitive effects • Use TCAs only for severe or refractory depression; may be beneficial for pain and insomnia; nortriptyline is less anticholinergic
Stimulant • Methylphenidate	Rapidly acting to improve energy, particularly in palliative care but limited efficacy for depression
Mood stabilisers • Lithium • Carbamazepine • Valproic acid	• May be used in combination with antidepressants for bipolar depression • Anticonvulsants used in aggression or behavioural disinhibition in brain injury

Table 1 Common First-line Psychotherapies and Pharmacotherapy in Cancer. (Continued)

Pharmacotherapy	
Drug	**Clinical Pearls**
Antipsychotics • Quetiapine • Olanzapine • Haldol • Clozapine	• Haldol, quetiapine, olanzapine used for delirium • Quetiapine, olanzapine help with insomnia, anorexia, anxiety and depression augmentation • Olanzapine or haldol for nausea • Clozapine is not a first-line antipsychotic in cancer, but it is safe to continue with chemotherapy in patients who require it for treatment-resistant schizophrenia with monitoring for agranulocytosis
Benzodiazepines • Diazepam • Lorazepam • Clonazepam	• Long-acting for alcohol withdrawal • Short-acting for panic or treatment-related claustrophobia • Medium-acting for temporary, constant anxiety
Hypnotics • Zopiclone/Zolpidem • Trazodone	• Zolpidem: less hangover and metallic taste than zopiclone • Trazodone: non-habit forming; helps anxiety and depression at higher doses

Abbreviations: NaSSA, noradrenergic and specific serotonergic antidepressant; NDRI, norepinephrine-dopamine reuptake inhibitor; SMS, serotonin modulator and stimulator; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

cognitive behaviour therapy and supportive-expressive therapy, although selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotic medication can also ameliorate symptoms of these disorders.

Adjustment disorder refers to a state of marked distress that occurs in response to a stressor, associated with significant impairment in functioning, but not with any other psychiatric disorder. Adjustment disorders are common at the time of initial diagnosis and treatment, during transitions in treatment and upon disease progression. Interventions to relieve these symptoms include psychological support and the provision of information, reinforcement of adaptive coping behaviours, social support and the alleviation of specific symptoms such as insomnia. There is very limited evidence, however, for the benefit of psychotropic medication in the treatment of adjustment disorders.

Anxiety and Depression

Anxiety disorders may present with a combination of physical symptoms, worry and fearful avoidance behaviour. The most common ones

in cancer patients are generalised anxiety, panic attacks and situational phobias, particularly fear of needles and blood, and claustrophobia. Symptoms of anxiety tend to peak at the time of diagnosis, follow-up appointments, recurrence or other changes in clinical status. Fear of cancer recurrence and fear of death and dying are also common but do not fit well into any of the current diagnostic categories of anxiety.

Depressive symptoms include lowered mood, loss of interest or pleasure, decreased or increased appetite and weight, insomnia or hypersomnia, psychomotor agitation or slowing, fatigue, thoughts of guilt and worthlessness, reduced ability to concentrate or make decisions, and frequent thoughts of death or suicide. These include cognitive-affective and somatic symptoms and may be confounded by the symptoms of cancer. The differential diagnosis of major depression includes adjustment disorder, medication- or substance-induced depression, an underlying medical condition, bipolar disorder and hypoactive delirium.

Oncologists should enquire about cancer-related symptoms and psychosocial factors that may be contributing to the mood disturbance. In some cases, supportive and empathic communication in the clinic may be the only intervention that is required. A range of effective psychotherapies are available to treat moderate or persistent anxiety and depression in cancer patients (Table 1). Patients with early-stage cancer and with traumatic stress symptoms may benefit from mindfulness or cognitive behavioural therapies, while supportive-expressive and meaning-based therapies may be more suitable after the acute phase of diagnosis and treatment and with advanced disease.

Severe mood symptoms justify a medication trial, and moderately severe symptoms that persist despite psychotherapeutic interventions may also be treated with antidepressant medication. Antidepressant medications of different classes are equally effective to treat depression and anxiety, although the SSRIs are generally considered the first-line treatment (Table 1). The treatment response to an antidepressant or antianxiety medication may take up to 4 to 6 weeks, so this period of time should generally be allowed before switching to a different drug when the response has been inadequate. When remission is achieved, the medication should

be continued for at least 6 months, after which it may be gradually tapered. When there is no response to several trials of first-line or second-line treatments, more complex steps in treatment algorithms can be considered. Electroconvulsive therapy (ECT) can be used when depression is severe and life-threatening or resistant to pharmacological treatment. There is also emerging evidence that ketamine is effective for the treatment of depression, and it may be particularly helpful in the context of a short life expectancy because of its immediate effect.

Demoralisation

Demoralisation is a psychological state characterised by feelings of hopelessness, loss of control, feeling trapped and isolated, losing the sense of meaning and purpose in life, and feeling a sense of failure and regret. These symptoms, also referred to as existential distress, can be triggered by changes in social and family roles and relationships, and loss of meaningful activities and goals. Demoralisation occurs in about 20% of cancer patients overall, but is even more common with advanced disease, and can impair compliance to treatment and the will to live. Evidence-based psychotherapeutic interventions shown to alleviate existential distress in patients with advanced cancer are Meaning-Centred Therapy, Dignity Therapy and Managing Cancer and Living Meaningfully (CALM) psychotherapy.

Pre-existing Major Mental Illness

Major mental disorders may complicate cancer treatment in several ways. Those affected may present late in the course of the disease for a variety of reasons and have more medical comorbidity because of lifestyle and medication effects. Changes in psychotropic medications that are made to avoid interactions with anticancer medications may destabilise the psychiatric condition and diminish the capacity for decision-making for treatment. Collaboration between mental healthcare specialists and oncology teams is essential in managing such patients.

Schizophrenia is a complex and severe mental disorder characterised by psychotic episodes with delusions, hallucinations or disorganised behaviour, or with negative symptoms, such as apathy, poverty of thought and

loss of social interest between episodes. Psychotic episodes can be triggered by the stress of the disease or treatment or by non-compliance with antipsychotic medication. Bipolar disorder is characterised by alternating episodes of depression and mania, which may include psychotic features. Mania is associated with elevated or irritable mood, decreased sleep, increased energy and activity and impaired insight and judgment. Personality disorders may be less easily recognised, but often complicate communication and relationships with the treatment team. Particular attention is needed in such cases to the establishment and maintenance of therapeutic relationships, and to sensitive communication with the patient and amongst team members, to ensure a consistent treatment approach.

Neuropsychiatric Disorders

Cancer and its treatment can cause neuropsychiatric disturbances that range from personality and behavioural changes to delirium, which is the most frequent neuropsychiatric disorder in hospitalised cancer patients and in those with advanced disease. Delirium is characterised by fluctuating awareness and cognition and is associated with prolonged hospital stays and increased mortality. Hyperactive delirium is marked by agitation, hallucinations and delusions, whereas hypoactive delirium is characterised by drowsiness, confusion and psychomotor slowing. The most common predisposing factors to delirium are older age, impaired hearing and vision, and pre-existing cognitive or neurological disturbances. The main treatment is to correct underlying causes such as medications (e.g. benzodiazepines, anticholinergic drugs, steroids, opioids, polypharmacy), infection, metabolic disturbances or pain. Non-pharmacological approaches that may be of value to minimise or prevent delirium include strategies to improve orientation, circadian rhythms and mobility. Hyperactive delirium with agitation may require treatment with antipsychotic medication (see Table 1).

Conclusion

Psychiatric disorders are common in cancer patients, and screening for these conditions should be routine in cancer clinics. More severe, complex or persistent symptoms may trigger referral to specialised

psychiatric services. The first line of intervention should include empathic communication, psychoeducation, ensuring adequate social and family support and relief for pain and other physical symptoms. Psychotropic medication may be helpful, but individual and family-based psychological interventions are most often the primary treatment modality. A combined and integrated approach to the physical and psychological well-being of cancer patients and their families is needed to prevent and treat psychiatric disorders and to ensure holistic and patient-centred care.

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Dr de Vries has reported no potential conflicts of interest.

Dr Li has reported no potential conflicts of interest.

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Cancer Pain

6.7

M. Fallon[1]

R. Giusti[2]

[1]*Edinburgh Cancer Research Centre, Institute of Cancer Genetics, University of Edinburgh, Edinburgh, UK*

[2]*Medical Oncology Unit, Sant'Andrea Hospital of Rome, Rome, Italy*

Prevalence and Aetiology of Cancer Pain

Pain is common in cancer patients, particularly in the advanced stages of disease, when its prevalence is estimated to be more than 70%, contributing to poor physical and emotional well-being. The most comprehensive systematic review indicates pain prevalence ranging from 33% in patients after curative treatment, to 59% in patients on anticancer treatment, and to 64% in patients with metastatic, advanced or terminal disease.

Although effective pain relief can be achieved in up to 90% of patients with cancer, numerous studies have shown that pain remains inadequately controlled in many patients. A lack of effective pain control can adversely affect treatment outcomes and quality of life.

In cancer patients, pain may be caused by the tumour itself and/or anticancer treatment (e.g. mucositis, chemotherapy-induced peripheral neurotoxicity [CIPN]), including diagnostic or therapeutic procedures. Cancer patients may also experience pain from comorbidity-related disorders that are unrelated to the disease or its treatment. Cancer survivors often have chronic treatment-related pain; ~30% will have CIPN still present 6 months or more after completing chemotherapy.

Assessment and Classification of Cancer Pain

Initial and ongoing assessment of pain should be an integral part of cancer care and indicate when additional comprehensive assessment

is needed. The regular self-reporting of pain intensity with the help of validated assessment tools is the first step towards effective and individualised treatment. One of the 0-10 standardised scales such as the Numerical Rating Scale (NRS), where 0 is 'no pain' and 10 is 'the worst imaginable pain', can be used. Alternatively, we can also use validated scales such as the Edmonton Symptom Assessment System (ESAS), which addresses nine common symptoms of malignant disease including pain. This tool is designed to assist in the assessment of pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being and shortness of breath. Moreover, understanding the patient's experience of cancer pain treatment is important. These aspects should be better evaluated through patient-reported outcomes (PROs). PRO data are collected using questionnaires that patients complete during clinical trials as well as in regular practice. These questionnaires are designed to capture important information about disease- or treatment-related symptoms (see Chapter 2 for further information). It is important in any setting that all clinicians use the same language, which should be clear and consistent to give patients the opportunity of understanding it and answering as accurately as possible. The intensity of pain and the treatment outcomes should be assessed regularly and consistently, using a 0-10 scale and a specific question: "What was your worst pain in the last 24 hours?". The worst pain question correlates best with the impact of pain on function. Observation of pain-related behaviour and discomfort is indicated in patients with cognitive impairment, to assess the presence of pain; it is important to assess all components of suffering, such as psychosocial distress. Patients should be asked about mood, anxiety and general quality of life.

Assessment of the pain descriptors improves the choice of balanced analgesia, often leading to reduced opioid therapy, with the use of adjuvant analgesics in neuropathic pain and radiotherapy in bone pain.

Pain can be:

(i) Nociceptive: caused by ongoing tissue damage, either somatic (such as bone pain) or visceral (such as gut or hepatic pain);

(ii) Neuropathic: caused by damage or dysfunction in the nervous system, such as in brachial or lumbosacral plexopathy or in spinal cord compression by tumour;

(iii) Nociceptive and neuropathic: most patients with advanced cancer have at least two types of cancer-related pain, resulting from a variety of pathophysiologies.

Management of Cancer Pain

Analgesics

Paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), morphine and other opioids are regarded as mainstays of cancer pain treatment. Paracetamol and NSAIDs are universally accepted as part of cancer pain treatment at all stages of the World Health Organization (WHO) analgesic ladder. Some authors propose the abolition of the second step of the WHO analgesic ladder, in favour of the early use of low doses of strong opioids. This is not in the current WHO guideline and the evidence base is currently weak. Several relevant systematic reviews are available regarding the efficacy of paracetamol and NSAIDs for cancer pain management, either when used alone or in combination with opioids. Analgesic treatment should start with drugs indicated by the WHO analgesic ladder, appropriate for the severity of pain. There is no significant evidence to support or refute the use of paracetamol alone or in combination with opioids for mild to moderate pain, and this is the same for NSAIDs.

Mild analgesics (paracetamol, NSAIDs) should not be given alone for initiation of management of moderate or severe pain. Patients may be started on a combination of paracetamol and/or NSAIDs with an opioid, such as oral morphine, if indicated by pain severity as measured on a validated numerical or visual analogue pain rating scale. Alternatively, low doses of a step III opioid could be considered.

Data do not show important differences between morphine, oxycodone and hydromorphone administered orally. These drugs can represent a first-choice opioid for moderate to severe cancer pain (step III).

Transdermal fentanyl and buprenorphine are alternatives to oral opioids. Both drugs can be the preferred step III opioids for some patients. For patients who cannot swallow, they represent an effective and non-invasive route of administration. Preferred opioids for patients with moderate to severe dysfunction or on dialysis are buprenorphine or fentanyl, as indicated in the European Society for Medical Oncology (ESMO) guidelines.

The subcutaneous route is simple and effective for the administration of morphine and should be the primary alternative route for patients who cannot receive oral or transdermal opioids; intravenous infusion should be considered when subcutaneous infusion is contraindicated; intravenous administration can be used for titration of opioids when rapid pain control is required (further detailed information is available in the 2018 ESMO Clinical Practice Guidelines on Management of Cancer Pain in Adult Patients). When switching from oral administration of morphine to subcutaneous or intravenous administration, the relative analgesic potency is the same for both routes (between 3:1 and 2:1). Although rectal opioids are effective, appropriate formulations are often not readily available and are not acceptable to many patients, so this route of administration should be used only when other routes are not possible or available.

Co-analgesic or Adjuvant Drugs

Adjuvant analgesics (sometimes called co-analgesics) are drugs which have a primary indication other than pain relief, such as antidepressants and anticonvulsants, but also have an analgesic action in some pain states. Adjuvant drugs, such as those used in bowel obstruction, (e.g. octreotide), are distinct from adjuvant analgesics, the latter having particular neurobiological mechanisms in both central and peripheral pain networks. There is insufficient evidence to demonstrate a specific analgesic drug for a particular type of neuropathic pain. Choice is usually based on a detailed patient assessment, looking at all symptoms and the likely tolerability of each potential adjuvant analgesic (Table 1).

Table 1 *Adjuvant Analgesics used for Neuropathic Pain.*

Class	Examples
Antidepressants	Tricyclics (e.g. imipramine); serotonin-norepinephrine reuptake inhibitors (SNRIs, e.g. duloxetine)
Anticonvulsants	Gabapentin, pregabalin, topiramate, carbamazepine, phenytoin, valproate, oxcarbazepine, lamotrigine, levetiracetam
Topical agents	Capsaicin, lidocaine patch, EMLA® cream
Oral sodium channel blockers	Mexiletine, tocainide, flecainide
Alpha-2 adrenergic agonists	Clonidine, tizanidine
N-methyl-D-aspartate receptor agonists	Dextromethorphan, ketamine
GABA agonists	Baclofen
Miscellaneous	Calcitonin

Complicated Pain Syndromes

Acute pain syndromes: most acute cancer pain syndromes are related to a diagnostic test or treatment. However, some are disease-related, such as pain due to acute haemorrhage into a tumour, bone pain from a pathological fracture, and visceral pain from acute obstruction or perforation of a hollow structure.

