The essentials of acute oncology

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ABSTRACT

The general medical physician will often encounter patients who develop acute complications of their cancer diagnosis or anti-cancer treatment. Here we provide an overview of emergency solid tumour oncology to guide the initial management of these patients.

Introduction

Acute oncology describes a systematic approach to the investigation and management of patients who develop complications of their cancer diagnosis or anti-cancer treatment. This is a rapidly evolving landscape following the development of novel radiation and systemic anti-cancer therapies, which often have new and unpredictable toxicities. Given the rising incidence and prevalence of cancer, and the fact that most patients present to their local hospital with acute complications, this is increasingly relevant to general medical physicians. In this review, we provide an overview of emergency solid tumour oncology to guide the initial management of patients outside of cancer centres.

New cancer diagnosis or cancer progression

Metastatic spinal cord compression

Metastatic spinal cord compression (MSCC) occurs in 3–5% of patients with cancer.[1] MSCC is caused by epidural extension of vertebral metastases or following pathological compression fractures. MSCC is a medical emergency, because prompt investigation and early diagnosis facilitate the delivery of palliative therapies, which minimise symptoms and the risk of irreversible neurological disability.[2] MSCC is most common in breast, lung and prostate cancer, lymphoma or myeloma, but should be urgently investigated in any patient with cancer presenting with red flag symptoms (Table 1).[3,4]

Definitive investigation is a whole-spine magnetic resonance imaging (MRI) scan within 24 h of presentation, because patients can present with multilevel disease. Initial management comprises dexamethasone (16 mg followed by 8 mg twice daily) with proton pump inhibitor (PPI) cover, analgesics and antiemetics. Steroids should be avoided before biopsy in patients in whom a new diagnosis of lymphoma is suspected. All patients should be discussed with the neurosurgical team for assessment of spinal stability. In patients with no known cancer diagnosis, full radiographic staging should be performed to identify a primary cancer and suitable biopsy site. Tumour markers, including serum paraprotein, prostate-specific antigen (PSA), alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), human chorionic gonadotrophin (hCG) and cancer antigen 125 (CA125), can aid diagnosis.

The choice of therapy for MSCC is multifactorial, including the intrinsic radiosensitivity of the primary tumour, patient prognosis, the severity of MSCC, and spinal stability. In general, patients with good performance status and single-level disease should be offered neurosurgical decompression. Patients with poor performance status and multilevel disease are usually better candidates for palliative radiotherapy. Pretreatment neurological function is the strongest predictive factor for neurological outcome.[5] Median overall survival has been estimated at 6 months and is better in ambulant versus non-ambulant patients.[6]

Key points

Patients with cancer presenting with back pain and red-flag symptoms should have a whole-spine MRI scan within 24 h of presentation.

Neutropenic sepsis should be suspected in any unwell patient with cancer within 60 days of receiving systemic anti-cancer therapy; patients should receive broad-spectrum intravenous antibiotics within 1 h and should not wait for full blood count results.

Patients with cancer are often prescribed glucocorticoids, especially as supportive care; all unwell patients should be assessed for adrenal insufficiency.

Do not assume that nausea and vomiting are always treatment related; consider other differential diagnoses.

Multiple targeted drugs have recently been identified with an elevated risk of pneumonitis and this should be carefully investigated for in any patient presenting with breathlessness or a dry cough.

KEYWORDS: Acute oncology, red flag, neutropenic sepsis, adrenal insufficiency, pneumonitis

DOI: 10.7861/clinmed.2022-0561

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Table 1. Investigation and management of common cancer-related emergencies[3,4]

