15 Considerations for Medications Commonly Utilized in the Oncology Population in the Intensive Care Unit

Anne Rain Tanner Brown, Michelle Horng, and Terri Lynn Shigle

Contents

A. R. T. Brown (✉) · M. Horng
Critical Care/Nutrition Support, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: artanner@mdanderson.org; mhorng1@mdanderson.org

T. L. Shigle
Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: tshigle@mdanderson.org

J. L. Nates, K. J. Price (eds.), *Oncologic Critical Care*,
https://doi.org/10.1007/978-3-319-74588-6_23

Abstract

An increasing number of oncologic patients are presenting to the intensive care unit with complications from both their chronic disease states and cancer therapies due to improved survival rates. The management of these patients is complex due to immunosuppression (from the malignancy and/or treatment), metabolic complications, and diverse medication regimens with the potential for significant drug-drug interactions and overlapping adverse effects. This chapter will provide clinicians with an overview of non-chemotherapy medications frequently encountered in the critically ill oncologic patient, with a focus on practical considerations.

Keywords

Oncology · Critical care · Cancer · Drug interactions · Pharmacology · Intensive care · Critically ill · Drug monitoring · Adverse events · Immunocompromised

Introduction

As advances in cancer therapies continue to improve, a growing number of patients are living with cancer. As such, there is an increased probability for critical care providers to encounter cancer patients within the intensive care unit (ICU). Furthermore, oncologic patients require increased utilization of resources in the ICU due to disease-related complications and/or treatment-related adverse events [124]. Metabolic complications present difficult challenges in the management of critically ill cancer patients [72]. Immunosuppression, secondary to the cancer itself or cancer-related therapies (e.g., chemotherapy, corticosteroids, hematopoietic cell transplant, etc.), places patients at an increased risk for infection. In addition, many new chemotherapy and targeted therapies have numerous adverse effects that not only increase the risk for ICU admission but require multiple other therapies to help manage these side effects.

Medication regimens for critically ill cancer patients are complex. Many patients require a large number of concomitant medications to manage the critical, oncologic, and supportive care issues encountered. Accordingly, avoidance and detection of drug-drug interactions and overlapping adverse effect profiles is of high concern. The intent of this chapter is to provide critical care practitioners with an overview of non-chemotherapy medications that are frequently encountered during the care of a critically ill cancer patient in hopes of increasing awareness of such therapy. It should be emphasized that this chapter is not all-inclusive in respect to the medications discussed and details provided, and clinicians are advised to seek additional information as applicable. In addition, medication doses are reflective of a patient with normal renal function and clinicians should refer to drug dosing references for organ dysfunction adjustments unless otherwise noted.

Antimicrobial Agents

Gram Positive Agents

Risk for methicillin resistant *staphylococcus aureus* (MRSA) and vancomycin resistant *enterococcus* (VRE) as shown in Table 1 may be heightened in the oncology population due to increased exposure to the healthcare setting and antimicrobials [11]. While initial therapy of patients with febrile neutropenia may not require coverage for MRSA, empiric antibiotic regimens for all patients progressing to sepsis or septic shock or those patients with additional risk factors should be broadened to include an agent targeting aerobic

Table 1 Considerations for MRSA/VRE coverage

MRSA	VRE
Vascular access devices	Previous VRE infection
Gram positive bacteremia prior to speciation	High rates of hospital endemicity
Known colonization or prior infection with MRSA	Known colonization
Clinical instability (hypotension or shock)	
Skin or soft tissue infection	
Pneumonia requiring ICU admission	
Penicillin resistant *Streptococcus pneumoniae*	
High rates of hospital endemicity	
Severe mucositis if FQ prophylaxis + ceftazidime is employed as empiric therapy	

MRSA methicillin resistant *staphylococcus aureus*, *VRE* vancomycin resistant enterococcus, *ICU* intensive care unit, *FQ* fluoroquinolone
Adapted from [11, 43]

gram positive cocci [102]. For MRSA, consider early addition of vancomycin, linezolid, or daptomycin. For VRE, consider early addition of linezolid or daptomycin. Selection of a specific agent should be based on patient-specific (e.g., end organ function) as well as an infection-specific factors (e.g., source of infection). As mentioned in Table 2, use of linezolid may compromise bone marrow function; this does not preclude use of linezolid in patients with pancytopenia or thrombocytopenia, but it does justify a risk-benefit analysis inclusive of alternative options prior to therapy initiation [126]. Consider an infectious diseases (ID) consult if MRSA or VRE is isolated in the context of systemic infection [11, 43]. Discontinuation of MRSA and/or VRE therapy should be considered if a pathogen is not identified within 48–72 h of obtaining all pertinent cultures.

Gram Negative Agents

Empiric intravenous (IV) antibiotics with antipseudomonal coverage should be initiated immediately in high-risk patients with febrile neutropenia and may include piperacillin/tazobactam, ceftazidime, cefepime, meropenem, or imipenem-cilastatin [11, 43]. Unfortunately, frequent exposure to antimicrobials and repeated hospitalization result in greater risk of acquiring resistant gram-negative organisms [114].