1. Acute pain syndromes that are directly related to the tumour may necessitate urgent treatment of the underlying lesion, in addition to aggressive pain control.

2. Acute pain can be associated with all types of antineoplastic therapy, including chemotherapy, hormonal therapy, immunotherapy and radiotherapy (oral mucositis, CIPN, other chemotherapy-related acute pain syndromes such as arthralgia or myalgia, hand-foot syndrome or palmar-plantar erythrodysaesthesia, radiotherapy-induced bone pain, radiation plexopathy, enteritis and proctitis).

Chronic pain syndromes: approximately three quarters of cancer patients who have chronic pain have nociceptive (somatic or visceral) or neuropathic syndromes, as a direct effect of the neoplasm.

Other causes of chronic pain in cancer patients are antineoplastic treatments and disorders that are unrelated to the disease or its treatment. A significant barrier to better understanding chronic cancer pain

syndromes, their prevalence and their consequences, is the lack of consistent diagnostic criteria for specific syndromes.

Very useful and detailed algorithms for the assessment and treatment of cancer-related neuropathic pain, treatment of pain due to bone metastases and invasive management of refractory pain are included in the 2018 ESMO Clinical Practice Guidelines on Management of Cancer Pain in Adult Patients.

Interventional Analgesia for Pain Control

Approximately 10% of cancer patients have pain that is difficult to manage with oral or systemic medications combined with non-pharmacological approaches.

Patients who are refractory to all combined conventional strategies and/or who have unacceptable persistent side effects should be considered for an interventional analgesic technique.

Non-pharmacological Pain Interventions

Based on recent literature, it is not possible to draw conclusions about the effects and safety of non-pharmacological interventions with respect to pain reduction among patients with advanced cancer. That said, there is an evolving literature on acupuncture and transcutaneous electrical nerve stimulation (TENS), which shows promise.

An understanding of the central neurobiological mechanisms of pain leads to the *de facto* conclusion that anything which facilitates relaxation, good sleep, anxiety and mood management will have a positive impact on attenuating pain transmission in the central and descending spinal cord pain networks.

Psychological and Spiritual Care

We are integrated beings with very sophisticated higher functions. Increasingly, scientific research has elucidated and improved mechanistic understanding of the term ‘total pain’. Our levels of pain will be adversely affected by anxiety, depression, distress, sleeplessness. Hope remains the fundamental mechanism of coping. This is not hope for cure,

rather it is hope for what is important to the individual, and often relates to family. Spiritual care may improve spiritual well-being and quality of life, and can impact on depression, anxiety and hopelessness for cancer patients. More rigorously designed research is needed to demonstrate this clinically and catch up with the rapidly evolving basic science understanding. In the interim, we know that attention to the whole person is an integral part of pain assessment and management.

Declaration of Interest:

Dr Fallon has reported no potential conflicts of interest.

Dr Giusti has reported no potential conflicts of interest.

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Haematological Complications

6.8

Introduction: Haematological Complications in Cancer Patients

Haematological complications are a major source of morbidity and mortality in patients with cancer. Solid tumours can provoke disruption of normal function of the cellular and non-cellular components of blood, including polycythaemia or anaemia, leucocytosis or leucopaenia, thrombocytosis or thrombocytopaenia, thrombosis or haemorrhage, and other abnormalities. Most anticancer therapeutic modalities, including – but not limited to – cytotoxic chemotherapy, targeted agents, immunotherapy, surgery, irradiation and radioactive treatment, can themselves trigger or exacerbate the aforementioned haematological complications. In daily practice the clinician often faces the challenges of having to treat these complications and to adjust anticancer treatment accordingly, and this process requires high skills in recognising and treating haematological conditions in a timely manner and without compromising therapeutic efficacy. In this chapter we summarise the main haematological complications encountered in patients with solid tumours and the basic principles of their management.

Giannis Mountzios (Ed.)

Anaemia

6.8.1

M. Aapro

Genolier Cancer Centre, Clinique de Genolier, Genolier, Switzerland

Background and Evaluation

The European Cancer Anaemia Survey (ECAS), which involved around 15 000 patients diagnosed with solid or haematological tumours, showed an anaemia (haemoglobin [Hb] <12 g/dL) prevalence of 39% of patients at diagnosis, and this percentage increased with longer follow-up. The major aims of anaemia management are the reduction or resolution of anaemia symptoms, particularly fatigue, and an improved quality of life (QoL) with the minimum invasive treatment that corrects the underlying causes and proves to be safe.

Anaemia is not always related to the cancer or its treatment; chronic bleeding, other inflammatory conditions and malnutrition have to be ruled out. Impaired erythropoietic activity and disturbed iron homeostasis can be consequences of an increased release of inflammatory cytokines, due to the underlying cancer and/or toxicity of cancer therapy. Furthermore, vitamin B12 and folate deficiency are relatively rare causes of anaemia in cancer patients but should absolutely be excluded in potentially malnourished patients.

Management

Therapeutic options for the treatment of (chemotherapy-induced) anaemia include erythropoiesis-stimulating agents (ESAs), iron preparations for intravenous (i.v.) or oral administration (p.o.), red blood cell (RBC) transfusions and combinations of these treatments. One should consider the presence and severity of symptoms, the rapidity of Hb fall and the duration of chemotherapy, if any, to adapt the treatment of patients and

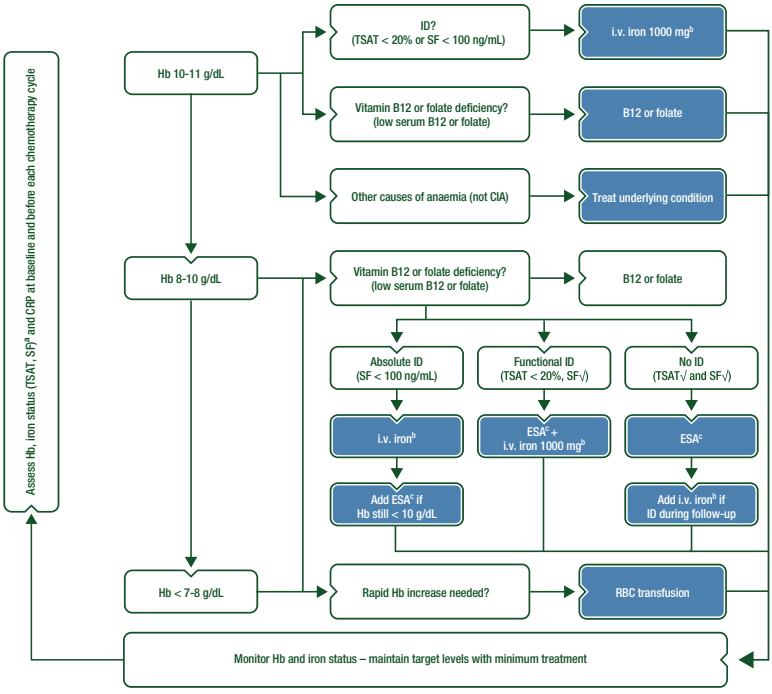

Figure 1 Management of chemotherapy-induced anaemia in patients with solid or haematological malignancies.

From: Aapro M, Beguin Y, Bokemeyer C, et al; ESMO Guidelines Committee. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2018; 29(Suppl 4): iv96-iv110.

Abbreviations: √, normal; CIA, chemotherapy-induced anaemia; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; ID, iron deficiency; i.v., intravenous; RBC, red blood cell; SF, serum ferritin; TSAT, transferrin saturation.

[a] Other parameters for impaired iron status: % hypochromic cells (%HYPO) > 5% and Hb content of reticulocytes (CHr) < 28 pg.

[b] i.v. iron given as a single dose of 1000 mg iron or an equivalent total dose in several infusions as feasible with available i.v. iron formulations. Oral iron to be considered only for patients with ferritin < 30 ng/mL and non-inflammatory conditions (CRP < 5 mg/L).

[c] ESA dosing should follow approved labels (i.e. ~450 IU/week/kg body weight for epoetins alpha, beta and zeta; 6.75 µg/kg body weight every 3 weeks or 2.25 µg/kg body weight weekly for darbepoetin alpha; 20 000 IU once weekly for epoetin theta, which may be doubled after 4 weeks upon insufficient response). ESA dose escalations or a change to another ESA in patients who do not respond within 4–8 weeks are not recommended; ESA should be stopped in this case.

their anaemia. Iron deficiency must be ruled out (by measuring ferritin, which in cancer patients should be >100 µg/L [otherwise it is considered an absolute iron deficiency in cancer patients and must be treated as such] and transferrin saturation [>20% is normal and iron supplementation should not be considered]). Iron deficiency in patients with active cancer is best managed with i.v. iron: European Society for Medical Oncology (ESMO) guidelines suggest a single 1000 mg dose if possible (follow label recommendations); avoid iron dextran. In patients under chemotherapy and Hb <10 g/dL, ESAs can be used if the chemotherapy is expected to continue. Transfusions are reserved for emergencies, and only one packed RBC unit should be administered at a time.

ESAs and transfusions are both accompanied by a modest increase in the risk of thrombosis. Iron should not be infused on the same day as anthracyclines and modern preparations carry a negligible risk of allergic reactions (check the label). None of these treatments leads to a proven risk of cancer development, as long as they are used within their label or guideline.

Declaration of Interest:

Dr Aapro has been involved in studies on anaemia by Amgen, Roche and Vifor and consulted for erythropoietin and iron producers.

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Febrile Neutropaenia

6.8.2

M. Aapro

Genolier Cancer Centre, Clinique de Genolier, Genolier, Switzerland

Definition of Febrile Neutropaenia

Febrile neutropaenia (FN) is defined by ESMO as an oral temperature >38.3°C or two consecutive readings of >38.0°C for 2 h and an absolute neutrophil count $<0.5 \times 10^9$/L, or expected to fall below 0.5×10^9/L.

Incidence, Morbidity, Mortality and Microorganisms

FN remains one of the most frequent and serious complications of chemotherapy. Many standard-dose chemotherapy regimens are associated with 6-8 days of neutropaenia, and FN is observed in approximately 8 cases per 1000 patients receiving cancer chemotherapy. FN is responsible for considerable morbidity, as 20%-30% of patients present complications that require in-hospital management with overall in-hospital mortality in the range of 10%. The mean cost per hospitalisation in Western countries is in the range of 13 500€.

Several factors increase the risk of FN and its complications: among them, age (probably reflecting comorbidity), poor performance status and/or cardiovascular disease.

Positive microbiological detection rates by standard blood cultures vary, depending on whether or not patients have received prophylactic antibiotics. It is crucial to understand that different centres experience different patterns of frequency of causative pathogens, and antimicrobial policies have to be adapted to the epidemiology of the centre.

Chemoprophylaxis

Antimicrobial use should be limited to patients at extremely high risk for FN in some specific protocols.

Indications for Primary Prophylaxis of FN with G-CSF

Most guidelines recommend that granulocyte-colony stimulating factor (G-CSF) be administered prophylactically if the risk of FN is greater than 20% for all planned cycles of treatment. For patients with an intermediate risk (10%-20%), it is important to consider the patient's age and, in particular, coexisting morbidities; additionally, COVID-19-era recommendations suggest to err on the side of liberal use of preventative G-CSF.

A decision algorithm adapted from the European Organisation for Research and Treatment of Cancer (EORTC) guidelines (see Further Reading) about primary prophylactic G-CSF use is presented in the ESMO guidelines (see Further Reading).

Dose Schedule, Route of Application of G-CSF and Pegfilgrastim

Use 5 μg/kg/day of G-CSF subcutaneously (s.c.) 24–72 h after the last day of chemotherapy until sufficient/stable post-nadir absolute neutrophil count (ANC) recovery (achieving a target ANC of $>10\times10^9$/L is not necessary). Pegfilgrastim or lipegfilgrastim are long-acting agents given once. European Medicines Agency/Food and Drug Administration (EMA/FDA)-approved biosimilars can obviously be considered.

Management of FN: Patient Education and Local Policies

Success in FN management requires prompt recognition of, and reaction to, potential infection. Vital to this is educating outpatients to monitor symptoms, including body temperature, and clear written instructions on when and how to contact the appropriate service in the event of concerns. **The first administration of therapy should be given in the hospital within one hour from the admission of a patient with FN**.

Delay in antibiotic administration has been associated with significant prolongation of hospital stay and increased mortality. As shown in Table 1, a scoring index can help decide to hospitalise or not a patient with FN.

Table 1 Multinational Association of Supportive Care in Cancer (MASCC) Febrile Neutropaenia Risk Index.

Characteristic	Score
Burden of illness: no or mild symptoms	5
Burden of illness: moderate symptoms	3
Burden of illness: severe symptoms	0
No hypotension (systolic BP >90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumour/lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient status (at onset of fever)	3
Age <60 years	2

Patients with scores ≥21 are at low risk of complications.
Points attributed to the variable 'burden of illness' are not cumulative. The maximum theoretical score is therefore 26.
Abbreviation: BP, blood pressure.

Declaration of Interest:

Dr Aapro has been involved in studies on G-CSF usage by Amgen, Roche and Sandoz and consulted for various biosimilar G-CSF producers.

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Thrombocytopaenia

6.8.3

G. Mountzios

4th Oncology Department and Clinical Trials Unit, Henry Dunant Hospital Center, ONCOLIFE Institute Founder, Athens, Greece

Incidence

Thrombocytopaenia occurs in approximately 10% of patients with cancer, and can be potentially life-threatening, mainly due to the rare possibility of a major bleeding event. Thrombocytopaenia is a disorder characterised by a reduction in platelet number to <150 000 cells/μL of blood. In cancer patients, thrombocytopaenia may have multiple causes, such as in chemotherapy-associated thrombocytopaenia, heparin-associated thrombocytopaenia, direct bone marrow infiltration by cancer cells, as well as consumptive coagulopathies, immune-mediated mechanisms, especially in haematological malignancies, and infection. In patients with solid tumours treated with chemotherapy, bleeding due to thrombocytopaenia is seen in 9%-15% of cases, especially when platelet counts fall below 10 000/μL; severe thrombocytopaenia is also associated with poor clinical outcomes and significantly increased morbidity and resource utilisation.

Grades

According to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, thrombocytopaenia is classified with the following system:

- Grade 1: Platelets 75 000-99 000/μL
- Grade 2: Platelets 50 000-<75 000/μL
- Grade 3: Platelets 25 000-<50 000/μL
- Grade 4: Platelets <25 000/μL

Clinical Features

Mild to moderate thrombocytopaenia is generally asymptomatic, but occasionally patients may report 'easy' bruising to body surfaces after exertion of mechanical pressure. In severe thrombocytopaenia, patients may report mild to moderate bleeding events such as haematuria, epistaxis, haemoptysis, haematemesis, melaena and menorrhagia. On clinical examination in cases of severe thrombocytopaenia, generalised bruising with haemorrhagic petechiae and purpura in the skin and mucosal surfaces may be evident. Haematological evaluation with platelet count, morphology, presence of schistocytes (in disseminated intravascular coagulation [DIC]) and platelet function tests may be necessary in certain cases.