Cancers most commonly causing particular complication	Presenting symptoms and signs	Investigations	Management
MSCC			
Breast cancer Lung cancer Lymphoma Myeloma Prostate cancer	Persistent back pain Limb weakness Sensory loss Bladder dysfunction Altered bowel habit Loss of anal tone	FBC, U/E, clotting, group and save, calcium Whole-spine MRI Post-void bladder scan Rectal examination Consider CT CAP + PSA, hCG, AFP, LDH, CA 125 and serum paraprotein if no known malignancy	Manage patient lying flat with neutral spinal alignment Dexamethasone (16 mg – >8mg BD) + PPI cover Analgesia Antiemetics Discuss spinal stability with neurosurgeons Venous thromboprophylaxis as per local guidelines
Raised ICP and vasogenic oedema			
Breast cancer Cancer of unknown primary Colon cancer Lung cancer Melanoma	Headache Vomiting Changes in vision Seizures Decreased GCS VIth nerve palsy Papilledema Cushing's reflex	FBC, U/E, LFT, blood sugar, bone profile, clotting, group and save Chest X-ray Urgent CT/MRI of head Consider CT CAP + PSA, hCG, AFP, LDH and CA 125 if no known malignancy	Elevate head of bed to 30° Dexamethasone (16 mg – >8 mg BD) + PPI cover Analgesia Antiemetics Discuss with neurosurgeons if any signs of midline shift, cerebral oedema, hydrocephalus and/or acute haemorrhage Discuss with ITU if GCS score <12 and keep nil by mouth Aim for euvolaemia Consider hypertonic saline and mannitol in refractory cases
SVCO			
Breast cancer Germ cell tumours Lung cancer Lymphoma Thymic cancers	Shortness of breath Cough Dysphagia Head, neck and upper limb oedema Cyanosis Stridor Non-pustatile JVP	FBC, U/E, LFT, clotting, group and save Chest X-ray CT scan of chest with contrast Consider CT CAP + PSA, hCG, AFP, LDH and CA 125 if no known malignancy	If patient has known malignancy, consider dexamethasone (16 mg – >8 mg BD) + PPI cover O_2 if hypoxic Endovascular stenting Radiotherapy Chemotherapy
Malignant hypercalcaemia			
Breast cancer Lung cancer Myeloma Renal cell carcinoma	Depression Nausea and vomiting Constipation Abdominal pain Polydipsia/polyuria Dehydration Confusion	Serum total calcium, PTH, PTHrP, PO4, vitamin D, U/E, albumin ECG Consider CT CAP + PSA, hCG, AFP, LDH and CA 125 and serum paraprotein if no known malignancy	Intravenous fluids for 24 h Review nephrotoxic medication First line: bisphosphonates as per local trust guidelines In refractory cases, repeat bisphosphonates, calcitonin, glucocorticoids or denosumab (off-label indication) can be trialed Seek endocrinology advice

AFP = alpha fetoprotein; BD = twice daily; CA 125 = cancer antigen 125; CAP = chest, abdomen, and pelvis; CT = computed tomography; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FBC = full blood count; GCS = Glasgow Coma Score; hCG = human chorionic gonadotrophin; ITU = intensive treatment unit; JVP, jugular venous pressure; LDH = lactate dehydrogenase; LFT = liver function test; MRI = magnetic resonance imaging; PPI = protein pump inhibitor; PSA = prostate-specific antigen; PTH = parathyroid hormone; PTHrP = parathyroid hormone-related peptide; U/E = urea/electrolytes.

Vasogenic oedema and raised intracranial pressure

Vasogenic oedema and raised intracranial pressure (ICP) can complicate primary brain tumours and secondary brain metastases. Vasogenic oedema is caused by disruption of the blood–brain barrier following tumour secretion of a variety of angiogenic factors, such as vascular endothelial growth factor (VEGF).[7] Raised ICP occurs following tumour mass effect or obstructive

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Table 2. Investigation and management of common treatment-related toxicities[3,4,18]