Oncology patients are at increased risk of infections with gram negative organisms from translocation from the gastrointestinal (GI) tract, particularly in patients with mucositis or graft versus host disease (GVHD). Risk of acquiring multi-drug resistant (MDR) gram negative organisms is increased by the use of prophylactic fluoroquinolones in patients with chemotherapy-induced neutropenia [33, 71, 78]. Initial empiric coverage of extended spectrum beta lactamase (ESBL) organisms and carbapenem resistant enterobacteraciae (CRE) should be based on patient-specific factors including prior exposure of antipseudomonal prophylaxis for febrile neutropenia patients and prior infections or microbiologic culture results. Double antipseudomonal gram-negative coverage may be warranted in patients with a history of *P. aeruginosa* or other MDR organism colonization or in hemodynamically unstable patients. Combination therapy with an aminoglycoside should be preferred in patients recently treated with fluoroquinolone prophylaxis (Table 2) [11]. Consider an infectious disease consult for patients with multidrug resistant organisms (MDRO).

Antiviral Agents

Oncology patients, particularly those with hematologic malignancy and/or history of HCT, are at risk for viral infections as a result of their underlying malignancy, chemotherapy, prolonged neutropenia, impaired cell-mediated immunity, and/or treatment complications (e.g., GVHD)

Table 2 Oncologic considerations for select antibiotics

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
Linezolid [67, 109]	Treatment of gram positive resistant organisms (MRSA, VRE)	**Dosing** PO, PT, IV: 600 mg q12h **Administration** PO, PT: Administer without regard to food IV: Administer over 30–120 min	**Monitoring** Obtain weekly CBC **AE/toxicities** Serotonin syndrome, lactic acidosis (rare) Bone marrow suppression (thrombocytopenia is the most common)	MAO inhibitors (caution with concurrent use or within 2 weeks)	• Prolonged therapy (≥ 2 weeks) may increase risk of serious hematologic toxicity • IV formulation contains 600 mL/day D5W (caution in fluid overload and/or hyponatremia) • Not a preferred agent in resistant *E. faecalis* infections susceptible to beta-lactams
Aminoglycosides [14, 51, 89, 92, 97, 99, 111]	MDROs, including pseudomonas and enterobacteriaceae	**Dosing** *Tobramycin/ Gentamicin* IV: 5–7 mg/kg/ dose *Amikacin* IV: 15–20 mg/ kg/dose Repeat dosing based on predicted trough	**Monitoring** Draw 4 h and 10 h random levels to calculate expected peak and trough Target peak for EIAD: *Tobramycin/Gentamicin* 20 mcg/mL; *Amikacin* 40 mcg/mL (For organisms with MICs of 2 mcg/mL and 4 mcg/mL, respectively) Target trough for EIAD: *Tobramycin/Gentamicin* < 2 mcg/mL, *Amikacin* < 4 mcg/mL **AE/toxicities** Ototoxicity Nephrotoxicity	Avoid/minimize concomitant use of neurotoxic and nephrotoxic medications	• EIAD approach aims to facilitate peak of 10 x MIC and minimize trough / probability of accumulation • Peak levels are associated with efficacy while trough concentrations are associated with nephrotoxicity • Nephrotoxicity is also exposure dependent and may develop with prolonged therapy despite EIAD approach • Use with caution in patients with neuromuscular disorders

MRSA methicillin resistant staphylococcus aureus, *VRE* vancomycin resistant enterococcus, *PO* by mouth, *PT* per enteral tube, *IV* intravenous, *CBC* complete blood count, *AE* adverse effects, *MAO* monoamine oxidase, *D5W* 5% dextrose in water, *MDROs* multidrug resistant organism, *EIAD* extended interval aminoglycoside dosing, *MIC* minimum inhibitor concentration

[136]. Infection with herpes simplex (HSV), herpes zoster (HZ), cytomegalovirus (CMV), and respiratory viruses (e.g., respiratory syncytial virus [RSV]) are of prominent concern. A review of the pharmacologic options for management of these infections is presented in Table 3.

Many oncology patients admitted in the ICU may already be receiving antiviral prophylaxis against herpes simplex virus (HSV) and herpes zoster (HZ) with acyclovir or valacyclovir. In addition to HSV/HZ, another common pathogen observed in patients with hematologic malignancy/post-HCT is cytomegalovirus (CMV). CMV is a beta herpes virus with a seroprevalence in the United States (US) of around 60% [130]. Typically, most people are asymptomatic when primary infection with CMV occurs and then the virus enters a latent infectious state in mononuclear leukocytes. Reactivation can occur in many instances, but in relation to the oncology patient population, this can be seen during times of immunosuppression (e.g., chemotherapy administration) and critical illness as well as in the elderly [34]. Prophylaxis against CMV is not routine, given the toxicity profile of traditional anti-CMV therapy (i.e., ganciclovir and foscarnet); rather a strategy of pre-emptive monitoring has been adopted with treatment reserved for patients with presumed or documented infection [136]. Recently, the Federal Drug Agency (FDA) approved letermovir for CMV prophylaxis in HCT CMV seropositive recipients. Given the more acceptable toxicity profile of this agent and the morbidity/mortality associated with CMV infection, use of letermovir will likely increase in hopes of preventing CMV reactivation [84].

Despite preventive strategies and increased awareness, respiratory viral infections may occur, with RSV, influenza, parainfluenza, and human metapneumovirus responsible for the majority of cases. Progression to lower respiratory tract infection often presents as dyspnea and hypoxia, which can prove fatal. Unfortunately, limited options currently exist for managing these viral infections (e.g., neuraminidase inhibitors for influenza, ribavirin for RSV) and therapy is primarily supportive. Studies are needed to further elucidate high-risk patients and determine efficacy of novel antiviral agents [23]. Other viruses that may be notable for complications in cancer patients include adenovirus, human herpesvirus 6 (HHV6), polyomaviruses (BK and JC), and Epstein-Barr virus (EBV).