Principles of Management

Due to the short lifetime of platelets (48-72 h), asymptomatic mild to moderate chemotherapy-induced thrombocytopaenia usually resolves spontaneously and does not require any treatment. In cases of severe thrombocytopaenia associated with bleeding events, supportive transfusion therapies may be implemented with platelet concentrates, fresh frozen plasma (FFP) and plasma-derived or recombinant concentrates, both during the acute episode and in prevention. These treatments may rarely be associated with complications and/or adverse events in cancer patients, such as allergic reactions or anaphylactic reactions, transfusion-associated graft-versus-host disease, transfusion-transmitted bacteraemia, transfusion-related acute lung injury, acute haemolytic transfusion reactions and febrile non-haemolytic transfusion reactions. When autoimmune mechanisms are involved in the pathogenesis of thrombocytopaenia, immunosuppressive treatment with steroids (usually 0.5-1 mg methylprednisone/kg of body weight i.v. or by mouth [p.o.]) may prove useful. Since prolonged thrombocytopaenia may constitute a factor for treatment delays, potentially affecting clinical outcomes, several molecular factors are under early clinical development in treatment-associated thrombocytopaenia, such as thrombopoietin-receptor agonists.

Prevention of Bleeding (Table 1)

Table 1 Indications for Platelet Transfusions.
Modified from: De Leeuw K, Schrijvers D. Bleeding disorders. In: Kasmidis, PA, Schrijvers D, André F, Rottey S (Eds). ESMO Handbook of Oncological Emergencies. Oxon: Taylor and Francis, 2005; 131-139.

Trigger (platelets/μL)	Clinical status
<10 000	Absolute indication for platelet transfusion, independent of clinical status
10 000-20 000	Presence of coagulation disorders Infection with fever >38°C (and rapid increase of platelets) Local injuries Severe mucositis, active bleeding Biopsy (except bone marrow biopsy)
<50 000	Surgery

Chemotherapy-induced Thrombocytopaenia

1. If platelets <10 000/μL: platelet transfusion of 6-8 units of RBC every 1-2 days until platelet counts remain >10 000/μL
2. For invasive procedures: platelets >30 000/μL
3. For surgery: platelets >50 000/μL

Declaration of Interest:

Dr Mountzios has received advisory and consultation fees from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Takeda, Novartis, Amgen, Pfizer, Takeda, GlaxoSmithKline, Sanofi; travel and accommodation fees from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Takeda, Novartis, GlaxoSmith-Kline, Sanofi, Amgen; and was principal investigator in sponsored clinical trials from Novartis, Roche, Merck Sharp & Dohme, AstraZeneca, Merck, Bristol-Myers Squibb, Amgen, Immunomedics, GlaxoSmith-Kline, Sanofi, Gilead.

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Bleeding

6.8.4

M. Aapro

Genolier Cancer Centre, Clinique de Genolier, Genolier, Switzerland

Background

Bleeding has been reported in up to 10% of cancer patients. It can be related to the underlying cancer (occult in gastrointestinal [GI] tract cancers, endometrial cancer bleeding), to drugs used by patients causing gastric bleeding (acetylsalicylic acid, non-steroidal anti-inflammatory agents, anticoagulants) or to disease-related coagulation disorders. Thrombocytopaenia is the most frequent clinical cause of severe bleeding and is often related to cytotoxic drug side-effects.

Evaluation

Chronic bleeding leads to anaemia and its signs (pallor) and symptoms such as fatigue, or dyspnoea in severe cases. Acute bleeding is related to the same clinical picture, with possibly haematochezia or melaena, haematemesis, vaginal bleeding or hypotension. The management of bleeding is divided into two approaches: treating the underlying cause and correcting its consequences on circulating blood volume.

Disseminated Intravascular Coagulation

DIC is a rare cause of bleeding but should be always suspected in patients presenting thrombocytopaenia. It is an acquired syndrome characterised by widespread activation of the blood coagulation system and by excessive consumption of haemostatic factors and secondary fibrinolysis. In cancer patients it is most often related to mucin-secreting adenocarcinomas and acute promyelocytic leukaemia. It is also caused by severe infections. The International Society on Thrombosis and Haemostasis

(ISTH) has established a DIC diagnostic scoring system consisting of global haemostatic test parameters (https://www.isth.org/page/reference_tools, date last accessed 15 April 2022). A score of ≥5 from the parameters below is indicative of this syndrome:

- Platelet count <100 000/mm^3, or a rapid decline in platelet count (>100 = 0; <100 = 1; <50 = 2)
- Fibrinogen level (>1 g/L = 0; <1 g/L= 1)
- Prolonged prothrombin time (<3 sec = 0; >3 sec but <6 sec = 1; >6 sec = 2)
- Increased D-dimer level and fibrin degradation products (no increase = 0; moderate increase = 1; strong increase = 2)

Treatment of thrombocytopaenia (see below), use of cryoprecipitate (8–10 U) in bleeding manifestations if fibrinogen level is <1 g/L and FFP are all suggested. Heparin is beneficial in the treatment of DIC with venous thrombosis or pulmonary embolism.

Vitamin K Antagonists, Heparin and Direct Oral Anticoagulants

Vitamin K antagonist-related bleeding is reversed by vitamin K administration and, rarely, FFP or prothrombin complex concentrate (PCC) may be necessary in major bleeding related to warfarin. Protamine sulphate reverses the effect of unfractionated heparin completely, and of low-molecular-weight heparin (LMWH) partially.

A recent review by Kaide and Gulseth (2020) provides a concise overview of the current and future approaches for reversing the anticoagulation effects of direct oral anticoagulants (DOACs), particularly factor Xa (FXa) inhibitors. Until recently, options for the management of major bleeding in patients who were receiving FXa inhibitors were limited to non-specific strategies, including supplementation of clotting factors with PCCs. The anticoagulant activity of the direct thrombin inhibitor dabigatran can be reversed by idarucizumab. Andexanet alfa is a modified FXa molecule reversing the anticoagulant effects of FXa inhibitors (rivaroxaban and apixaban).

Specific Bleeding Settings

Laser coagulation may be used in the local treatment of GI or bronchial bleeding. Arterial embolisation may stop bleeding in different organ systems. Surgical intervention may be necessary to control local bleeding. Haemostatic radiation should be discussed in case of urogenital or pulmonary bleeding.

Declaration of Interest:

Dr Aapro has reported no potential conflicts of interest in this context.

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Thromboembolic Events

6.8.5

N. Tsoukalas

Oncology Department, 401 General Military Hospital, Henry Dunant Hospital Center, Athens, Greece

Background and Clinical Consequences

Cancer is strongly associated with thrombosis as historically reported by Dr Armand Trousseau. Cancer-associated thrombosis (CAT) not only has many negative clinical and emotional consequences for oncology patients but also imposes an economic burden on healthcare systems.

Venous thromboembolism (VTE) occurs in up to 20% of patients with cancer, contributes significantly to morbidity and mortality (up to seven-fold) and interferes with cancer treatment. CAT is the second leading cause of death in cancer patients. Moreover, oncology patients have higher rates of VTE recurrence and bleeding with anticoagulants. Finally, CAT can be the first clinical manifestation of an undiagnosed cancer.

Pathophysiology

The underlying mechanisms of high thrombotic burden (HTB) development in cancer patients are complex and multifaceted. Some of the factors contributing to the cancer-induced state of hypercoagulability include direct coagulation pathway activation, induction of inflammatory responses and inhibition of fibrinolytic activity. Innate immune cells play a critical role in thrombosis development, provoking a dynamic cross-talk between coagulation and inflammation pathways called immuno-thrombosis. Inflammatory cells, chemokines and cytokines are also present in the microenvironment of all tumours. Understanding the pathways involved in cancer-related thrombo-inflammation could enable the development of synergistic therapies that also target 'the other half of the tumour' that is the inflammatory components of the microenvironment.

Incidence

The incidence of CAT varies due to tumour-related factors (e.g. primary cancer site, histology, adenocarcinoma, grade, metastasis), treatment-related factors (e.g. surgery, chemotherapy, anti-angiogenesis treatment, immunotherapy and supportive care treatments) and patient-related factors (e.g. advanced age, high body mass index [BMI], blood disorders, renal and hepatic insufficiency, atrial fibrillation). Some biomarkers (e.g. tissue factor [TF], TF-bearing microparticles, soluble P-selectin, thrombin generation) are predictive markers for VTE risk in cancer patients.

Assessment of Thrombotic Risk

The Khorana score assesses VTE risk by specific cancer patient characteristics prior to chemotherapy, such as: very high-risk cancer types (score 2: pancreas and stomach), high-risk types (score 1: lung, gynaecological, bladder, testicular, lymphoma), platelet count, leucocyte count, haemoglobin or use of erythropoietins and BMI. According to the Khorana score assessment, cancer patients can be stratified into three groups (low risk: 0, intermediate: 1-2 and high: ≥3) regarding the risk of thrombosis. Ambulatory active cancer patients undergoing chemotherapy with a Khorana score ≥2 are eligible for thromboprophylaxis.

Principles of Thromboprophylaxis

The principles of thromboprophylaxis in the clinical setting apply to major cancer surgery, hospitalisation for acute medical illness and active cancer outpatients undergoing antineoplastic treatment. There is an alignment on recommendations regarding thromboprophylaxis and treatment of CAT among scientific societies such as ESMO, the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN) and ISTH. Specifically, cancer patients undergoing elective major abdominal or pelvic surgery should receive in-hospital and post-discharge prophylaxis with LMWHs for up to 1 month after surgery. Hospitalised patients with active malignancy and acute medical illness should be offered thromboprophylaxis as well. For high-risk outpatients (Khorana score ≥2) with active cancer, prior to starting a new

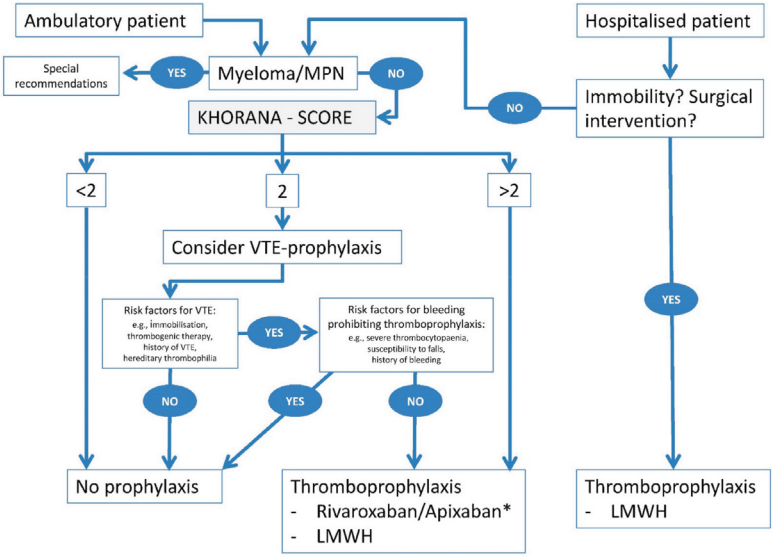

Figure 1 Algorithm for individual decisions for primary thromboprophylaxis in cancer patients.

From: Kirschner M, do Ó Hartmann N, Parmentier S, et al. Primary Thromboprophylaxis in Patients with Malignancies: Daily Practice Recommendations by the Hemostasis Working Party of the German Society of Hematology and Medical Oncology (DGHO), the Society of Thrombosis and Hemostasis Research (GTH), and the Austrian Society of Hematology and Oncology (ÖGHO). Cancers (Basel) 2021; 13:2905.

Abbreviations: LMWH, low-molecular-weight heparin; MPN, myeloproliferative neoplasm; VTE, venous thromboembolism.

* DOACs (direct oral anticoagulants) not approved for primary prophylaxis in ambulatory cancer patients.

treatment, thromboprophylaxis with LMWHs or specific DOACs should be considered in the absence of risk of bleeding and drug-drug interactions. A proposed algorithm for primary thromboprophylaxis in cancer patients is illustrated in Figure 1.

Principles of Treatment

Regarding the treatment of CAT, initial anticoagulation may involve LMWHs, unfractionated heparin (UFH), fondaparinux or rivaroxaban for the initial 5 to 10 days for a cancer patient with newly diagnosed VTE. For long-term anticoagulation, LMWHs, edoxaban or rivaroxaban

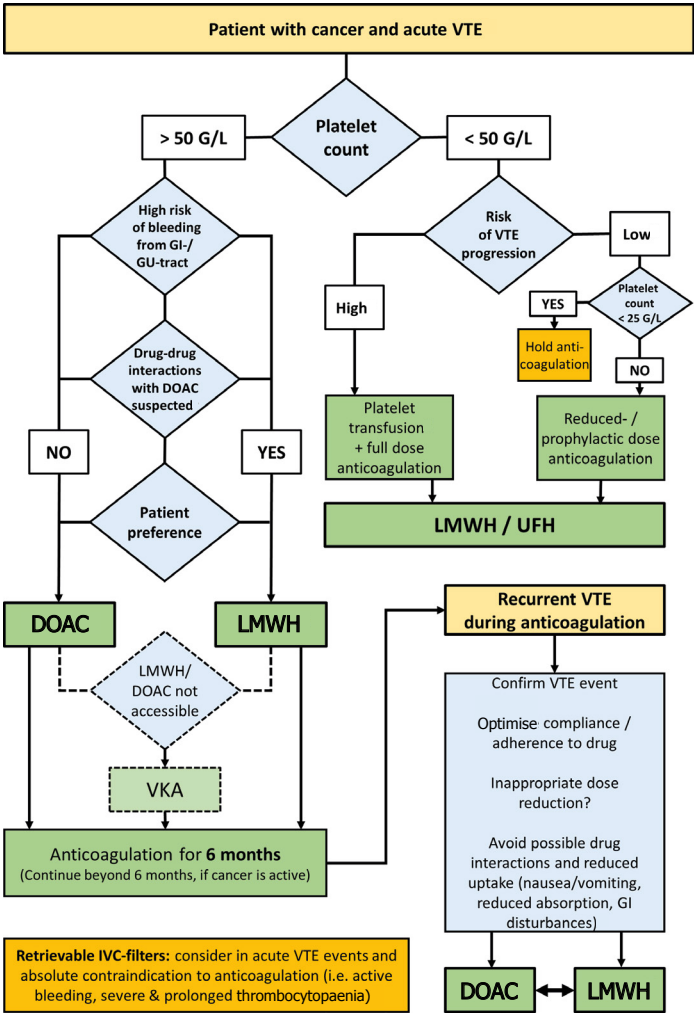

Figure 2 Treatment algorithm for patients with cancer and acute VTE.
From: Moik F, Pabinger I, Ay C. How I treat cancer-associated thrombosis. ESMO Open 2020; 5:e000610.

Abbreviations: DOAC, direct oral anticoagulant; IVC, inferior vena cava; GI, gastrointestinal; GU, genitourinary; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism; VKA, vitamin K antagonist.

can be used for at least 6 months. There is an increase in major bleeding risk with DOACs, particularly observed in GI and potentially genitourinary malignancies. Also, drug-drug interactions should be checked prior to using DOACs. Notably, incidental pulmonary embolism (PE) and deep vein thrombosis (DVT) should be treated in the same manner as symptomatic VTE. A proposed algorithm for treatment of VTE in cancer patients is illustrated in Figure 2.

Conclusion

Increased thrombosis awareness among physicians and nurses who deal with CAT could drive the management of thrombosis across the continuum journey of oncology patients. On the other hand, patients need to be informed about the importance of CAT and be able to recognise the symptoms of VTE. Classic clinical symptoms are not present in all cases of acute VTE. These symptoms may include pain, unilateral oedema and heaviness in the extremities distal to the site of the venous thrombosis for DVT, and unexplained shortness of breath, chest pain and tachycardia for PE.