Anti-cancer therapies most commonly causing particular complication	Initial investigations	Differential diagnoses	Grading	Management
Nausea and vomiting				
Cranial radiotherapy Abdominal radiotherapy Chemotherapies: Carboplatin Clofarabine Cisplatin Cyclophosphamide Docetaxel Epirubicin Ifosfamide Irinotecan Melphalan Methotrexate Oxaliplatin Streptozocin	Bloods including FBC, U/E, bone profile, blood cultures if clinically indicated Consider: AXR CT scan of head	Hypercalcaemia Raised intracranial pressure Bowel obstruction Gastrointestinal infection	Grade 1: Loss of appetite without alteration in eating habits; intervention not indicated Grade 2: Oral intake decreased without significant weight loss, dehydration or malnutrition; outpatient IV hydration; medical intervention indicated Grade 3: Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalisation indicated Grade 4: Life-threatening consequences	**Grade 1, 2** Assess for clinical or biochemical dehydration Do not assume that nausea and vomiting are always treatment related; consider other differential diagnoses Prescribe appropriate anti-emetic for diagnosis, in line with local guidelines Avoid using cyclizine with metoclopramide or domperidone (antagonistic effects) Prescribe only one of antiemetics with similar actions (eg domperidone/metoclopramide, levomepromazine/olanzapine) **Grade 3, 4** Intravenous fluids, additional and parenteral antiemetics in line with local guidelines Consider syringe driver
Diarrhoea				
Abdominal/pelvic radiotherapy 5-Fluorouracil Capecitabine	Bloods, including FBC, U/E, bone profile and magnesium Stool cultures for microscopy, sensitivity and culture, viral PCR and ova, cysts and parasites *Clostridium difficile* testing and abdominal X-ray should be performed if clinically indicated If grade 3 or above, consider sigmoidoscopy if no improvement after 24–48 h	Gastrointestinal infection Constipation with overflow diarrhoea Hyperthyroidism Inflammatory bowel disease Celiac disease Ischaemic colitis	Grade 1: increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline Grade 2: increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared with baseline; limiting instrumental activity of daily living Grade 3: increase of ≥7 stools per day over baseline; hospitalisation indicated; severe increase in ostomy output compared with baseline; limiting self-care activity of daily living Grade 4: life-threatening consequences; urgent intervention indicated	**Grade 1, 2** Loperamide 4 mg then 2 mg after every stool, max 16 mg/24 h **Grade 3, 4** Consider admission, intravenous fluids, start stool chart, hold loperamide until stool cultures results if recent hospitalisation or antibiotics (consider *C. difficile*) In refractory cases, oral codeine, budesonide or subcutaneous octreotide may be required Seek gastroenterology advice

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Table 2. Investigation and management of common treatment-related toxicities[3,4,18] (Continued)

Anti-cancer therapies most commonly causing particular complication	Initial investigations	Differential diagnoses	Grading	Management
Pneumonitis				
Thoracic radiotherapy Bleomycin Irinotecan Paclitaxel	Chest X-ray CTPA to exclude cancer progression or pulmonary embolism Arterial blood gas For grades 3 and above, consider bronchoscopy if not improving	Pneumonia PE Progressive disease Lymphangitis carcinomatosis	Grade 1: Asymptomatic or clinical or diagnostic observations only; intervention not indicated Grade 2: Symptomatic; medical intervention indicated; limiting instrumental activities of daily living Grade 3: Severe symptoms, limiting self-care activities of daily living; oxygen indicated Grade 4: Life-threatening respiratory compromise urgent intervention indicated (eg tracheotomy or intubation)	**Grade 1** Monitor as outpatient **Grade 2** High-dose prednisolone with PPI cover **Grade 3, 4** Consider alternative diagnoses IV methylprednisolone 1–2 mg/kg OD with PPI cover Avoid high-flow O_2 in bleomycin lung toxicity

CTPA = computed tomography scan of pulmonary arteries; FBC = full blood count; IV = intravenous; OD = once daily; PE = pulmonary embolism; PO = per oral; PPI = protein pump inhibitor; QDS = four times daily; SC = subcutaneous; U/E = urea/electrolytes.

hydrocephalus and manifests as severe vasogenic oedema. Although presentation varies depending on the site of the lesion, common symptoms include headache, vomiting, changes in vision and seizures. Physical examination can reveal a decreased Glasgow Coma Score (GCS), VIth nerve palsy, papilledema, and the triad of bradycardia, hypertension and bradypnea known as Cushing's reflex. Patients should undergo urgent neuroimaging with computed tomography (CT) and/or MRI. Signs of imminent neurological compromise include midline shift, cerebral oedema, hydrocephalus and acute haemorrhage.[3] A GCS score <12 warrants urgent intensive treatment unit (ITU) assessment. Initial management includes high-dose dexamethasone (16 mg followed by 8 mg twice daily) with PPI cover, analgesics and antiemetics. Prophylactic anticonvulsants are not recommended for routine use.[8] In refractory cases, hypertonic saline and mannitol might be required.