Antifungal Agents

Antifungal coverage should be considered in febrile neutropenic patients on broad-spectrum antibiotics who have had a persistent fever for 4–7 days and no identified fever source [43]. Antifungal therapy should also be considered in critically ill ICU patients (regardless of the presence or absence of malignancy) with suspected infection who do not improve after 72 h of broad-spectrum antibiotics [110]. For empiric coverage of *Candida,* use of an echinocandin (anidulafungin, micafungin, or caspofungin) is preferred, especially in patients who have been recently treated with other antifungal agents, or if *Candida glabrata* or *Candida krusei* is suspected from previous culture data [47, 114].

Hematologic malignancy patients with prolonged neutropenia, status post allogeneic HCT, and/or chronic corticosteroid exposure (e.g., GVHD) are at risk for invasive aspergillosis infections [101]. Posaconazole or voriconazole are often utilized for prophylaxis against invasive aspergillosis in high-risk patients [29, 139, 146]. In the absence of contraindications (i.e., organ dysfunction, adverse effects) or development of a breakthrough infection, antifungal prophylactic regimens should be continued following ICU admission. For patients who develop breakthrough invasive aspergillosis while receiving prophylactic azole therapy, therapeutic drug monitoring (TDM) should be performed to assess adequacy of the current regimen, if available; however, the patient will likely need to be switched to another class of medications. Voriconazole remains the treatment of choice for *Aspergillus* infections (Table 4). However, if the patient is unable to tolerate voriconazole therapy, isavuconazonium or the liposomal formulation of Amphotericin B (AmB) are

Table 3 Oncologic considerations for select antivirals

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
Acyclovir [54, 136, 137]	HSV/HZ prophylaxis and treatment	**Dosing** Prophylaxis: PO, PT: 400–800 mg BID OR IV: 5 mg/kg or 2.5 mg/m2 q8–12 h (AdjBW) Treatment: IV: 10 mg/kg IBWq8h (Use adjBW for obese patients) **Administration** Administer over 1 h to reduce nephrotoxicity	**Monitoring** BUN, SCr, urine output **AE/toxicities** Nephrotoxicity	Monitor closely when used with other nephrotoxic medications	• Maintain adequate hydration • Avoid rapid infusion • Available as suspension for NG tube administration • Alternatively, valacyclovir, prodrug of acyclovir, may be utilized (not available IV)
Cidofovir [18, 53, 80]	Treatment of adenovirus Treatment of CMV	**Dosing** IV: 5 mg/kg q7 days OR 1 mg/kg 3x/week **Administration** High dose cidofovir must be given concomitantly with IV hydration and probenecid (2 gm PO 3 h prior to cidofovir dose, then 1 gm PO 2 and 8 h after completion of the infusion)	**Monitoring** SCr, urine output, and urine protein (at baseline and within 48 h of each dose), WBC **AE/toxicities** Nephrotoxicity Metabolic acidosis Neutropenia	Monitor closely when used with other nephrotoxic medications	• Inadequate HSV/HZ coverage when used as monotherapy – acyclovir/valacyclovir prophylaxis should be continued • Last line for CMV treatment given toxicity profile • Refer to package insert or [18] for renal dosage adjustment
Foscarnet [16, 38, 82]	Treatment of CMV	**Dosing** Induction: IV: 60 mg/kg q8h OR 90 mg/kg IV q12h Maintenance: IV: 90 mg/kg q24h Induction and maintenance is a minimum of 3 weeks; absolute duration also based on CMV PCR results **Administration** Administration rate not to exceed 1 mg/kg/minute. If given via peripheral IV, must be diluted not to exceed final concentration of 12 mg/mL	**Monitoring** CBC, SCr, urine output, electrolytes (Ca, Mg, K, Phos) Consider EKG **AE/toxicities** Nephrotoxicity, hypokalemia, hypomagnesemia, hypocalcemia, hypophosphatemia N/V/D Seizures (related to electrolyte imbalance)	Monitor closely when used with other nephrotoxic medications Monitor closely when used with other QTc prolonging medications	• Considered second line treatment for CMV if patient not responding/resistant to ganciclovir or as an alternative to avoid ganciclovir-associated myelosuppression • May be used to treat other viruses such as HHV6 • Provides HSV/HZ coverage-acyclovir/valacylovir prophylaxis should be discontinued upon initiation of treatment • Use as prophylaxis has fallen out of favor given toxicity profile • Refer to package insert for renal dose