It is essential for patients, the disease progression and health resources to improve perceptions about the magnitude of VTE and CAT risk in patients with malignancies, optimising the management of thrombosis in cancer patients.

Declaration of Interest:

Dr Tsoukalas has reported no potential conflicts of interest.

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Metabolic Complications of Cancer

6.9

M. Strijbos[1]
P. Dirix[2]
[1]GZA Ziekenhuizen Sint-Augustinus, Antwerp, Belgium
[2]Iridium Kankernetwerk, Antwerp; University of Antwerp, Antwerp, Belgium

Hypercalcaemia

Definition

Hypercalcaemia is defined as elevated calcium (Ca^{2+}) levels in the blood. Normal albumin-corrected serum calcium levels are 8-10 mg/dL or 2.0-2.5 mmol/L, but reference values may differ slightly between laboratories. Hypercalcaemia is a common metabolic complication of cancer and often infers a poor prognosis.

Causes

Osteolytic bone metastasis

Bone destruction by osteolytic metastasis is the leading cause of hypercalcaemia in cancer patients. It is caused primarily by osteoclast activation due to the tumoural secretion of parathyroid hormone-related protein (PTHrP).

PTHrP causes hypercalcaemia by promoting the activation of osteoclasts through inhibition of the expression of osteoprotegerin (OPG), the decoy receptor for receptor activator of nuclear factor kappa-B (RANK), and increasing the production of RANK ligand (RANKL) by osteoblasts, which causes osteoclast activation by binding to RANK present on their surface.

1,25-dihydroxyvitamin D

Elevated blood levels of 1,25-dihydroxyvitamin D (1,25-$[OH]_2D$) are the most frequent cause of hypercalcaemia in lymphoma, increasing intestinal calcium absorption. This could be related to increased 1α-hydroxylase activity in tumour cells, with an accelerated transition from 25-hydroxyvitamin D (25-[OH]D) to 1,25-$(OH)_2D$. In physiological conditions, increased serum calcium causes suppression of parathyroid hormone (PTH), thereby decreasing renal conversion to 1,25-$(OH)_2D$. In lymphoma and myeloma, malignant lymphocytes can produce PTH-independent 1,25-$(OH)_2D$ from 25-(OH)D, causing hypercalcaemia.

Ectopic PTH hormone production

Secretion of PTH by tumour cells other than parathyroid carcinoma is extremely rare. Reports have been published on ovarian carcinoma and small cell and squamous cell lung cancers.

Signs and Symptoms

Symptoms of hypercalcaemia may include, but are not limited to:

- Polyuria, thirst, nausea and vomiting, anorexia, abdominal pain, constipation
- Fatigue, altered mental state, confusion, depression, cognitive dysfunction
- Acute renal impairment, muscle weakness, peptic ulceration
- Hypertension, shortened QTc interval, dysrhythmias

Symptoms tend to be more severe with a more acute onset of hypercalcaemia.

Evaluation

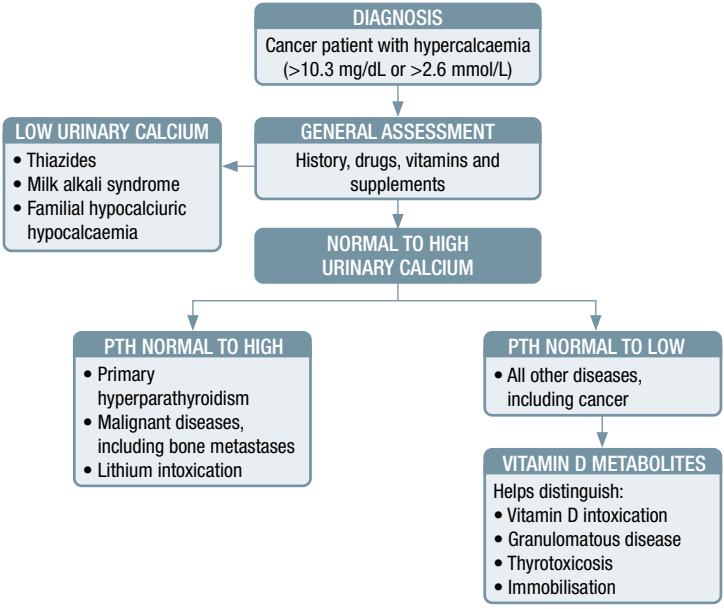

Figure 1 Diagnostic approach to patients with hypercalcaemia.
Adapted from: Strijbos M, Punie K. Hypercalcaemia. In: Provencio Pulla M (Ed.). ESMO Handbook of Oncological Emergencies. Viganello-Lugano: ESMO Press, 2016; 95-102.
Abbreviation: PTH, parathyroid hormone.

Management

Management of malignant hypercalcaemia should ideally focus on adequately treating the underlying malignancy, specifically by inhibiting bone resorption or the production of recombinant PTHrP.

The aggressiveness of treatment is proportionate to the severity of symptoms. In patients with serum calcium levels >3.5 mmol/L or 14 mg/dL, prompt treatment is required, whereas in milder forms, treatment can be deferred until the complete diagnostic workup has been completed.

In the initial phase, intravascular volume re-expansion is the cornerstone of treatment.

- Intravascular volume expansion: this results in inhibiting sodium reabsorption in the proximal tubule. As proximal calcium reabsorption is a passive process, depending on the gradient established by sodium reabsorption, calciuria increases.
- Increase urinary calcium excretion by using loop diuretics: however, *in vivo*, this calciuretic effect is counteracted by the volume contraction induced by the diuretic.
- Inhibition of bone resorption: with bisphosphonates or denosumab.
- Inhibition of bone resorption: with calcitonin. Calcitonin causes only a moderate decrease in serum calcium concentrations but acts very rapidly. This could help bridge the time of action of other agents.
- In restricted cases (lymphoma, myeloma) the addition of steroids might be considered, as in these diseases 1α-hydroxylase activity, which is inhibited by glucocorticoids, is increased.

Syndrome of Inappropriate Antidiuretic Hormone

Definition

In healthy individuals, the secretion of antidiuretic hormone (ADH) by the posterior hypophysis is stimulated by high serum osmolality. The release of ADH increases water reabsorption in the distal renal tubule and collecting duct.

The syndrome of inappropriate antidiuretic hormone (SIADH) is caused by the body's inability to regulate water excretion due to pathologically elevated levels of ADH. SIADH should be suspected in all clinically euvolaemic patients with hyponatraemia, hypo-osmolality and a urine osmolality >100 mOsmol/kg. Urinary sodium is typically >40 mEq/L.

Adrenal and thyroid functions should be normal, as both hypothyroidism and adrenal insufficiency can lead to euvolaemic hyponatraemia.

Causes

Cancer-related causes

Approximately 65% of all SIADH cases are related to cancer. The vast majority are caused by small cell lung cancer, but it is also seen in non-small cell lung cancer, head and neck cancer, primary brain cancers, Ewing sarcoma, lymphoma and leukaemia. The primary pathophysiological mechanism in paraneoplastic SIADH is ectopic production of ADH. In sporadic cases, alternative mechanisms of pituitary ADH secretion stimulation are present.

Drug-related causes

Cyclophosphamide. Administration of high-dose cyclophosphamide is associated with enhanced ADH release. In addition to the detrimental effects of ADH itself, the high fluid load typically administered with this drug adds to the water retention and thus hyponatraemia. Fatal hyponatraemia has been described with doses of 30-50 mg/kg or 6 g/m².

Selective serotonin reuptake inhibitors (SSRIs). Depression and anxiety are frequent symptoms in cancer patients, and SSRIs are the most frequently prescribed antidepressant class in these patients. Among the SSRIs, fluoxetine, citalopram and escitalopram present the highest risk of hyponatraemia, whereas paroxetine and sertraline have the lowest.

Anticonvulsants. Carbamazepine and oxcarbazepine, both anticonvulsants but also used to treat neuropathic pain, can trigger SIADH. Both drugs increase the sensitivity of the renal V2 receptor to ADH.

Central nervous system disturbances

Any central nervous system disorder can increase the release of ADH. Stroke, intracerebral haemorrhage, encephalitis and meningitis can all be associated with SIADH.

Signs and Symptoms

Symptoms in SIADH are the result of cerebral oedema caused by hyponatraemia. The severity is directly correlated to the rapidity of hyponatraemia onset. A rapid decrease of serum sodium concentration typically gives severe symptoms and results in a parallel reduction of

serum osmolality. As a result, the osmotic gradient between the intra- and extracellular environment forces water intracellularly, which is the cause of cerebral oedema.

Acute symptoms occur when sodium levels drop below 115-120 mEq/L. Chronic hyponatraemia with comparable sodium levels usually causes minimal symptoms.

Symptoms of acute hyponatraemia include:

- Headaches
- Lethargy
- Decreased awakening
- Altered mental state
- Seizures
- Coma

Symptoms of chronic hyponatraemia are often non-specific, but nausea, vomiting and vertigo, as well as memory loss, are often reported.

Evaluation

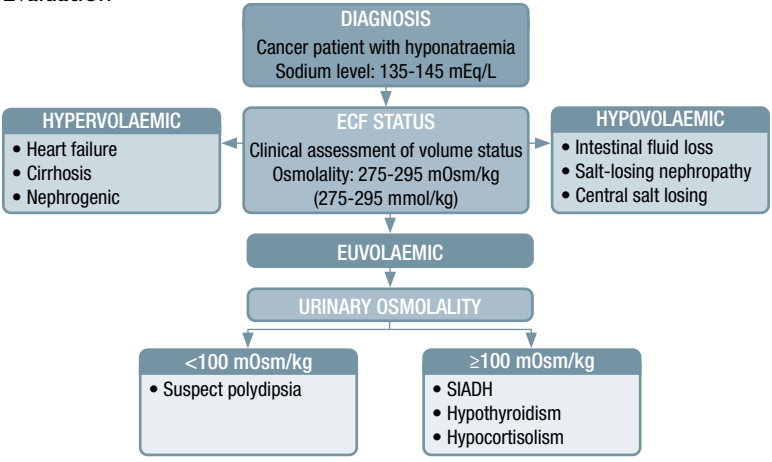

Figure 2 Diagnostic approach to patients with hyponatraemia.

Adapted from: Strijbos M, Punie K. Hypercalcaemia. In: Provencio Pulla M (Ed). ESMO Handbook of Oncological Emergencies. Viganello-Lugano: ESMO Press, 2016; 95-102.

Abbreviations: ECF, extracellular fluid; SIADH, syndrome of inappropriate antidiuretic hormone.

Management

As with most paraneoplastic syndromes, if SIADH is confirmed, treatment should be directed at the underlying disease. However, given the severity of symptoms, first-line therapy should focus on rapidly controlling them.

Given the excess of free water, fluid restriction is the mainstay of treatment. A restriction of 500-800 mL/day is recommended; however, this can be difficult for patients and should always be evaluated within the context of the general status of the patient and coexisting morbidities.

Alternatively, vaptans (vasopressin receptor antagonists) can be used. Fluid restriction should not be continued in that case, as their combination can lead to too rapid correction and worsening of symptoms.

In refractory cases, oral urea at a dose of 15-30 g three times a day can be used, often leading to serum sodium concentrations >130 mEq/L in 2-3 days.

Declaration of Interest:

Dr Strijbos has reported no potential conflicts of interest.
Dr Dirix has reported no potential conflicts of interest.

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Fatigue

6.10

F. Roila

S. Fatigoni

Medical Oncology, Santa Maria della Misericordia Hospital, Perugia, Italy

Cancer-related fatigue (CRF) is defined by the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) as a 'distressing, persistent subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning'. Different from fatigue in healthy people, CRF is often not relieved by sleep and rest.

CRF is the most common and distressing symptom experienced by cancer patients. It is reported by ~40% of patients at diagnosis, ~80% and ~90% of patients treated with chemotherapy and radiotherapy, respectively, and ~20%-50% of patients after the end of therapies. CRF persists for several years post-treatment in approximately one third of patients.

The underlying mechanism of CRF has not been fully elucidated. Some evidence suggests that fatigue is correlated with elevations in levels of pro-inflammatory cytokines, 5-hydroxytryptophan dysregulation, hypothalamic-pituitary-adrenal axis dysfunction, circadian rhythm disturbance and increased vagal tone.

CRF is a complex and multidimensional symptom with physical, emotional and cognitive components. Contributing factors can include: anaemia, cancer-related physical symptoms, medical comorbidities such as endocrine pathologies, cardiopulmonary disorders, hepatic, renal and neurological dysfunctions, nutritional and fluid imbalances, cancer therapies, and adverse events caused by other drugs.

CRF is too often under-reported by patients and under-considered by oncologists. For this reason, available guidelines suggest that all cancer patients should be routinely screened for the presence of CRF at their first oncological visit and re-evaluated during and at the end of therapy. Screening should be done using brief and validated tools such as the Numerical Rating Scale (NRS), a linear scale with 0 = 'no fatigue' at one extremity and 10 = 'fatigue as bad as could be' at the other. Fatigue intensity is graded as mild (values of 1-3), moderate (4-6) and severe (7-10). Patients with a NRS ≥4 should undergo a comprehensive and focused assessment with the aim to identify, and possibly correct, treatable contributing issues and comorbid conditions. The Brief Fatigue Inventory, a reliable and easily understood questionnaire, integrates the assessment of fatigue severity and its impact on important functional domains.

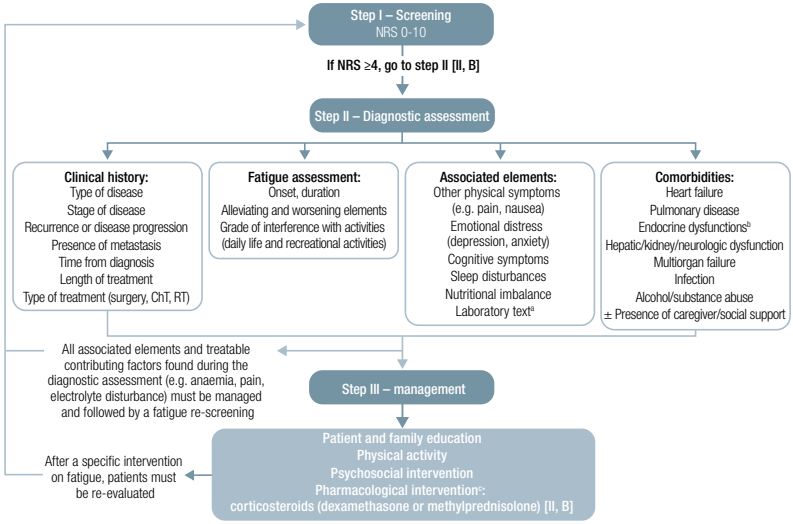

Figure 1 Practical assessment of CRF.

From: Fabi A, Bhargava R, Fatigoni S, et al. Cancer-related fatigue: ESMO Clinical Practice Guidelines for diagnosis and treatment. Ann Oncol 2020; 31(6):713-723.

Abbreviations: ChT, chemotherapy; CRF, cancer-related fatigue; NRS, numerical rating scale; RT, radiotherapy.

[a] Urinalysis for protein, blood and glucose, full blood count, urea and electrolytes, liver function, thyroid function, erythrocyte sedimentation rate, C-reactive protein, blood glucose, serum creatinine.