Superior vena cava obstruction

Malignant superior vena cava obstruction (SVCO) is caused by direct tumour invasion, external compression or tumour thrombus.[9] Increased venous pressure results in head, neck and upper limb oedema, cyanosis and swelling of subcutaneous vessels.[10] The most common cause is bronchogenic malignancy, followed by lymphoma, thymic and germ cell malignancies.[11] Investigation is with contrast-enhanced CT, which can assess the primary tumour, the site of occlusion or stenosis and the extent of tumour thrombus. In patients who are unstable and present with life-threatening complications, such as airway obstruction, stridor, hypotension or decreased GCS, urgent endovenous recanalisation with SVC stent placement should be organised.[12] In patients who are stable, accurate histological diagnosis is needed to direct anti-cancer therapy, because patients with small cell lung cancer, lymphoma or germ cell tumours might be more suitable for chemotherapy than for endovascular stenting. Prognosis varies significantly depending on the underlying tumour.[11] If tumour thrombus is present, anticoagulation should be considered.

Hypercalcaemia of malignancy

Malignant hypercalcaemia occurs in 20–30% of patients with advanced cancer,[13] following tumour secretion of parathyroid hormone-related peptide (PTHrP) and vitamin D, or cytokine release for osteolytic metastases.[14] Both mechanisms result in increased osteoblastic bone resorption and increased tubular calcium resorption.[15] Symptoms include depression, musculoskeletal pain and abdominal pain.[16] Investigation with serum total calcium, PTH, PTHrP, phosphate, vitamin D, serum creatinine and estimated glomerular filtration rate (eGFR) will enable a correct diagnosis in most cases. Grading is based upon local laboratory guidelines. In severe hypercalcaemia, patients are usually volume deplete, and intravenous fluid therapy forms the mainstay of initial management, promoting calciuresis.[17] Following 24 h of parenteral fluid therapy, intravenous bisphosphonates are used first line to reduce bone resorption, and calcium levels fall steadily over a period of 1–5 days (Table 1). In refractory cases, repeat bisphosphonates, calcitonin, glucocorticoids or denosumab (off label) can be trialled.[17]

Treatment-related toxicity

Chemotherapy

Cytotoxic chemotherapy causes cancer cell death by interfering with the cell cycle and inhibiting cell division. However, chemotherapy also causes cytotoxicity in rapidly proliferating non-cancerous

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Table 3. Common solid tumour chemotherapy toxicities[19]

Class of drug	Drug name	Cancer sites	Common toxicity
Alkylating agents	Carboplatin	Ovarian and small cell lung cancers, germ cell tumours	Ototoxicity, myelosuppression
	Cisplatin	Testicular, lung, cervical, bladder, head and neck, and ovarian cancers	Nephrotoxicity, myelosuppression
	Ifosfamide	Germ cell tumours	Urothelial toxicity, myelosuppression
	Lomustine	Hodgkin's, malignant melanoma, glioblastoma multiforme and neuroendocrine tumours	Myelosuppression
	Temozolomide	Glioblastoma multiforme and malignant glioma	Hepatotoxicity, myelodysplastic syndromes, secondary malignancy, myelosuppression
Antimetabolites	5-Fluorouracil, capecitabine	Gastrointestinal and breast cancers	Patients with DPD deficiency are at increased risk of severe and fatal toxicity, cardiotoxicity, myelosuppression
	Gemcitabine	Non-small cell lung cancer, pancreatic, bladder, ovarian and breast cancers	Myelosuppression
	Pemetrexed	Mesothelioma and non-small cell lung cancer	Myelosuppression
	Raltitrexed	Colorectal cancer	Myelosuppression
Antitumor antibiotic	Doxorubicin	Ovarian and breast cancers	Cardiotoxicity, myelosuppression
	Epirubicin	Breast, gastric, small cell lung, ovarian and colorectal cancers	Chemical cystitis, myelosuppression
	Bleomycin	Germ cell tumours	Pulmonary toxicity, myelosuppression
Topoisomerase inhibitors	Irinotecan	Colorectal cancer	Thromboembolism, interstitial lung disease, myelosuppression
	Etoposide	Small cell lung cancer and germ cell tumours	Myelosuppression
Mitotic inhibitors	Docetaxel	Breast, non-small cell lung cancer, gastric, head and neck, and prostate cancers	Myelosuppression, hepatotoxicity
	Eribulin	Breast	Myelosuppression
	Paclitaxel	Breast, ovarian, non-small cell lung cancer and pancreatic cancers	Cardiotoxicity, interstitial lung disease, myelosuppression
	Vincristine, vinorelbine	Breast and lung cancers	Myelosuppression, peripheral neuropathy
Glucocorticoids	Prednisolone, dexamethasone	Multiple tumour types	Adrenal insufficiency, weight gain, hyperglycaemia