			Diabetes insipidus (nephrogenic) QTc prolongation Anemia Granulocytopenia		adjustment (See Fig. 1 for calculation of CrCL in mL/min/kg)
Ganciclovir [40]	Treatment of CMV	**Dosing** Induction: IV: 5 mg/kg q12h Maintenance: IV: 5 mg/kg q24h Induction and maintenance is a minimum of 3 weeks; absolute duration also based on CMV PCR results **Administration** Administer by slow IV infusion over at least 1 h	**Monitoring** CBC, SCr **AE/toxicities** Pancytopenia Nephrotoxicity – especially in elderly and with use of concomitant nephrotoxic agents	Monitor closely when used with other nephrotoxic medications	• Considered treatment of choice for CMV • Provides HSV/HZ coverage-acyclovir/valacylovir prophylaxis should be discontinued upon initiation of treatment • Pancytopenia may occur at any time, but usually occurs during the first 1 to 2 weeks of treatment • May need to provide additional support with growth factors, red blood cell transfusion, or platelets • Use as prophylaxis has fallen out of favor given toxicity profile • Refer to package insert for renal dose adjustment
Letermovir [30, 84]	CMV prophylaxis	**Dosing** PO/IV: 480 mg daily PO/IV: 240 mg daily if patient also receiving cyclosporine Started between Day 0 and Day 28 after allogeneic HCT in CMV sero-positive recipients and continued through day 100	**Monitoring** CMV reactivation, SCr **AE/toxicities** Tachycardia Atrial fibrillation N/V/D Peripheral edema	Inhibits: CYP3A4 (moderate)	• Currently only FDA approved for prophylaxis of CMV • If patient unable to swallow tablet whole, use IV administration of letermovir (do not crush or administer via feeding tube). • With IV therapy, monitor serum creatinine closely in patients with CrCl <50 mL/min (IV vehicle, hydoxypropyl betadex, may accumulate leading to kidney injury)
Oseltamivir [21, 52]	Influenza	**Dosing** PO: 75 mg BID x 5–10 days Data in immunocompromised patients is lacking for dose and duration, but given prolonged viral shedding and increased risk for progression to LRTI,	**Monitoring** Signs/symptoms of unusual behavior – rare occurrence for neuropsychiatric events, SCr **AE/toxicities** Headache	N/A	• IDSA and CDC consider patients with malignancy and/or immunosuppressive therapy to be high risk for influenza progression to LRTI • Treatment should be initiated in symptomatic immunocompromised patients regardless of duration of

(*continued*)

Table 3 (continued)

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
		higher doses and longer duration may be considered	Vomiting Diarrhea/dyspepsia with suspension (contains sorbitol)		symptoms prior to diagnosis • Available as suspension for administration via feeding tube • Refer to package insert for renal dose adjustment
Ribavirin [22, 23, 42, 49, 58, 59, 60]	RSV treatment	**Dosing** Inhaled: 2 gm via SPAG unit over 3 h q8h x 5 days (Due to teratogenicity – must be administered in a scavenging tent) Two common PO / PT dosing strategies: 1. Fixed dose of 600 mg q8h 2. LD of 10 mg/kg followed by 20 mg/kg/day divided into three doses Optimal dose and duration of oral ribavirin not yet established	**Monitoring** Hemoglobin LFTs **AE/toxicities** Hemolytic anemia	N/A	• Due to short duration for treatment of RSV compared to Hepatitis C, adverse effects associated with long-term use not common • Ribavirin solution commercially available or can be compounded for administration via feeding tube • Recent increase in cost of inhaled ribavirin (~$30,000/day) –alternative methods for administration are being explored given lack of randomized controlled trials, concerns about occupational exposure, and high cost • Refer to [59] and [60] for dosing recommendations in renal dysfunction

HSV herpes simplex virus, *HZ* herpes zoster, *PO* by mouth, *PT* per enteral tube, *BID* twice daily, *IV* intravenous, *AdjBW* adjusted body weight, *IBW* ideal body weight, *BUN* blood urea nitrogen, *sCr* serum creatinine, *AE* Adverse effects, *N/A* not available, *NG* nasogastric, *CMV* cytomegalovirus, *SCr* serum creatinine, *WBC* white blood count, *PCR* polymerase chain reaction, *CBC* complete blood count, *Ca* calcium, *Mg* magnesium, *K* potassium, *Phos* phosphorus, *EKG* electrocardiogram, *N/V/D* nausea/vomiting/diarrhea, *HHV6* human herpesvirus 6, *CrCl* creatinine clearance, *HCT* hematopoietic cell transplant, *FDA* Food and Drug Administration, *LRTI* lower respiratory tract infection, *n/a* not applicable, *IDSA* Infectious Disease Society of America, *CDC* Center for Disease Control, *NG* nasogastric, *RSV* respiratory syncytial virus, *SPAG* small particle aerosol generator, *LD* loading dose, *LFTs* Liver function tests

[140 − age]/[serum creatinine in mg/dL × 72] [× 0.85 for females] = ml/min/kg

Fig. 1 How to calculate CrCL as mL/min/kg with modified Cockcroft and Gault equation for Foscarnet dosing. (Reference: (1) Foscarnet package insert)

appropriate alternative options for initial therapy. Posaconazole can be considered for salvage therapy [101].

Severe and prolonged immunosuppression also places patients at risk for mucormycosis infections. Posaconazole has been shown to be the most effective antifungal for prophylaxis against mucormycosis; of note, voriconazole is not active against mucormycosis. Liposomal AmB is recommended by the guidelines as the treatment of choice for mucormycosis infections; however, isavuconazonium has recently been approved with the indication as well [10]. Posaconazole is reserved for salvage therapy. Surgical interventions combined with medical treatments have been associated with higher survival rates in patients with mucormycosis when compared to pharmacologic therapy alone [28].

Cancer patients are commonly on numerous medications and chemotherapies that may interact with concomitant azole therapy. Azoles are potent inhibitors and substrates of cytochrome p450 enzymes; therefore, clinicians must be diligent about evaluating for drug-drug interactions (DDIs). In addition, azoles can cause QTc prolongation. Clinicians should monitor closely and optimize electrolytes, particularly in patients on multiple QTc prolonging medications.