[b] For example, hypothyroidism, hypogonadism, adrenal insufficiency and hypopituitarism, especially in patients receiving immunotherapy.

[c] Only for short-term use in metastatic cancer patients.

Pharmacological Treatments

The studies on CRF treatments generally present many limitations: lack of different types and stages of cancer, small numbers of patients, a different scale used to evaluate CRF. Finally, a significant placebo response has been observed in randomised placebo-controlled trials (for more detailed information, refer to the 2020 'Cancer-related fatigue: ESMO Clinical Practice Guidelines for diagnosis and treatment').

Psychostimulants

- *Methylphenidate* has been evaluated in several trials but its efficacy is not clearly shown despite 11 placebo-controlled trials and a meta-analysis. Only three studies showed a CRF improvement with methylphenidate compared with placebo.
- *Dexamphetamine* in 50 patients with advanced cancer receiving palliative care showed improvement in fatigue similar to placebo.
- *Modafinil* did not demonstrate efficacy in four placebo-controlled studies in patients undergoing chemotherapy or radiotherapy.
- *Armodafinil* in four randomised placebo-controlled trials showed similar efficacy as placebo in patients with multiple myeloma and primary brain tumours submitted to active treatments.

Other Pharmacological Treatments

- *Donepezil* in a double-blind, placebo-controlled trial in 142 patients with advanced cancer showed similar improvement of fatigue compared with placebo.
- *Paroxetine* in two randomised double-blind studies showed no difference with respect to placebo in reducing CRF, but paroxetine reduced depression more than placebo.
- *Dexamethasone*, 4 mg orally (p.o.) twice daily for 14 days, in a double-blind, placebo-controlled study in metastatic cancer patients, showed efficacy as a short-term therapy, but the long-term effects were not evaluated.

- *Methylprednisolone*, 16 mg p.o. twice daily for 7 days in patients with advanced cancer showed an improvement on the European Organisation for Research and Treatment of Cancer (EORTC)-QOL C30 questionnaire compared with placebo.

Nutriceutical Interventions

- A double-blind randomised trial evaluated 2000 mg of *Wisconsin ginseng* (a common type of American ginseng) versus placebo in 364 patients undergoing or having undergone curative intent treatment. A statistically significant difference was seen at 8 weeks, especially in patients receiving active cancer treatment.
- *L-carnitine* supplementation has been studied in two randomised trials in patients with advanced cancer and fatigue (mostly receiving radiotherapy or chemotherapy) without significant difference with respect to placebo.
- *Coenzyme Q10* showed no significant difference compared with placebo in two randomised studies in women with breast cancer submitted to chemotherapy.

Non-pharmacological Interventions

Physical Exercise

The role of physical exercise in patients with CRF has been documented by multiple systematic reviews and meta-analyses. An exact exercise prescription in patients with CRF does not exist; some guidelines encourage 150 minutes of moderate aerobic exercise per week, such as walking, cycling or swimming, with an additional 2 to 3 days per week of strength training such as weightlifting, unless contraindicated (e.g. in case of extensive lytic bone metastases, fever or infection).

Psychosocial Treatment

Information on the multifactorial nature of CRF and its potential causes and influencing factors should be given. Counselling should include recommendations for energy preservation, task prioritisation, activity pacing and advice on how to delegate less important activities.

Psychoeducation may be useful for patients to identify sources of psychosocial distress, to eliminate stress-producing activities when possible and to find a balance between rest and activity during the day.

Cognitive behavioural therapy is generally used to address the following factors: coping with the experience of cancer, fear of disease recurrence and dysfunctional thoughts and beliefs regarding fatigue, sleep dysregulation, etc.

Mind-Body Interventions

Mindfulness-based Stress Reduction

This combines meditation exercises with psychoeducational elements, cognitive-behavioural interventions and movement exercises. Studies have demonstrated a possible improvement of CRF, even if more studies are needed to identify its role.

Yoga

Yoga combines physical poses with a focus on breathing and meditation. Contrasting results for the impact of yoga on CRF have been published; therefore more studies are needed to clarify its possible benefit.

Acupuncture

Several randomised controlled trials have been published, many with methodological flaws. A recent meta-analysis showed acupuncture had an important impact on CRF, especially in breast cancer patients. More well-planned studies are also needed in this case.

Declaration of Interest:

Dr Roila has reported no potential conflicts of interest.

Dr Fatigoni declared meeting participation with PharmaMar, Janssen, Ipsen and Istituto Gentili.

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Care of the Dying Patient

7

N.I. Cherny

Department of Medical Oncology, Shaare Zedek Medical Center, Jerusalem, Israel

The period leading to death is characterised by increasing prevalence and severity of physical, psychological, existential and social problems.

- Successful management in this phase is critical for the patient, surrounding relatives, friends and oncologists and should involve the specialist palliative care team for advice and support for when symptom control and decision-making become more challenging.
- The goal is to minimise the distress engendered by this process through meticulous symptom control and supportive care, while maintaining the wellbeing and moral integrity of the care providers, often across more than one setting.

The care of dying patients requires careful evaluation of the patient and their family, refined communication skills, expertise in the management of symptoms and the coordination of a multidisciplinary care team.

Identifying That Death is Close

- Recognising that a patient is imminently dying is the prerequisite for providing appropriate end-of-life care.
- This requires a readiness to re-evaluate in the context of unexpected improvement or stabilisation.
- Dying patients differ in their capacity to acknowledge prognosis, with the majority only partially aware of the proximity of death, and requirements for disclosure and frank discussion vary greatly.
- As with most prognostic assessments, closeness to death is best expressed with a qualified statement such as: "Unless there is a

dramatic improvement in the near future, it appears that your mother is getting very close to dying".

- The development of new therapies makes it more difficult to provide accurate prognostic data. In such circumstances, discussions about 'hoping for the best but preparing for the worst' may be helpful to allow hope for improvement as well as a readiness to address end-of-life issues, should the treatment fail to halt the patient's deterioration.
- Well-conducted discussions about end-of-life care foster trust and non-abandonment for patients and carers and improve end-of-life outcomes for both the patient and the bereaved.

Advance Directives

- As a person approaches death, their ability to make decisions may become impaired.
- Encouraging advance care planning, directives or discussions with the patient prior to the terminal phase greatly reduces the burden on the substitute decision-maker and ensures the patient's choices are respected.
- When patient preferences for end-of-life care are unaddressed, or addressed ineffectually or insensitively, this may generate conflict, stress and sometimes moral distress.
- In many jurisdictions there is a medicolegal requirement to discuss and document these issues.

Where Should the Patient be Cared For

- There is not one best place to die and indeed a patient's and family's preferred place of death may change with increasing care needs.
- Factors influencing the decisions regarding home, hospital or inpatient hospice care for the dying patient include: the patient's care requirements, available resources (medical, family, nursing and physical) and patient and family preference.

- Home care generally requires the availability of family or other support to assist in patient care and, therefore, care resources should be evaluated before promoting this option.
- Since many cancer patients die in acute care hospitals, adequate provision must be made for their specific care needs.

Patient Care

The provision of a level of comfort satisfactory to the patient is an ethical imperative.

Physical Distress

- Constitutional problems of weakness, fatigue and loss of appetite become more evident as death approaches. In the terminal phase, these problems usually start to assume relatively less significance for patients, although not necessarily for families.
- Active assessment and pre-emptive management of symptoms become increasingly important, especially as the patient becomes less able to communicate.
  - Common symptoms include pain, dyspnoea, nausea, anxiety, delirium and respiratory secretions.
  - Common problems include immobility, pressure-area care, care of bladder and bowel, secretions, xerostomia and odours.
  - Mouth care, in particular, is a high-impact nursing task that is often underappreciated.
- Strategies for the routine management of pain and other physical symptoms have been described in previous chapters of this Handbook. Special considerations are listed in Table 1.
- Routes of administration of pain medication need to change in the last days when swallowing becomes unreliable, to continue symptom control and avoid opioid withdrawal.
- When symptoms prove resistant to therapeutic efforts, the patient should be reviewed by a palliative care specialist.

Table 1 Principles for the Management of Common Symptoms Among Dying Patients.

Symptom	Important notes
General	• Consider the non-oral route of administration (transdermal or parenteral) for patients unable to swallow
Dyspnoea	• Manage reversible causes (e.g., pleural effusion, pneumonia) • Explore pharmacological (opioids) as well as non-pharmacological measures where appropriate and feasible (oxygen therapy, fan, positioning, relaxation and breathing techniques) • When refractory in the final days of life, palliative sedation is commonly required
Delirium and agitation	• Address reversible causes • Consider sedating antipsychotics • Benzodiazepines may be required for more rapid control of agitation and anxiety, but they can occasionally cause paradoxical agitation if used alone
Terminal respiratory secretions	• Lying the patient on their side to facilitate postural drainage, gentle oropharyngeal suctioning and explaining to family and caregivers that this does not indicate that the patient is in distress • Antimuscarinic agents may be helpful with the risk of increasing delirium

Psychological and Existential Distress

- Existential and psychosocial issues greatly concern dying patients, including fear of death, issues related to loved ones and family, guilt, remorse, need for forgiveness or need to forgive and issues around meaning.
- Many patients will want to attend to issues of separation and farewell, legacy and leaving some form of final message to those they will leave behind, or to find spiritual solace with religious practices such as confession and prayer, or other non-religious expressions through special relationships, nature or music.
- Effective psychological and spiritual care interventions reduce distress and enhance coping even in these challenging circumstances.

Medications

- Only essential medications should be continued to ensure optimal symptom control and should be administered by the least invasive route that can provide adequate relief.

- Non-essential medicines include anticoagulants, antihypertensive and lipid-lowering medications and, in many instances, antibiotics.
- If the patient and/or family object to the withdrawal of a medication that is not causing patient harm, the medication should be continued.
- If the patient is likely to require rapid relief from severe symptom exacerbation, appropriate parenteral access (i.v. [intravenous] or s.c. [subcutaneous]) should be maintained.

Nutrition

- There are no data proving that artificial administration of nutrition by enteral and parenteral routes contributes to symptom relief in the imminently dying patient. In addition, these are medical interventions with the potential for associated morbidity.
- In cases where there are religious or culturally-based reservations regarding the discontinuation of nutritional support, it should be maintained unless there is evidence of it causing harm. Such conversations should be held with utmost sensitivity.

Hydration

- The need for hydration in the care of terminally ill patients remains controversial and, in some patients, particularly those with hypoalbuminaemia or fluid retention, it may be harmful.
- For patients who are cognitively intact, dehydration is a factor that can precipitate delirium and diminish interactional function, and a trial of hydration may be justified. Any trial of hydration needs careful explanation.
- In the comatose patient who is actively dying, the considerations are similar to those expressed with regards to nutrition.
- Mouth care and keeping the mouth and lips moist is something the family can help with.

Invasive Palliative Interventions

- Common situations that justify this sort of consideration include drainage procedures to relieve symptomatic distress caused by pleural and pericardial effusions or ascites, or tracheostomy for upper airway obstruction.
- Invasive interventions are used only in circumstances when symptoms cannot be adequately relieved with standard, non-invasive approaches and when they have a high likelihood of relieving distress and improving wellbeing without excessive risk.
- They should be avoided when death is imminent.

Artificial Ventilation

- Artificial ventilation should not generally be considered for dying patients.
- Rare exceptions to this rule apply:
  - When there are fixed religious or culturally-based reservations to the withdrawal of ventilatory support prior to death or,
  - If it is requested that death be postponed until a relative arrives from a distance or a specific deadline passes.
  - Expert palliative advice should be sought on palliation of respiratory distress prior to withdrawing ventilation (particularly non-invasive ventilation at home).

Disability Care

- With progression of illness and reduced overall function, there is an associated reduced ability to carry out independent activities of daily living.
- Transferring may require assistance and the environment of care may often require modification to improve access, safety and comfort with input from an occupational therapist and physiotherapist.
- Incontinence of urine, complicated by reduced mobility, urinary retention and faecal impaction, are all potential problems that can impact on a person's sense of dignity and cause severe distress in the deteriorating patient.

Nursing Intervention

- Common problems that require special attention include immobility, pressure care, care of bladder and bowel function, airway maintenance, oral care, secretions and odour.
- Meticulous nursing care and monitoring for symptom distress, rather than ongoing attention to the recording of patient data (such as pulse and blood pressure), is essential in the care of dying patients.
  - In cases where there are religious and cultural reservations regarding the discontinuation of vital sign monitoring, it should be continued unless it is clearly disturbing to the patient.

Anticipatory Care Planning for Emergencies

- Uncontrolled pain, dyspnoea, nausea and vomiting, agitated delirium and massive haemorrhage all constitute emergencies that warrant anticipatory interventions, including adequate timely availability of pharmacotherapy (Table 2).
- Specific drugs, doses and routes of administration should be appropriate to the patient's clinical situation.

Patients at Risk of Upper Airway Obstruction

- Consideration should be given to prophylactic tracheostomy to prevent death by asphyxiation.

Patients at Risk of Carotid Blow-out or Other Massive Haemorrhage

- Family coping resources will dictate the appropriateness of home care.
- The severe anxiety associated with a massive terminal haemorrhage should be managed with an anaesthetising dose of a rapidly acting benzodiazepine. Midazolam (5-10 mg) is recommended because of its rapid onset of action and versatility of administration (i.v., s.c. or i.m. [intramuscular]) in an emergency situation.

Table 2 Examples of Drugs Commonly Used to Manage Symptoms in the Dying Patient.

Emergency	Recommended medications
Dyspnoea[1]	Oxygen
	Opioids: usually parenteral morphine or transmucosal fentanyl reduce the distress of dyspnoea, although their use can be complicated with deteriorating renal function
	Benzodiazepine: usually midazolam Bronchodilators: in case of coexistent COPD
Pain[2]	Opioids: usually parenteral morphine or transmucosal fentanyl, although their use can be complicated with deteriorating renal function
	Dexamethasone
	Benzodiazepine: usually midazolam
Delirium[3]	Antipsychotics: olanzapine, levomepromazine or risperidone (parenteral route available). Olanzapine can be administered as an orodispersible preparation and chlorpromazine can be administered rectally
	Benzodiazepine: lorazepam or midazolam
Nausea and vomiting[4]	Antiemetic: levomepromazine, haloperidol, olanzapine
	Dexamethasone
Massive haemorrhage	Midazolam
Anxiety attack	Benzodiazepine: lorazepam or midazolam
Terminal respiratory secretions	Antimuscarinics: atropine, hyoscine butylbromide, scopolamine or scopolamine patch

Also see relevant ESMO guidelines:

[1]Hui D, Maddocks M, Johnson MJ, et al. Management of breathlessness in patients with cancer: ESMO Clinical Practice Guidelines. ESMO Open 2020; 5:e001038.

[2]Fallon M, Giusti R, Aielli F, et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Ann Oncol 2018; 29(Suppl 4):iv166–iv191.

[3]Bush SH, Lawlor PG, Ryan K, et al. Delirium in adult cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2018; 29(Suppl 4):iv143–iv165.

[4]Roila F, Molassiotis A, Herrstedt J, et al. MASCC and ESMO consensus guidelines for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol 2016; 27 (suppl 5):v119–v133.

Abbreviation: COPD, chronic obstructive pulmonary disease.

Using Sedation for Refractory Distress

- Palliative sedation is an option of last resort to provide relief of severe refractory symptoms (for example, agitated delirium, dyspnoea, pain and convulsions) in the terminal phase.