DPD = dihydropyrimidine dehydrogenase.

epithelial cells and acute emergency toxicity can present with nausea and vomiting, diarrhoea, pneumonitis or myelosuppression (Table 2).[3,4,18] The common toxicities of specific chemotherapeutic agents in solid tumours are presented in Table 3.[19]

Radiotherapy

There have been significant advances in linear accelerator technology with the development of image-guided intensity-modulated and stereotactic radiotherapy. Despite this, radiation toxicity can occur and is dependent on the site of treatment. Acute presentations typically include gastrointestinal toxicity and pneumonitis (Table 2). Radiotherapy can rarely cause acute oedema of the brain and spinal cord, and patients presenting with new neurological symptoms should have repeat brain or spinal imaging with CT or MRI. Treatment involves dexamethasone 4–8 mg twice daily.[3] Increasing the dexamethasone dose above 16 mg/day has not been shown to provide additional benefit.[20]

Targeted therapy

Targeted therapies interact with specific molecules involved with cell proliferation and growth. Toxicity is variable depending on the mechanism of action, and an overview is provided in Table 4.[19] The most common oral targeted therapies are tyrosine kinase inhibitors (TKIs), which typically cause rash, diarrhoea, fatigue, nausea, sore mouth and paronychia as side effects. Multiple targeted drugs have recently been identified with an elevated risk of pneumonitis and this should be carefully investigated for in any patient presenting with breathlessness or a dry cough.

Steroid therapy

Patients with cancer are often prescribed glucocorticoids, especially as supportive care. The risk of adrenal insufficiency should be considered in any unwell patient with cancer. Clinicians should enquire whether patients carry a Steroid Emergency Card.[21] Top-up

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Table 4. Common solid tumour-targeted therapies and their toxicities[19]

Drug class/target	Drug name	Cancer sites	Common or significant toxicities
ALK	Alectinib, brigatinib, ceritinib, lorlatinib	Non-small cell lung cancer	Diarrhoea
BRAF	Dabrafenib, encorafenib, vemurafenib	Melanoma	Electrolyte derangement, QTc prolongation, hepatoxicity, uveitis, iritis and retinal vein occlusion, cutaneous and non-cutaneous squamous cell carcinoma, new primary melanoma
	Sorafenib (and VEGF)	Renal cell, hepatocellular and thyroid cancers	QTc prolongation, thyroid dysfunction, hypocalcaemia, aneurysm, artery dissection in patients with or without hypertension
CDK4/6	Abemaciclib, palbociclib, ribociclib	Breast cancer	Interstitial lung disease, hepatotoxicity, myelosuppression
EGFR	Afatinib, erlotinib, gefitinib, mobocertinib, osimertinib	Non-small cell lung cancer	Diarrhoea, QTc prolongation
	Cetuximab, panitumumab	Colorectal and head and neck cancer	Electrolyte derangement, hypersensitivity reactions, interstitial lung disease
FGFR2	Pemigatinib	Cholangiocarcinoma	Hyperphosphataemia, eye and vision changes
HER2 monoclonal antibody	Trastuzumab, pertuzumab	Breast, gastric, oesophageal and lung cancers	Cardiotoxicity
HER2 antibody drug conjugate	Trastuzumab emtansine	Breast cancer	Hepatic toxicity, neurotoxicity, hypersensitivity reactions, interstitial lung disease
	Trastuzumab deruxtecan	Breast cancer	Myelosuppression, cardiotoxicity, pneumonitis
HER2 TKI	Lapatinib, neratinib (also EGFR), tucatinib	Breast cancer	Diarrhoea
KRAS (G12C)	Sotorasib	Non-small cell lung cancer	Hepatotoxicity, cough
MEK	Binimetinib, cobimetinib, trametinib	Melanoma and non-small cell lung cancer	Gastrointestinal perforation, hypertension
MET	Tepotinib	Non-small cell lung cancer	Interstitial lung disease, hepatoxicity
mTOR	Everolimus, temsirolimus	Neuroendocrine, renal cell and breast cancers	Suicidal thoughts, hyperglycaemia, nephrotoxicity
PARP	Niraparib, olaparib	Ovarian, fallopian and peritoneal cancers	Diarrhoea
PI3K	Alpelisib	Breast cancer	Hyperglycaemia
RET	Selpercatinib	Non-small cell lung cancer	Hypertension
ROS1	Crizotinib (also ALK) entrectinib	Non-small cell lung cancer	Cardiac failure
SMO	Vismodegib	Basal cell carcinoma	Diarrhoea
TRK	Entrectinib (also ROS1), larotrectinib	NTRK fusion-positive solid tumours	QT prolongation, hepatoxicity
VEGF	Bevacizumab	Colorectal, breast, renal cell, non-small cell lung, ovarian, cervical and hepatocellular cancers	Osteonecrosis of the jaw, aneurysm, and artery dissection in patients with or without hypertension, necrotising fasciitis, congestive heart failure, posterior reversible encephalopathy syndrome
	Axitinib, cabozantinib, lenvatinib, nintedanib, pazopanib, regorafenib (and others), sorafenib (and BRAF), sunitinib (and others), vandetanib	Renal cell, thyroid (lenvatinib, vandetanib), non-small cell lung (nintedanib), colorectal, GIST and hepatocellular cancers (regorafenib)	Aneurysm and artery dissection in patients with or without hypertension