Pneumocystis Jiroveci Pneumonia

Prophylaxis and treatment for pneumocystis jiroveci pneumonia (PJP) should be considered in patients with risk factors (neutropenic, immunosuppressed, long-term or high-dose steroids) who are not improving on standard antimicrobial therapy. Prophylactic therapy is usually given to oncologic patients receiving certain types of chemotherapy (i.e., alemtuzumab, purine analogs), HCT patients, or patients on immunosuppression with chronic and/or high-dose steroids. The choice of prophylaxis (e.g., sulfamethoxazole-trimethoprim [SMZ-TMP], pentamidine) is typically based on patient- and/or disease-specific factors (Table 5). Prophylaxis is usually continued until immunosuppression therapy has been discontinued and counts have recovered (absolute neutrophil count [ANC] >1000), CD4 > 200, or according to the specific chemotherapy regimens as noted on the package insert or protocol [32].

For treatment of PJP infection, sulfamethoxazole-trimethoprim (SMZ-TMP) remains the drug of choice (Table 5). However, certain circumstances preclude use of SMZ-TMP, such as an allergy to sulfa medications, the desire to avoid agents that may suppress the bone marrow (e.g., HCT patients pre-engraftment), or persistent SMZ-TMP-related hyperkalemia. In such situations, alternative agents such as clindamycin/primaquine should be considered.

Antiepileptics

Seizures are a common neurologic complication in oncologic patients, secondary to primary brain tumors, metastases, radiation toxicity, and metabolic abnormalities [57]. Selection of an antiepileptic drug (AED) warrants special consideration in the oncologic patient due to interactions with chemotherapy, side effects, and unique mechanisms of certain brain tumors. Enzyme inducing anticonvulsants such as phenytoin may lead to insufficient serum levels of concomitantly administered chemotherapy. Conversely, enzyme inhibiting anticonvulsants such as valproate may lead to toxic levels of chemotherapy [17]. AEDs that are substrates for P-gp (phenobarbital, carbamazepine, lamotrigine,

Table 4 Oncologic considerations for select antifungals

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
Voriconazole [8, 50, 98, 101, 120]	Prophylaxis against invasive Aspergillosis Antifungal of choice for invasive Aspergillosis Step-down oral therapy for candidiasis due to *C. krusei or C. glabrata* (as feasible, following initial treatment with an echinocandin)	**Dosing** **Treatment**: PO (IV, PO: 6 mg/kg ABW) IV: 6 mg/kg ABW* q12h x2 doses, then 4 mg/kg q12h **Prophylaxis:** PO: 200 mg q12h • Administer 1 h before or 1 h after a meal. • Avoid grapefruit juice **For obese patients*: use AdjBW	**Monitoring** Measure trough 2–5 days after initiation *Prophylaxis*: >1 mcg/mL *Treatment*: >1 mcg/mL Limited data, but target trough concentration< 5–6 mcg/mL to minimize toxicity **AE/Toxicities** Visual disturbances, hallucinations, skin reaction, neurotoxicity, QTc prolongation, hepatotoxicity	Inhibitor of CYP2C9, CYP3A4, and to a lesser extent, CYP2C19 P-gp inhibitor	• For subtherapeutic levels, increase IV therapy no more than 50% at a time (max 6 mg/kg twice daily). Increase PO therapy from 200 mg twice daily to 300 mg twice daily. Nonlinear pharmacokinetics result in unpredictable serum concentrations. • Caution with use of IV formulation in patients with renal dysfunction due to β-cyclodextrin solvent. Use PO therapy if feasible. • Suspension available for administration via feeding tube • Long-term use associated with rare cases of melanoma or squamous cell carcinoma • Long-term use associated with periostitis and skeletal disease due to elevated fluoride levels from triflourinated triazole chemical structure
Posaconazole [8, 56, 98, 101, 125]	Salvage therapy for invasive Aspergillosis Second line treatment for *Mucormycosis*	**Dosing** **Treatment**: IV/PO DR tablets: 300 mg q12h x2 doses, then 300 mg **Prophylaxis:** *DR tablets*: PO: 300 mg q12h x2 doses, then 300 mg q24h thereafter	**Monitoring** Measure trough 7 days after initiation *Prophylaxis*: >700 ng/mL *Treatment*: >1000 ng/mL Limited data on target trough concentration **AE/Toxicities** Nausea, vomiting, hepatotoxicity, QTc prolongation	Potent inhibitor of CYP3A4 Substrate and inhibitor of P-gp	• Long half-life of 26 to 31 h • The suspension form is *not* recommended. Variable bioavailability with food, fat, and acidity. *DR tablets*: • Not interchangeable with oral suspension due to increased absorption of tablet form. • Does not have to be administered with high-fat meal. • Can *not* be crushed for use in feeding tube. Use IV formulation in patients unable to swallow the tablet.
Isavuconazonium [41, 101, 119, 145]	Treatment for *Mucormycosis* Alternative primary therapy for invasive Aspergillosis	**Dosing** **Treatment dose**: IV/PO: 372 mg q8h x6 doses, then 372 mg q24h	**AE/Toxicities** Nausea, vomiting, diarrhea, skin reaction, hepatotoxicity	Substrate and moderate inhibitor of CYP3A4	• Limited data on isavuconazonium TDM. Does not need to be routinely monitored. • QTc shortening • IV formulation is β-cyclodextrin solvent free • Poor penetration to eyes, CNS, CSF fluid • Most well-tolerated anti-fungal from GI standpoint