- The term 'refractory', which should be distinguished from 'difficult', refers to symptoms that cannot be adequately controlled despite aggressive efforts to identify a tolerable therapy that does not compromise consciousness, and where further invasive and non-invasive interventions are unlikely to provide relief within a tolerable time frame.
- For patients with decisional capacity, the aims, benefits and risks of the proposed sedation should be discussed.
- If the patient permits, it is preferable to conduct this discussion with the participation of significant family members.
- This shared process often triggers important discussions between patients and their families while the opportunity still exists.
- If an adult patient lacks decisional capacity and there is no advance directive, permission needs to be obtained from a legally recognised proxy.
- In the care of terminally ill patients who have no advance directive and no healthcare proxy, and who are in severe distress while actively dying, acting in the patients' best interests and the provision of comfort measures (including, if necessary, the use of sedation) is the 'standard of care' and should be the default strategy for clinician treatment decisions.

Administration of Sedation

- The most commonly used medication in this setting is midazolam, a short half-life benzodiazepine with a rapid onset of action. Administration initially requires dose titration to achieve adequate relief, followed subsequently by provision of ongoing therapy to ensure maintenance of effect.
- Using midazolam, sedation is initiated with parenteral bolus doses, usually starting with 2.5 mg repeated every 10-15 minutes until adequate sedation is achieved, with a maintenance infusion which can be started at 1-3 mg/h. If frequent additional bolus doses are necessary, the infusion rate should be adjusted appropriately.
- Other options include lorazepam, levomepromazine, chlorpromazine, phenobarbital or propofol.

- In some circumstances, deep sedation may be initiated from the outset and continued until death: if the suffering is intense, refractory, death is anticipated within a short time, and the patient's wish to be permanently unaware is explicit, or in the setting of an end-of-life catastrophic event such as massive haemorrhage or severe terminal dyspnoea.

Patient Monitoring

- For imminently dying patients, the only critical parameters for ongoing observation are those pertaining to comfort. Respiratory rate is monitored primarily to ensure the absence of respiratory distress and tachypnoea.
- In dying patients, gradual deterioration of respiration is anticipated and should not alone constitute a reason to decrease sedation.
  - If the patient wishes to be less sedated and is not expected to die in the coming hours, support from the specialist palliative care team should be sought to define the ongoing management plan including monitoring.
  - If obtundation with respiratory depression occurs in a patient undergoing respite sedation, titrated administration of a benzodiazepine antagonist (flumazenil) may be appropriate.

Family Wellbeing

- Family members suffer empathically with the distress of the patient.
- Prompt and effective communication along with timely relief of patient symptoms is critical to family care.

Information and Communication

- Communication from healthcare providers needs to be honest, direct and compassionate, and must allow for the concerns and opinions of the family to be heard and appreciated.
- The goals of care should be discussed with emphasis on the priorities of the patient and the maintenance of adequate comfort.

- Special counselling is required if there is a potential for catastrophic death, such as a haemorrhage or asphyxiation.
- When a family member is sedated, families should be allowed and encouraged to be with the patient. In many situations the opportunity to say goodbye may be of critical importance.
- Families often need repeated reassurance that other methods have been sufficiently trialled and/or carefully considered but were ineffective, that sedation is unlikely to shorten the patient's life, and that it can be discontinued or lightened if considered appropriate.

Care Education

- Irrespective of the place of care, family members require guidance and possibly training regarding ways in which they can contribute to the comfort care of the patient, including toileting, transfers and feeding.
- Other ways for the family to continue to be of help to the patient include: being with, talking to, touching the patient, providing mouth care, and managing the atmosphere of the patient's care (e.g. providing the patient's preferred music, scents, singing of beloved songs, prayer or readings).
- Family coping should be regularly assessed.
- Often family members require counselling as to how to respond to questions by the patient regarding the imminence of death or requests by the patient for euthanasia or assisted suicide.
- Family members require guidance regarding care of their own needs for adequate rest and respite and should ideally have 24-hour access to the care team in case of uncontrolled symptoms and/or in the event of the death of the patient.

Emergency Provisions

- The family needs to know what to do and who to call in case of uncontrolled symptoms and/or in the event of the death of the patient.
- Twenty-four hour telephone availability of a member of the care team, or designated cover during the out of hours period, is essential.

Preparing the Family for the Dying Process

- When death is imminent, the family should be forewarned of the process that they are likely to witness.
  - Emphasis should be placed on changes in respiratory rate and pattern (a common cause of family distress) and the likelihood of diminished consciousness.
- The family should be informed that all attempts will be made to ensure that the patient will be peaceful and comfortable, and that the sustained cessation of breathing will be the sign that death has occurred.

Conflict Resolution

- Occasionally, in these circumstances hostile feelings and conflict develop between the grieving family and the healthcare providers.
- The most common conflict arises when a family member refuses to accept the moribund state of an incompetent patient and insists that everything possible be done to prolong the life of the patient.
  - Family meetings are important in this situation.
  - The healthcare providers must start by patiently listening to their concerns.
  - Distinction must be made between achievable and unachievable goals.

When Death Occurs

- If possible, adequate provision for family privacy and time with the body of the patient after death has occurred is desirable.
- Awareness and respect for personal, cultural and/or religious practices related to death is important, and provision for privacy and necessary cultural practices should be made.
- An offer of condolences from clinicians may be very comforting for a distressed family.

After a Patient Death

Family

- After the death of the patient, the family should be offered the opportunity to meet with the care providers to give them the opportunity to ventilate grief and discuss any outstanding concerns that they may harbour about the care delivered in the last days of life.

Staff Care

- The death of a patient stresses the physical and emotional resources of the professional staff.
- Staff require emotional recuperation, which can be facilitated by expressions of mutual support and appreciation, and debriefing.
- Debriefing should allow the clinicians to talk about their relationship and impressions of the patient and the family, express emotions and review hardships and successes in the care of the patient.

Conclusion

- Patients who are dying have a right to adequate relief of physical and psychological symptoms, and they and their families have a right to adequate support.
- The care of patients in the final stages of cancer requires a high level of clinical vigilance and skill and interdisciplinary cooperation in order to ensure that the passage from life to death is as free from suffering as possible.
- Participation in this process challenges the clinician's emotional resources and medical skills. There is, however, the potential for professional satisfaction in helping to orchestrate end-of-life care and provide a 'good death' or the 'least bad death'.

Declaration of Interest:

Professor Cherny has reported no potential conflicts of interest.

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Rehabilitation in Cancer – Role of Exercise and Nutrition

8

N.H. Hart[1,2,3,4]

N.M. Iyengar[5,6]

[1]*Caring Futures Institute, College of Nursing and Health Sciences, Flinders University, Adelaide, SA, Australia*
[2]*Cancer and Palliative Care Outcomes Centre, Queensland University of Technology, Brisbane, QLD, Australia*
[3]*School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia*
[4]*Institute for Health Research, University of Notre Dame Australia, Perth, WA, Australia*
[5]*Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA*
[6]*Department of Medicine, Weill Cornell Medical College, New York, NY, USA*

Safeguarding Exercise Capacity During and After Cancer Treatment

Introduction and Scope

Cancer incidence continues to increase worldwide due to a growing and ageing population. As a leading cause of morbidity and mortality, there were an estimated ~19 million new cancer diagnoses and ~10 million cancer deaths worldwide in 2020. With the continual development of new cancer treatments and the provision of current mainstay therapies, cancer patients and survivors are living longer, culminating in an estimated ~18 million people living with and beyond cancer in the United States alone; a magnitude relative to population size likely observed in other nations worldwide. Accordingly, this unique and growing patient population is the focus of quality survivorship care, with a diverse range of cancer-related consequences and long-term treatment toxicities negatively

impacting physical and psychosocial health. Accessible, affordable and effective strategies to reduce, prevent or reverse these deleterious outcomes are clinically important and urgently needed.

Impaired Cardiorespiratory Fitness

Cardiorespiratory dysfunction (reduced heart-lung health) is a common health and often subclinical consequence of cancer, underpinning compromised physical fitness, usually from primary cancers affecting cardiac, respiratory or pulmonary tissues (such as lung cancer), or from receiving targeted or systemic cancer treatments which damage these tissues (such as radiation or chemotherapy). Compromised cardiorespiratory fitness is clinically problematic, and directly associated with higher morbidity and mortality in cancer patients and survivors. Cytotoxic chemotherapeutic agents notoriously alter the quality of circulating oxygenated blood, reducing the capacity of skeletal and smooth muscle to function, inclusive of the heart. This can lead to a multitude of cardiorespiratory problems, including peri- and myocarditis, arrhythmia, cardiomyopathy, reduced ejection fraction, myocardial ischaemia or infarction, hypertension and heart failure. Radiotherapy to the chest and neighbouring areas can produce localised damage of cardiac, respiratory and pulmonary tissues. Endocrine therapies are also drivers of changes to muscle mass, quality and function, which may underpin increases in fatigue and reductions in physical activity as precursors to deterioration in cardiorespiratory fitness.

Reduced Muscle Mass and Strength

Muscle is the largest endocrine organ in the body, which also exerts dominance over bone as the primary source of regulatory mechanical load. Accordingly, the consequences of reduced muscle mass, quality and strength are considerable and widespread. Muscle wasting and cancer-induced sarcopaenia (cancer cachexia) are evident in up to 70% of cancer patients and survivors, depending on tumour type and assessment. Manifestly, low muscle mass underpins performance status and functional independence, and is associated with dose-limitation of cancer

treatments, increased incidence and severity of treatment toxicities (such as chemotherapy-induced peripheral neuropathy), cancer-related symptoms (such as cancer-related fatigue) and reduced responsiveness to cancer treatments, culminating in frailty, poor prognosis, reduced quality of life (QoL) and ultimately increased morbidity and mortality.

Increased Fat Mass

Excess subcutaneous and visceral adipose tissues are associated with worsened outcomes after cancer diagnosis in most cases, and, together with low muscle mass, comprise cancer-induced sarcopaenic obesity. Specifically, higher levels of fat mass are associated with cancer progression, greater treatment toxicities, dose-limitation of cancer treatments and reduced treatment efficacy. Furthermore, heightened trunk fat mass increases the incidence and prevalence of comorbidities (such as metabolic syndrome, type II diabetes and cardiovascular disease), culminating in poor overall and cancer-specific survival.

Reduced Bone Health

Muscle and bone are inextricably linked; thus, the deterioration of muscle mass, quality and strength promotes the loss of bone mass, quality and strength. Skeletal tissue is also the most common location for metastatic carcinomas to deposit and is a primary hallmark of multiple myeloma (myeloma bone disease). Indeed, changes in endocrine function induced by hormone therapy, cytotoxic chemotherapy and the pathogenic features of bone metastases all facilitate reduced bone health and compromised bone strength through dysregulating bone metabolism, via various mechanisms and at different rates. Unfortunately, these events lead to induced skeletal fragility and an increased potential for skeletal complications (such as bone pain, bone fracture and vertebral compression). Further, adult survivors of childhood cancers (such as acute lymphoblastic leukaemia and lymphoma) or adult haematological malignancies (such as Hodgkin and non-Hodgkin lymphoma) are also skeletally compromised, often due to treatment pathways (including stem cell transplantation) or intensive treatment regimens (such as chemotherapy).

Physical Activity and Cancer Outcomes

Physical activity, particularly of moderate-to-vigorous intensity, has been linked with reduced cancer incidence and recurrence, together with improved cancer control and patient/survivor health-related QoL. Over the past decade, a series of epidemiological studies have reported pre-diagnosis and post-diagnosis benefits observed in physically active persons, highlighting an association but not cause and effect or dose and response. Despite such observations, strong inferences derived from epidemiological studies must have a biological plausibility. Pre-diagnosis physical activity has been linked with tumour vessel normalisation at diagnosis, which may reduce cancer aggressiveness and its propensity to metastasise. Post-diagnosis physical activity has also been linked to reductions in all-cause and cancer-specific mortality ranging from approximately 26%-69%, depending on the type, duration and frequency of physical activity reported and tumour type investigated (e.g. breast, colorectal and prostate cancers). Similarly, physical activity during treatment has been linked to improved treatment completion rates, potentially underpinning observed higher survival rates in these cohorts. An array of biological mechanisms have been proposed, with early evidence provided through pre-clinical models, canvassing endogenous systemic or localised endocrine-paracrine or targeted anti-cancer effects. Pragmatic and randomised controlled clinical trials are needed.

Exercise as Medicine in the Management of Cancer

Exercise consists of purposeful, prescriptive and programmable activities of a specific nature, which are progressive and can deliver a precise dose to elicit a desired response. In particular, exercise uses multiple modalities and intensities to target multiple biophysical systems, and, as such, may influence numerous pathways implicated in the pathogenesis of cancer and its medical treatments. Exercise medicine for cancer patients and survivors has moderate-to-strong evidence from randomised controlled trials in the neoadjuvant and adjuvant settings to reduce, prevent and, in some cases, reverse cancer-driven adversities and treatment-related toxicities. Specifically, exercise is a safe medicine when prescribed and supervised by certified and accredited professionals, and has

been shown to improve aerobic fitness, increase muscle strength, reduce cancer-related fatigue, preserve bone mass, reduce fat mass, reduce anxiety and increase cancer-specific and health-related QoL.

A growing body of pre-clinical evidence supports the synergistic and independent ability of exercise to alter tumour biology and influence disease-specific endpoints including progression-free survival and overall survival. However, this line of inquiry is still in its infancy, with the underlying biological mechanisms yet to be fully elucidated. Furthermore, few clinical trials have been conducted, or are underway, seeking to translate the effects of exercise medicine on cancer-specific outcomes from pre-clinical animal models to human patients. For example, completed trials by Hart and colleagues (2017 and 2018) sought to suppress tumour growth in sites of sclerotic and osteolytic bone metastases through targeted exercise, with results imminent; and currently active, multicentre international trials in colorectal cancer (the CHALLENGE trial, led by Courneya and colleagues) and prostate cancer (the INTERVAL-GAP4 trial, led by Newton and colleagues) seeking to understand if physical activity or prescribed exercise can improve overall survival. These intensive human trials represent the first ventures into this field. However, more research investment and well-designed research trials are needed to develop high-quality evidence that will influence standard of care in clinical practice, inclusive of exercise oncology.

Owing to the large body of established evidence since 1985 through to the present day, national and international professional associations (Exercise and Sports Science Australia [ESSA] and the American College of Sports Medicine [ACSM]) have produced open-access updated clinical exercise guidelines for the provision of exercise medicine to cancer patients and survivors, emphasising that exercise medicine prescriptions must be tailored to target individual patient needs, avoiding generic guidelines. And, in 2022, the International Bone Metastases and Exercise Working Group (IBMEWG) released clinical exercise recommendations for healthcare providers and exercise professionals to support people with bone metastases to engage safely with prescribed exercise. To ensure cancer patients and survivors can access exercise, oncologist-facilitated referrals to qualified exercise and rehabilitation professionals provide a streamlined

approach to deliver tailored exercise prescriptions. In 2019, the ACSM published heir guiding document for oncologists to help their patients to access exercise services as they move through cancer.