GIST = gastrointestinal stromal tumor; TKI = tyrosine kinase inhibitor.

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glucocorticoid therapy should be prescribed during 'sick days', such as when presenting to the emergency department with acute illness.

Immunotherapy

The acute toxicity of immunotherapy is discussed in another article within this edition.

Neutropenic sepsis

Febrile neutropenia or neutropenic sepsis is a medical emergency and represents a potentially life-threatening complication of systemic anti-cancer therapy. Neutropenic sepsis can be diagnosed in a patient presenting with a temperature over 38.0°C and an absolute neutrophil count (ANC) of $<1.0\times10^9$/L. However, fever might not always be present and can be masked by concomitant steroid therapy. Therefore, neutropenic sepsis should be suspected in any unwell patients within 60 days of receiving systemic anti-cancer therapy.

Initial evaluation should involve a detailed cancer history, including chemotherapy regimen and any prophylactic antibiotic administration. Physical examination should assess circulatory and respiratory function, and patients with should receive prompt resuscitation. Intravenous broad-spectrum antibiotics should be given within 1 h of blood cultures being taken.[22] Their administration should not wait for the full blood count results. Empirical antibiotic treatment should be based on local guidelines, epidemiological patterns of causative pathogens and antimicrobial resistance.[23] Invasive aspergillosis should be considered in patients with prolonged, profound neutropenia; *Pneumocystis jirovecii* pneumonia should be considered in patients treated with corticosteroids; and invasive candidiasis should be considered in those with mucositis. C reactive protein (CRP) levels lack specificity, and an elevated CRP in isolation should not be the sole trigger to prompt initiation of antimicrobial therapy. The use of procalcitonin is currently exploratory.[24]

Advice about the use of granulocyte colony-stimulating factor (G-CSF) should be sought from the acute oncology team; however, G-CSF is indicated if the patient is septic, has an ANC $<0.5\times10^9$/L or is at elevated risk of complications.[22] G-CSF can be stopped once the ANC is above 1×10^9/L. Assessment of risk of medical complications using the Multinational Association of Supportive Care in Cancer (MASCC) should be performed. Select low-risk patients can be managed as outpatients following a period of observation after initial empiric therapy.[22] Mortality varies depending on the MASCC score: under 5% if the MASCC score is ≥21, but potentially up to 40% if the MASCC score is <15.[23,25] Prognostic factors include the degree and duration of neutropenia, older age, poor performance status, obesity and metastatic bone marrow infiltration.[25] ■

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