IV intravenous, *ABW* actual body weight, *PO* oral, *AdjBW* adjusted body weight, *AE* adverse events, *P-gp* P-glycoprotein, *NG* nasogastric, *DR* delayed release, *PK* pharmacokinetics, *TDM* therapeutic drug monitoring, *CNS* central nervous system, *CSF* cerebral spinal fluid, *GI* gastrointestinal

Table 5 Oncologic considerations for Pneumocystis jiroveci pneumonia (PJP)

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
Sulfamethoxazole/ Trimethoprim [24, 32]	Drug of choice for treatment and prophylaxis of PJP	**Dosing** **Prophylaxis:** PO/PT: 80 mg TMP daily or 160 mg TMP three times weekly **Treatment:** IV/PO/PT: 15–20 mg/kg TMP given in divided doses 3–4x/day (usually 5 mg/kg q8h or q6h)	**Monitoring** CBC, LFTs, SCr/BUN **AE/toxicities** Agranulocytosis, hyperkalemia, nephrotoxicity, Stevens-Johnson syndrome, QTc prolongation	Inhibitor of CYP2C8 Substrate of P-gp	• PJP prophylaxis usually given for 3–12 months after last chemotherapy treatment • PJP prophylaxis in HCT starts at day +30 and continues for 6–12 months (or longer if still receiving immunosuppressive therapy) • IV formulation requires large volume of D5W as diluent (caution in fluid overload and/or hyponatremia) • High sorbitol content of oral suspension may contribute to diarrhea • Although treatment of choice for PJP, in hematologic malignancy/ HCT, alternative therapy may need to be considered given bone marrow suppressive effects and concomitant use with other nephrotoxic medications (risk vs. benefit analysis)
Clindamycin/ Primaquine [32]	Preferred alternative PJP treatment	**Dosing** **Treatment:** Clindamycin IV (600 mg q6h or 900 mg q8h) plus Primaquine 30 mg (base) PO/PT daily	**Monitoring** CBC, visual color check of urine, glucose, electrolytes **AE/toxicities** Primaquine-hemolytic anemia, methemoglobinemia, QTc prolongation Clindamycin – diarrhea (*C difficile* infection)	Clindamycin: Substrate CYP3A4 (minor) Primaquine: Substrate of CYP2D6 (major) and CYP3A4 (major)	• Primaquine is contraindicated in patients with known G6PD deficiency. • Primaquine can be compounded into a suspension for administration via a feeding tube • Preferred alternative therapy for patients unable to receive SMZ-TMP

(*continued*)

Table 5 (continued)

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
Pentamidine [32, 37]	Alternative PJP therapy	**Dosing** **Prophylaxis:** Nebulized pentamidine 300 mg every 28 days IV (limited data): 300 mg q21 days until patient able to tolerate oral alternative therapy **Treatment:** IV: 4 mg/kg every 24 h infused over at least 60 min for 21 days. May reduce dose to 3 mg/kg due to toxicities	**Monitoring** Glucose, CBC, EKG, LFTs **AE/toxicities** Bronchospasm, cough, fatigue, dizziness, fever, leukopenia, QTc prolongation, cardiac dysrhythmia		
Atovaquone [32]	Alternative PJP prophylaxis or treatment	**Dosing** **Prophylaxis:** PO/PT: 1500 mg daily with food **Treatment:** PO/PT: 750 mg BID with food Administer with high fat meal to enhance oral absorption	**AE/toxicities** Diarrhea, transaminase elevations	Do not co-administer with rifampin	• Substantially more expensive than alternative oral regimens • Not recommended for severe PJP infections • Only available as an oral suspension
Dapsone [32]	Alternative PJP prophylaxis	**Dosing** **Prophylaxis:** PO/PT: 100 mg daily or 50 mg BID	**Monitoring** CBC, LFTs, reticulocyte **AE/toxicities** Hemolytic anemia, methemoglobinemia, rash, serious dermatologic reactions (rare)		• Use with caution in patients with known G6PD deficiency • Use with caution with patients with hypersensitivity to sulfonamides

SMZ-TMP sulfamethoxazole-trimethoprim, *PJP Pneumocystis jiroveci pneumonia*, *PO* oral, *TMP* trimethoprim, *IV* intravenously, *CBC* complete blood count, *LFTs* liver function tests, *SCr* serum creatinine, *BUN* blood urea nitrogen, *AE* adverse effects, *P-gp* P-glycoprotein, *D5W* 5% dextrose in water, *HCT* hematopoietic cell transplant, *BID* twice daily, *G6PD* glucose-6-phosphate dehydrogenase, *NG* nasogastric, *EKG* electrocardiogram

topiramate, and felbamate) may result in insufficient intraparenchymal levels [88].

Patients with brain tumors are more prone to refractory epilepsy, requiring the use of multiple AEDs with different mechanisms. With the introduction of more well-tolerated AEDs, many practitioners are avoiding enzyme inducers as first-line agents [88]. While non-CYP-450 enzyme-inducing AEDs such as levetiracetam, gabapentin, and lamotrigine may be preferable in cancer patients receiving chemotherapy, levetiracetam may be preferred as an initial option in the ICU as it is available for IV administration, does not appear to be affected by P-gp expression, and has favorable pharmacokinetic properties (Table 6) [57, 142].