Nutrition During Cancer Treatment and Follow-up

Introduction / Scope

Poor diet or nutrition practices are thought to contribute to the development and aggressiveness of cancer, in addition to reduced responsiveness to primary cancer therapies and increased toxicity profiles. In particular, the increasing worldwide pandemic of childhood and adult obesity underpins many chronic diseases including cancer, where a maladaptive metabolic state in obese individuals presents a negative cascade of consequences on optimal bodily function and repair, including a suboptimal or dysfunctional immune system. Further, specific types of cancers require specialist nutrition interventions, such as head and neck cancer patients and survivors with xerostomia, or prostate and breast cancer patients on hormone therapies. Similarly, advanced cancer patients or palliative cancer patients in pre-cachectic or cachectic states have specific nutritional requirements (such as effective mitigation of muscle wasting). Accordingly, accessible, affordable and effective nutritional strategies to support cancer patients and survivors during and following treatment are essential.

Role of Nutrition in Cancer Patients

Nutrition is an important component of supportive and palliative care, providing a critical foundation for cancer patients and survivors to complete and recover from treatment, and to engage with, and adapt from, physical activity or exercise. Diets that promote a reduction in systemic inflammation, provide adequate protein to mitigate muscle protein degradation (improving adaptation to exercise or preventing muscle wasting), or are high in satiety (to reduce feelings of hunger for patients aiming to lose weight) could be useful. Dietary interventions should be tailored to the individual cancer patient's needs. However, some general rules may include the reduced consumption of refined carbohydrates and saturated fats, selecting lean meat (such as skinless chicken and fish) over

processed meat, choosing complex carbohydrates (such as multigrain bread) rather than refined carbohydrates (like white bread) and limiting dietary fat intake. Cancer patients and survivors should also be encouraged to consume five or more servings of fruit and vegetables per day of different colours, and thereby maximise soluble fibre intake. Critically, cancer patients and survivors should limit alcohol consumption.

Nutrition Plans and Programmes During Oncology Treatment and Follow-up

In 2021, the European Society for Clinical Nutrition and Metabolism (ESPEN) and European Partnership for Action Against Cancer (EPAAC) released a thorough set of practical nutrition guidelines for cancer patients and survivors across the full disease trajectory, published in *Clinical Nutrition*. In 2020 the Clinical Oncology Society of Australia (COSA) also released their position statement on cancer-related malnutrition and sarcopaenia. And in 2021 the European Society for Medical Oncology (ESMO) released their clinical practice guidelines for cancer cachexia in adult patients. Together, these global guidelines focus on targeting malnutrition, the provision of nutritional support to minimise muscle-bone loss, and the use of nutrition to address metabolic derangements from cancer and its treatments that may underpin sarcopaenic obesity and other affiliated consequences, including cachexia. Beyond these multidisciplinary guidelines for clinicians, cancer patients and survivors are encouraged to attend food education programmes and cooking lessons tailored specifically to them to assist in lifestyle behaviour modification and adoption in the long term.

Lifestyle Changes During Cancer Treatment and Follow-up

Lifestyle and the Four Most Common Cancers: Breast, Colorectal, Lung and Prostate

Following a cancer diagnosis, patients are highly receptive to lifestyle modification recommendations or referrals by their treating oncologist or haematologist. Effective lifestyle modifications have the potential to

improve cancer outcome, treatment effectiveness and QoL, whether for curative intent or palliative treatment. For example, colorectal and prostate cancer patients should aim to lose weight through diet and exercise prior to surgery (if overweight or obese) to reduce the risk of complications and improve recovery time. Further, breast and prostate cancer patients receiving hormone therapy should engage in diet and exercise interventions to help increase or preserve muscle and bone mass and strength while preventing subcutaneous and visceral fat gain. In scenarios where patients receive chemotherapy and/or radiation, diet and exercise programmes before, during and following treatment may improve their ability to complete the treatment course, better tolerate treatment toxicities and improve recovery time. There are, of course, unique circumstances related to these cancers. For example, lymphoedema is a common problem for breast cancer patients, whereas urinary incontinence and sexual dysfunction are common problems for colorectal and prostate cancer patients. However, most cancer centres have specialist nurses or practitioners capable of managing these unique pathologies. Lastly, lung cancer patients present a unique challenge. For example, aerobic exercise can be poorly tolerated due to the presence of tumour (and/or scar tissue) in the lungs; thus resistance exercise may be preferred in this patient population.

How to improve Quality of Life During Cancer Treatment and Follow-up: Measures and Practical Advice

Exercise and nutrition programmes are clearly beneficial for most cancer patients and survivors; however, despite overwhelming evidence underpinning improvements in cancer-specific and health-related quality of life when incorporated within supportive and palliative care, there remains a strong need to develop appropriate healthcare and operational systems, referral pathways and accessible programmes for patients that are relatively inexpensive. A key challenge is to reduce barriers and increase awareness, while providing education and clear pathways for clinicians to follow in otherwise time-restricted conditions. In essence, clinicians could aspire to include baseline assessments of physical activity and nutrition and periodically reassess patient lifestyle changes throughout

their cancer journey. Similarly, cancer patients and survivors should seek advice from certified or accredited clinical exercise physiologists and practising dieticians to optimise their cancer care plan.

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Living With and Beyond Cancer

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C. Massarotti[1]

S.M. Smith[2]

M. Lambertini[3]

L. Schapira[4]

[1]*Physiopathology of Human Reproduction Unit, IRCCS Ospedale Policlinico San Martino, Genova; Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health (DINOGMI), School of Medicine, University of Genova, Genova, Italy*

[2]*Division of Hematology/Oncology, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, USA*

[3]*Department of Medical Oncology, Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova; Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genova, Italy*

[4]*Division of Medical Oncology, Department of Medicine, Stanford University School of Medicine, Stanford Cancer Institute, Stanford, CA, USA*

During the last two decades, a continued improvement in cancer survival has been observed, as a result of both early detection and more effective treatments. With increased lifespan comes an increased need to address potential late adverse effects of therapies, such as gonadotoxicity and cognitive impairment, and their impact on the quality of life (QoL) of long-term survivors. The discussion of possible long-term and late effects is an important part of oncology consultations before, during and after anticancer therapies.

Reproductive Issues

Need for Fertility Consultation in Cancer Patients

Cancer diagnosis in patients of reproductive age is associated with potential adverse effects of treatments on gonadal and reproductive function;

therefore, ovarian function and/or fertility preservation are recognised as important issues to be addressed. Several scientific societies have developed specific guidelines focused on ovarian function and/or fertility preservation to emphasise the importance of oncofertility counselling in all young women with cancer who are candidates for treatments potentially gonadotoxic. A specific checklist for helping physicians during oncofertility counselling was recently prepared by EU-REFER (EUropean REcommendations for female FERtility), a network of fertility specialists.

Cryopreservation techniques have been used for fertility preservation since the late 1990s: sperm, embryo and oocyte preservation before therapies are considered standard techniques, while ovarian tissue cryopreservation is still labelled as 'experimental' in most countries even if more than 100 live births have occurred following re-implantation. Moreover, the use of gonadotropin-releasing hormone (GnRH) agonists during chemotherapy is recommended as a strategy for preserving ovarian function in young breast cancer patients, with more limited and controversial evidence in women with other diseases.

The only fertility preservation method currently available for adult males and pubertal boys is sperm cryopreservation before gonadotoxic therapies. For women, instead, the indication to use one or more of the available techniques varies depending on numerous factors, among them age and ovarian reserve at the time of diagnosis, type of cancer, proposed anticancer therapies, and the woman's plan for future childbearing. Therefore, oncofertility counselling should always be individualised and performed by a multidisciplinary team that must include a reproductive medicine specialist. While pre-treatment oncofertility counselling has been adopted as standard of care in most European countries, less attention is given to the role of oncofertility specialists in the care of survivors. Indeed, cancer survivors report several gynaecological issues that would benefit from long-term follow-up in a unit with expertise in sexual and reproductive health, such as low rates of overall sexual satisfaction, decreased contraception prescription and compliance, increased use of emergency contraception, as well as poor management of postmenopausal symptoms. In this scenario, cancer patients require counselling during and after therapies, even when they do not want

(or cannot yet have) a pregnancy, highlighting the need for expertise in sexual and reproductive health. Continuity of care could, ultimately, also increase the reproductive potential, empowering women to make deliberate and informed choices on when and how to attempt a pregnancy if desired, but also offer much needed support for other gynaecological issues like effective contraception, both areas known to improve QoL.

Fertility Issues

Fertility evaluation in cancer patients must be done by a specialist in reproductive medicine and personalised for every patient. Sperm analysis concomitant with the cryopreservation procedure estimates reproductive potential in men. Age, antral follicular count (AFC) and anti-Müllerian hormone (AMH) levels are predictors of ovarian reserve and of response to a controlled ovarian stimulation for fertility preservation. Based on this information and on the expected gonadotoxicity of anticancer therapies, the reproductive medicine physician counsels the patient about the opportunity to undergo a fertility preservation procedure. Women with poor ovarian reserve at baseline are less likely to retain spontaneous fertility after treatment and also less likely to respond optimally to fertility preservation procedures. Cryopreservation procedures represent an extra chance in case of premature ovarian insufficiency or azoospermia following therapies. The utilisation rate for frozen embryos is reported to be 10%-23% in small cohorts of cancer patients, cryopreserved sperm is used by 4%-10% of patients, while data about frozen oocytes and ovarian tissue utilisation rates, although still incomplete and inconclusive, are around 5%. For *BRCA*-mutated patients, reproductive technologies have the further advantage of enabling pre-implantation genetic testing (PGT-M) to avoid transmitting the mutation to the offspring.

GnRH agonists during chemotherapy have the advantage of helping women retain not only fertility but also ovarian function, thus avoiding the numerous adverse effects of premature ovarian insufficiency. Hence, they can also be offered to women who have completed their reproductive plans and are not interested in fertility preservation but are concerned about the risk of developing premature ovarian insufficiency.

Pregnancy in Cancer Survivors

The likelihood of pregnancy in women with a prior cancer diagnosis is reduced by ~38% compared with the general population of similar age. This is partially due to fertility issues and partially to traditional reservations about the long-term safety of pregnancy after hormone-sensitive cancers. The most recent data suggest that pregnancy is safe in women with hormone receptor-positive breast cancers. However, 5 to 10 years of adjuvant endocrine therapy result in a negative effect on women's fertility, not only as a consequence of exposure to gonadotoxic therapies but also due to age-related physiological decrease in fertility. The POSITIVE study, an international prospective clinical trial, is investigating the safety of temporary interruption of endocrine therapy (up to 2 years) to attempt a pregnancy. The study's primary aim is to investigate the risk of breast cancer recurrence and secondary aims are the evaluation of various fertility- and pregnancy-related endpoints. The POSITIVE study is currently ongoing with an estimated enrolment of 500 patients.

Importantly, only the collaboration between women, reproductive medicine specialists and oncologists can minimise the risks and maximise the chances of success. There is no perfect time to try for a pregnancy after cancer and only the combination of information about the individual risk of relapse and the individual woman-specific reproductive potential should be used to counsel women on the safety and chances of pregnancy. Thanks to the information acquired from a multidisciplinary, long-term model of care, the patient can be adequately counselled on the best way to achieve a pregnancy (i.e. trying to conceive spontaneously versus using reproductive technologies or her cryopreserved material versus using an oocyte donor and/or a gestational carrier). Reported birth outcomes after prior exposure to anticancer therapies appear similar to the ones expected in the healthy population, but some studies have reported an increased risk of premature delivery and low birthweight of the newborn in cancer patients, particularly those who conceive within 1 year following the completion of anticancer therapies. Hence, pregnancies in cancer patients should be followed more closely than those in the healthy population.

Cognitive Impairment After Cancer Treatment

Cancer-related cognitive impairment refers to a syndrome of neurological deficits associated with cancer or cancer treatment. Deficits classically include difficulties with memory, processing speed, attention and executive function.

Estimates of the incidence of cancer-related cognitive impairment vary widely across studies, ranging from 15% to more than 75% of cancer survivors. This variability is related to differences across disease types (central nervous system versus other disease sites), treatment modalities (cytotoxic chemotherapy, endocrine therapy, radiation therapy) and personal predisposing factors including age and psychological conditions. Some patients present with cognitive impairment at the time of diagnosis, while others develop impairments during or following cancer treatment. Cognitive impairment can be diagnosed objectively with formal neuropsychological testing, or subjectively based on patient-reported outcomes. Patients tend to report greater deficits than are apparent on objective tests, contributing to the variability in incidence reported in the literature.

Magnitude of the Problem

Based on objective neuropsychological testing, most cancer-related cognitive impairments are considered mild or moderate in severity. Regardless of objective severity, deficits can have a substantial impact on cancer survivors' QoL and daily functioning, impacting their ability to fulfil social and occupational responsibilities. Duration of symptoms is variable; some impairments resolve within months after completion of cancer therapy, while others persist for many years. Neuroimaging studies have shown structural changes more than 10 years after completion of cancer therapy. Emerging research is focusing on elucidating the neurobiological basis for cancer-related cognitive impairment, with the aim of identifying risk factors and therapeutic targets.

Treatment

Treatment of cancer-related cognitive impairment includes behavioural and pharmacological interventions. While there have been a number of

studies, primarily among breast cancer survivors and brain tumour survivors, the quality of the data is limited and there is no consensus on the best therapy. Behavioural approaches include cognitive rehabilitation (repeated individual or group sessions with a trained clinician), cognitive training (skills-based exercises conducted in-person or remotely) and physical activity interventions. Pharmacological approaches are another area of active research. In small studies, stimulants such as methylphenidate have shown some benefit in a subset of childhood cancer survivors and adults with brain tumours, but no or minimal benefits were seen in breast or ovarian cancer survivors. Dementia medications such as donepezil have shown improvement in memory in breast cancer survivors in a small study and a larger more definitive trial is ongoing. Given the prevalence and associated morbidity of cancer-related cognitive impairment, there is a need for more rigorous interventional trials to inform treatment and management.

Survivor Care Plans

A major challenge identified by cancer survivors is the transition that follows the end of active treatment given with curative intent. An essential task is to resume care with their general practitioner or primary care physician.

Coordination of Care

To enhance communication among patients, general practitioners and oncologists, the U.S. Institute of Medicine (now National Academy of Medicine) published a report in 2006 recommending that every patient receive a Survivor Care Plan (SCP). The impetus for the care plan was derived from use in paediatric oncology models and was intended to provide succinct information about prior exposures and ongoing concerns that would facilitate customisation of surveillance and general health maintenance. Despite prompting a decade of research, the evidence of benefit of SCPs on health outcome is patchy, while it is clear that they have not been consistently implemented or integrated into primary care practice. SCPs have the potential to assist patients as they re-establish care with their general practitioner after completing cancer-directed therapy.

Resources and Services for Cancer Survivors

While most agree there is a need to provide supportive care interventions and resources to patients and family caregivers across the disease continuum, these are often not available at the point of care or are unaffordable. Cancer survivorship programmes are intended to assist with referrals that are specific to this population, such as physical rehabilitation, sexual health and fertility, psycho-oncology, nutrition, as well as disease-specific symptom management. Recognising the shortages in skilled clinicians and funding sources, many centres are now developing programmes in self-management. Through supportive interventions as well as psychoeducation delivered in groups or individually, together with referrals to specialists, cancer survivorship programmes create a supportive and collaborative environment to assist recovery after cancer treatment. Oncofertility units can provide counselling and guidance about family planning, in addition to skilled reproductive assistance services and gynaecological care. Many cancer centres provide survivorship care in collaboration with palliative care and supportive services.

Models of Survivorship Care

Cancer survivors vary in their needs for specialised services and resources and current efforts across many countries are exploring ways of providing appropriate referrals based on models of risk stratification. To date, there are no standard algorithms or guidelines that have been vetted for clinical use and are applicable to the diverse population of cancer survivors, and this remains an area of active research.

There are several models for delivering medical care to cancer survivors and these involve cancer clinicians as well as general practitioners. Cancer survivors may be referred to a survivorship clinic led by a general practitioner, an oncology clinician or a multidisciplinary team, while others continue to receive follow-up care from their cancer care team. Primary care physicians are ideally situated to handle chronic health problems and to coordinate care. Efforts are underway to integrate survivorship care into the scope of primary care practice and to develop shared and collaborative care models between generalists and cancer clinicians.

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Dr Smith has reported no potential conflicts of interest.
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Professor Schapira has reported no potential conflicts of interest.

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Ethics in Supportive and Palliative Care

10

I. Boukovinas[1]

E. Angellier[2]

[1]*Bioclinic Thessaloniki, Thessaloniki, Greece*
[2]*Institut Curie, Saint Cloud, France*

Every year approximately 2.5 million people die from terminal illnesses in Europe (1.5 million due to cancer). On each occasion, the medical team and the patient's loved ones are faced with a unique story. We can help them to make decisions at the end of life by dedicating to them a unique strategy that considers the elements of their medico-bio-psycho-social history:

- What do we expect from treatments? From our experience, how can we evaluate their comfort and needs? Is there a plan in place to support care at the end of life?
- How can we evaluate the patient's trust, abilities (to understand, appraise, reason and choose), thoughts and beliefs? Can he/she tell us, or do we have a surrogate decision maker in place or documentation of previously expressed preferences?
- What do we, as a team, think and believe? Do teams need more education in ethics to act with patients' preferences placed before their own, and to listen without judgement to what patients have to say? If the patient's preferred place of death is home, can the team refuse to support if they consider it 'dangerous', for example in the face of overwhelming symptoms?
- What informs decision-making? What does the law state and what are the societal norms?

Respect for Autonomy and Consent

While not the only ethical principle to understand and apply, the idea of patient autonomy plays a central role in the patient-physician relationship. Stahl et al (2017) illustrate this point: they assert that patients have a right to choose the healthcare services they need for their own *wellbeing*, and physicians have a corollary obligation to accommodate the patient's choices, either by providing the requested interventions directly or by referring the patient to someone who will. By contrast, the way we were educated calls on us to act reasonably to preserve and restore the patient's health and refuse to act otherwise. Physicians can succeed in this task only if they practice in accordance with their conscience. It is essential, in addition to possessing the virtues of truth, to be aware of the dynamics of the temporal nature of the truth and the relevance of the nature of the patient's autonomy.

Our technology-driven society has forgotten something that scholars call the 'dying role', and the importance of this role for people when life is ending. People want to share memories, transmit wisdom, gift keepsakes, solve problems in relationships, organise their inheritance, make peace with their god, and make sure the people they leave behind will be fine. They want to finish their story on their own terms.

To deny this dying role, often in an attempt by the clinician to 'keep the hope alive' or for fear of the reaction to being truthful, is to deny people of things, thoughts, actions, proposals and pilgrimages that offer significant value at the end of life over pursuing treatments of unlikely benefit.

The history of consent is rooted in Europe in the history of individualisation. It is formalised almost 'as a response to' scandals in care or research, paternalism, medical atrocities of the 20th century, and fully integrates the field of healthcare, with particular reference to regulation and law. The European Court of Human Rights and the Oviedo Convention, signed and ratified by 16 of the 28 EU countries, and signed without ratification by 5 others, insist on it, and both relate to the principle of autonomy as a quasi-absolute. They leave much to the states to regulate the details of information and the fields of consent (care, research, medical data) but, by insisting on this value, they relegate to the background

the three other fundamental values of medical ethics which are beneficence, justice and non-maleficence. Reducing the ethics of care to that of consent risks leading to minimalist ethics (Callahan, 1981).

The French National Consultative Ethics Committee (2005) defines three levels of autonomy that allow us to move forward in thinking:

- Autonomy of action – we could resume it to a physical autonomy, i.e. the ability and the power to act
- Autonomy of thought – the power to conduct a coherent and reflective argument, a deliberation, through the acquisition of knowledge of one's illness and the exercise of one's critical mind
- Autonomy of will – the ability to decide on an alternative and take initiatives.

Two pitfalls hinder autonomy: (1) public health imperatives, which place the value of justice in the foreground – for example, the increasing costs of healthcare leads to questioning the patient's freedom to engage in it, particularly in the absence of real effectiveness; and (2) patient vulnerability. The model of an egalitarian contract between the two protagonists is not operative. Moreover, doctors have a duty (Beauchamp and Childress, 1979) attached to the benevolent promotion of human wellbeing, a human being understood in his/her interdependence with other humans, and in community.

Risks are also emerging, such as leaving the patient alone to decide, with the risk of transferring responsibility. One can wonder whether the absolutisation of autonomy is not the expression of an individualistic ideology where each person is left alone and abandoned to the anguish of his or her own free choice? (Engelhard, 1996).

The European Court of Human Rights considers that the imposition of medical treatment without the consent of the patient – adult and of sound mind – constitutes an infringement of the physical integrity of the person concerned, which may call into question the rights protected by Article 8 of the European Convention on Human Rights (https://www.echr.coe.int/documents/guide_art_8_eng.pdf) and Article 5 of the Oviedo Convention (https://rm.coe.int/168007cf98), which stipulates that: "An intervention in the health field may only be carried out

after the person concerned has given free and informed consent to it. This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. The person concerned may freely withdraw consent at any time."

Withholding or Withdrawing Life-prolonging Treatment

In Europe, some countries authorise or recommend withdrawing or withholding potentially life-sustaining treatments, including hydration and nutrition (at the time of publication: France, United Kingdom, Portugal, Norway, Denmark, Hungary, Spain, Sweden, Germany and Austria), while in other countries this is not permitted by law.

As an example, is clinically assisted hydration and/or nutrition considered to be a treatment or basic care? Some elements can help us to discern: can the patient feed themself alone or not at all? What is the stage of their illness? Is the patient still receiving anticancer treatments or have all such treatments been discontinued? One must consider the risks (oedema, fluid overload, the need to undergo an interventional procedure) versus the benefits in terms of life extension and symptom control and, importantly, the patient's view. Sometimes a collective discussion is necessary, to review the benefit/risk balance, the aim (is it life duration or quality of life?) and wishes of the patient and their family, the disease stage, and the medical team's understanding of the treatment objectives.

Supporting Healthcare Professionals to Manage Patients and Their Families at the End of Life

Patients and their families know that every life ends in death. They also assume that doctors will tell them when time is running short and, if they want to be told, what to expect, and how to best navigate these unexplored and frightening waters.

So, doctors will have to engage with the fact that death is inevitable, and as their patients approach the end of their life, it could be precious

to restore their dignity to the extent it was accepted traditionally when death was considered as a natural fact, the flip side of life.

But most physicians have not been trained in these aspects of the human experience. Medical school and residency have historically provided little or no training on how to continue to care for patients when disease-modifying treatments no longer work. To change attitude, we must improve the education and training of young physicians and their professional and clinical culture, to help them develop a set of competencies and essential tasks in palliative care. We could also help teams with supervision and practice analysis, which is often done in palliative care teams but not in oncology teams. The request for 'unnecessary' treatment is something that challenges a doctor: he/she has no obligation to provide a treatment that is considered futile, especially when resources are limited.

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Dr Boukovinas has reported no conflicts of interest.
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Further Reading

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Research in Supportive and Palliative Care

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C.H. Ruhlmann[1,2]

J. Herrstedt[3,4]

[1]*Department of Oncology, Odense University Hospital, Odense, Denmark*
[2]*Department of Clinical Research, University of Southern Denmark, Odense, Denmark*
[3]*Department of Clinical Oncology and Palliative Care Units, Zealand University Hospital Roskilde and Naestved, Roskilde, Denmark*
[4]*Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark*

There were an estimated 4 400 000 new cancer cases in Europe in 2020 (GLOBOCAN) and approximately 45% of these were aged 70 years or more. This number is expected to increase to approximately 5 300 000 in 2040. Because almost 100% of the increase will be in the 70+ years age group, the percentage of cancer patients aged 70 years or above is expected to increase to 55% in 2040. The number of cancer deaths was approximately 2 000 000 in 2020 and, despite the significant increase in incidence, only a minor increase in cancer mortality is expected due to improvements in diagnosis and treatment. This means that the typical future cancer patient will be old (55% in the 70+ years age group in 2040) and belong to the group of long-term survivors. Research efforts that have led to the approval of successful cancer treatments have often excluded older, frail and comorbid patients, hence there is an urgent need for cancer research in this rapidly growing population of older patients.

The scope of this chapter does not allow for an exhaustive listing of all the research issues in supportive and palliative care. However, in the following sections some of the important ones are highlighted.

Ongoing Research

Older Cancer Patients

Several problems exist when selecting antineoplastic therapy in older patients. Age-related organ deficiency, comorbidities and polypharmacy must be considered. Several tools have been developed to optimise decision-making. Geriatric assessment has been validated as a useful tool but is time-consuming. Current research focuses on the need for a simpler instrument to use in daily practice. The G8 questionnaire can be completed in less than 5 minutes and can be used to select older cancer patients in need of a full geriatric assessment. The average European cancer patient over 70 years old has three comorbidities, often resulting in polypharmacy. Several ongoing studies are investigating polypharmacy, potential inappropriate medications (PIMs) and drug-drug interactions, and the significance of drug-related adverse events (AEs) resulting in reduced tolerability to antineoplastic therapy and unplanned hospitalisation. Biological assessment is a growing research area and biomarkers, such as the *ARAP1* gene, activin A and myostatin, are candidates for future research.

Cardiotoxicity

Cardiac disease is the most frequent non-malignant cause of death in cancer survivors and treatment-induced cardiotoxicity is often the main cause or a contributing factor. Although many of the newer targeted agents are cardiotoxic, cardiomyopathy and heart failure are mostly driven by the use of conventional antineoplastic agents, in particular anthracyclines. According to a study using left ventricular global longitudinal strain with either cardiac magnetic resonance or three-dimensional speckle tracking echocardiography, it was possible to diagnose myocardial damage before a decrease in left ventricular ejection fraction could be measured. Larger randomised studies using one of these modalities are ongoing.

Chemotherapy-induced Peripheral Neurotoxicity

A number of antineoplastic agents induce peripheral neurotoxicity, which is often irreversible and treatment-symptomatic. Fifty-five studies

are registered on ClinicalTrials.gov as recruiting and approximately one third of these focus on one of two different preventive strategies. Some of these trials are investigating early diagnosis of chemotherapy-induced peripheral neurotoxicity (CIPN), before nerve damage becomes symptomatic. Early diagnosis will enable the treating physician to change the antineoplastic treatment to a non-neurotoxic regimen. Other studies are investigating the effect of potentially CIPN-preventive drugs such as ganglioside-monosialic acid, calmangafodipir and cannabinoids.

Quality of Life

Research that includes patients with advanced disease is an expanding area and there is an increased awareness of quality of life (QoL) and symptom control as required outcomes in clinical trials. QoL and symptom control are measured by validated patient-reported outcome (PRO) tools depending on the specific study (e.g. European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30, EQ-5D, McGill Quality of Life Questionnaire, Hospital Anxiety and Depression Scale, etc). At the time of publication, approximately 520 phase III ongoing clinical trials (various cancer treatment interventions) include QoL assessments. However, very few of these trials have QoL as the key primary endpoint. For future studies, depending on the stage of disease and line of therapy, QoL should be treated as a primary endpoint in the same way as treatment efficacy.

Areas of Greatest Need

Palliative Treatment and End-of-Life Care

The need for supportive and palliative care during a cancer patient's life fluctuates, reflecting not only the progression of the disease but also the specific physical and non-physical needs of the patient. While moving from management of treatment-related AEs to management of symptoms induced by progressive disease and ultimately to end-of-life care, the scientific level of evidence decreases. Usually, there are no opposing ethical issues in conducting randomised, placebo-controlled clinical trials (e.g. an antiemetic clinical trial) in patients undergoing curative or early palliative treatment, and as a result the level of evidence will

be high. However, patients with end-stage disease are often fragile and vulnerable, and the ethical aspects of a randomised clinical trial in this setting will often hamper the set-up and approval of otherwise important trials for the improvement of cancer-related symptoms; hence the evidence for symptom control will remain low. Data from qualitative studies as well as from randomised controlled trials indicate that patients with advanced disease are not reluctant to participate in clinical trials. The time might be ready for a paradigm shift as researchers become aware of patients' willingness for trial participation. Moreover, clinical validation, comparison and accuracy testing of prognostication tools is warranted to help patients and clinicians in the decision-making process on further aggressive antineoplastic treatment for late-stage disease.

Toxicity Induced by Targeted Therapies Including Immune Checkpoint Inhibitors

During the last decade, new targeted therapies have been introduced and their indications for use are expanding. While AEs from kinase inhibitors, poly(ADP-ribose) polymerase (PARP) inhibitors and immune checkpoint inhibitors (ICIs) are well described in terms of acute toxicity and during short-term follow-up, little is known about the risk and management of long-term side effects in a population of long-term survivors that is still growing.

Following the introduction of ICIs, a new set of AEs, immune-related AEs (irAEs), appeared. Their management is based on the treatment of idiopathic autoimmune disease, and little is known about potential chronic immune-related complications. In the era of expanding indications for the use of ICIs, the population of patients with durable responses will increase, and in turn the population of patients living with irreversible irAEs (e.g. thyroid dysfunction, diabetes, pituitary dysfunction) will increase. There is a need for real-life assessment of long-term irAEs and QoL, as well as studies focusing on early detection of the rare and life-threatening irAEs where early and aggressive treatment is crucial to the outcome. Furthermore, studies designed for the treatment of specific irAEs are warranted to generate evidence on treatment options, dosage and duration of treatment, as well as the risks and benefits of rechallenging with immunotherapy.

Declaration of Interest:

Dr Ruhlmann has received an honorarium from Swedish Orphan Biovitrum.
Dr Herrstedt has received an honorarium from Swedish Orphan Biovitrum

Further Reading

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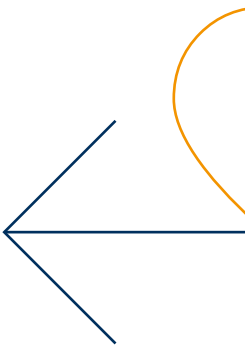
ESMO HANDBOOK OF SUPPORTIVE & PALLIATIVE CARE

Edited by Snežana M Bošnjak, Ivana Bozovic-Spasojevic, Giannis Mountzios and Jayne Wood

There is now substantial evidence that the early provision of supportive and palliative care integrated with oncological care for patients with a diagnosis of cancer improves quality of life, symptom management and life expectancy. The role of the oncologist is to consider the impact of the disease and treatment on each patient's life while delivering the best quality anticancer treatment. This requires the development of skills in supportive and palliative care, the adoption of a fully integrated, multidisciplinary model of working and a philosophy of care whereby the focus is on the integration of patient- and cancer-directed interventions. In the ever-changing landscape of anticancer treatments, we must rise to the challenge to ensure that our patients receive patient-centred, holistic, individualised care to achieve the very best clinical outcomes.



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