Immunosuppressants

Recipients of a HCT, particularly allogeneic HCT, require immunosuppression to prevent GVHD [149]. Tacrolimus, sirolimus, or cyclosporine are often utilized for GVHD prophylaxis (Table 7). Similar to the approach in solid organ transplant patients, these medications are managed within a narrow therapeutic window in attempt to decrease both the risk of GVHD as well as toxicities of therapy. Additionally, practitioners should remain cognizant of DDIs with these agents [1].

Corticosteroids are universally utilized immunosuppressants in oncology patients. Often times, corticosteroids are included in different chemotherapy regimens, especially to treat diseases such as diffuse large b-cell lymphoma or acute lymphoid leukemia. High-dose corticosteroids are also utilized to treat a wide range of complications in cancer patients, including but not limited to GVHD, diffuse alveolar hemorrhage (DAH), idiopathic pulmonary syndrome (IPS), and spinal cord compression (SCC) (Table 7). Collaboration between the oncology and critical care teams is recommended when initiating or stopping corticosteroids in the ICU to avoid untoward interactions with ongoing oncologic treatments.

Antifibrinolytic/Antihemophilic Agents

Diffuse Alveolar Hemorrhage (DAH)

Prognosis in patients with DAH secondary to cancer therapy or sepsis is poor [39]. Pulse dose corticosteroids (methylprednisolone 1–2 mg/kg/day) with or without antifibrinolytic therapy has been used in practice but has not been consistently associated with reductions in ICU or hospital mortality, ventilator days, or ICU and hospital

Table 6 Oncologic considerations for seizures

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
Levetiracetam [19, 138]	Prophylaxis or treatment of seizures	**Dosing** IV or PO/PT (immediate release tablet): 1000–3000 mg/day, divided doses q12h *max 4500 mg/day PO/PT: administer without regard to food **Administration** IV: 15 min, for SE, max 2–5 mg/kg/min	**AE/toxicities** CNS depression, toxic epidermal necrolysis, Stevens-Johnson syndrome, and aggression		• Dosing may be limited by somnolence • Prophylaxis may be warranted in patients receiving CAR T-cell therapy

IV intravenously, *PO* oral, *SE* status epilepticus, *AE* adverse events, *CNS* central nervous system, *CAR* chimeric antigen receptor

Table 7 Oncologic considerations for immunosuppressants

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
Tacrolimus [9, 104, 147, 148]	GVHD prevention	**Dosing** Starting dose CIVI: 0.03 mg/kg/day (age ≤50 y/o, no interacting medications) 0.015 mg/kg/day if one or more criteria met: age >50 y/o, renal dysfunction, interacting medication(e.g., voriconazole) Starting dose PO (in two divided doses): 0.12 mg/kg (age ≤50, no interacting medications) 0.06 mg/kg (age >50, renal dysfunction, interacting medication (e.g., voriconazole))	**Monitoring** Serum level: 5–15 ng/mL With continuous IV infusion can draw random level With PO dosing, should draw a trough 30 min prior to dose Wait at least 24–36 h after starting/ adjusting dose for steady state **AE/toxicities** Neurotoxicity, PRES, nephrotoxicity, hypertension, diabetes, TMA-TTP, electrolyte imbalance (hypomagnesemia, hyper/ hypokalemia), infection	Substrate of CYP3A4 (Major) Drug-food interaction: Avoid grapefruit and pomegranate	• IV to PO conversion is 1:3 or 1:4 • Dose based on IBW • Minimal renal excretion – no dose modification needed • Clearance lowered in patients with severe hepatic dysfunction – likely dose modifications needed • Dose reductions 50–75% required when used concomitantly with voriconazole or posaconazole • If unable to swallow capsules, content of capsule may be mixed with water and flushed through feeding tube • SL administration may be used by opening the contents of the capsule under the tongue – decrease dose in half if switching from PO to SL
Cyclosporine [93, 148]	GVHD prevention	**Dosing** Starting dose CIVI: 3 mg/kg/day Starting dose PO-in two divided doses: 10 mg/kg/day **Administration** Neoral®/Gengraf® and Sandimmune® are not bioequivalent and cannot be used interchangeably	**Monitoring** Goal: 200–400 ng/mL With continuous IV infusion can draw random level With PO dosing, should draw a trough 30 min prior to dose Wait at least 24–36 h after starting / adjusting dose for steady state **AE/toxicities** Neurotoxicity, PRES, nephrotoxicity, hypertension, hepatotoxicity, TMA-TTP, electrolyte imbalance (hypomagnesemia,	Substrate of CYP3A4 (Major) Drug-food interaction: Avoid grapefruit and pomegranate	• IV to PO is 1:2–3 or 1:4 conversion dependent upon formulation • Dose based on IBW • Minimal renal excretion – no dose modification needed • Clearance lowered in patients with severe hepatic dysfunction – likely dose modifications needed • Dose reductions 25–50% required when used concomitantly with

			hyperkalemia), hyperuricemia, infection, gingival hyperplasia, malignancy		voriconazole or posaconazole • Suspension is available for administration via feeding tube
Sirolimus [1, 35, 108]	GVHD prevention	**Dosing** PO: 12 mg LD x1, then 4 mg daily OR 6 mg LD x1, then 2 mg daily	**Monitoring** Goal: 3–12 ng/mL Trough drawn 30 min prior to dose Due to long half-life, recommended to wait 3–4 days to check level after loading dose and reasonable to wait 1 week after dose adjustment **AE/toxicities** Hyperlipidemia, hypertriglyceridemia, hypertension, nephrotoxicity, hepatotoxicity (VOD), TMA-TTP	Substrate of CYP3A4 (Major) Drug-food interaction: Avoid grapefruit and pomegranate	• No IV formulation available • Suspension is commercially available for administration via feeding tube • Dose reductions 50–90% required when used concomitantly with voriconazole or posaconazole
Corticosteroids [2, 44, 45, 70, 79, 81, 85, 87, 106, 112, 113, 129, 135, 140, 141, 143]	GVHD treatment DAH IPS SCC	**Dosing** **GVHD treatment** Methylprednisolone 2 mg/kg IV in two divided doses followed by slow taper **DAH/IPS** Methylprednisolone 2 mg/kg IV in two to four divided doses followed by slow taper **Other dosing strategy for DAH** Methylprednisolone 500–1000 mg IV/day (in one to two divided doses) x 3–4 days, then taper to 1 mg/kg/day x 3 days followed by slow taper over 2–4 weeks **SCC** Dexamethasone 4–10 mg IV q6 h (doses range from 16 mg/day to 96 mg/day in four divided doses)	**Monitoring** Blood pressure, blood glucose, electrolytes, body weight, HPA axis suppression; IOP and bone mineral density (with long term use) **AE/toxicities** Hypertension, hyperglycemia, increased infection risk, steroid psychosis, myopathy, adrenal suppression, edema / fluid retention, electrolyte disturbances, visual impairment, increased IOP osteoporosis (Long term use)	Dexamethasone major CYP3A4 substrate and weak inducer of CYP3A4	• Concomitant use in patients receiving immune or cellular therapy should be avoided unless specifically treating toxicity related to treatment

GVHD graft vs host disease, *CIVI* continuous intravenous infusion, *PO* by mouth, *AE* adverse effects, *PRES* posterior reversible encephalopathy syndrome, *TMA-TTP* thrombotic microangiopathy-thrombotic thrombocytopenic purpura, *IBW* Ideal body weight, *NG* nasogastric, *SL* sublingual, *LD* loading dose, *IV* intravenous, *VOD* veno-occlusive disease, *DAH* Diffuse alveolar hemorrhage, *IPS* Idiopathic pulmonary syndrome, *SCC* Spinal cord compression, *IOP* intraocular pressure

length of stay in the literature [77, 113, 143]. Treatment with steroids or antifibrinolytic therapy can be considered in patients at high risk of rapid clinical deterioration or death (Table 8). Agents such as recombinant factor VIIa have been used to achieve hemostasis in non-hemophiliac patients with DAH [100]. Additionally, a case series of six patients successfully used intrapulmonary factor VII as adjunctive treatment for DAH with doses ranging from 30 to 60 mcg/kg [12]. The potential benefit of antifibrinolytic and antihemophilic therapies must be weighed against the risk of thrombotic events [150].

Thrombocytopenia

Spontaneous bleeding complications due to thrombocytopenia are common in the critically ill oncologic patient population [75]. Most patients can be managed by observation and supportive care alone. Use of antifibrinolytic agents have been used in emergency treatment of severe thrombocytopenia-associated bleeding to reduce transfusion requirements without increased risk in thromboembolic events (Table 8) but have not been shown to decrease mortality [7].

Disseminated Intravascular Coagulation (DIC)

Routine use of aminocaproic acid, tranexamic acid and recombinant FVIIa in patients with cancer-related DIC is not recommended. Practitioners may consider use of tranexamic acid in patients with therapy-resistant hyperfibrinolytic DIC bleeding (Table 8). Platelet transfusion to maintain platelets $>50 \times 10^3$/L, and transfusion of fresh frozen plasma (15–30 ml/kg) with careful monitoring, is the primary therapy in patients with DIC and active bleeding [134].

Gastrointestinal (GI) Bleeding

A large randomized control trial (RCT) is currently underway to examine the use of tranexamic acid for the treatment of GI bleeding [118].

Thrombolytics

Hepatic sinusoidal obstruction syndrome (SOS), previously referred to as veno-occlusive disease (VOD), is a potentially life-threatening complication with a wide-ranging incidence. Severe SOS is associated with a mortality rate greater than 80% [27]. SOS is characterized by a prothrombotic, hypofibrinolytic state as a result of endothelial damage and hepatocellular injury to sinusoidal endothelial cells. Hallmark symptoms include weight gain, painful hepatomegaly, fluid retention/ascites, and hyperbilirubinemia; the reported incidence varies in part due to variable definitions and evaluated populations [36]. SOS is a complication that occurs typically within 3 weeks of a myeloablative HCT but can also be observed in patients with risk factors of pre-existing liver disease, total body irradiation or abdominal/liver radiation, or exposure to certain hepatotoxic drugs, such as inotuzumab or gemtuzumab (list of VOD/SOS risk factors is not all-inclusive) [27, 36]. Defibrotide was FDA approved in the United States in 2016 for the treatment of severe hepatic SOS after publication of a pivotal phase III trial [117]. Its proposed mechanism of action is to reduce endothelial cell activation and injury and promote restoration of the thrombo-fibrinolytic balance [116]. Due to the severity of illness associated with SOS, many patients are transferred to the ICU for continued management and administration of defibrotide (Table 9).

Uric Acid Reducing Agents

Over 50% of oncologic patients with high-risk for tumor lysis syndrome (TLS) require ICU admission, and nearly 1/3 of those will present with acute kidney injury (AKI). Clinicians should be familiar with the management of hyperuricemia to help preserve renal function. Hyperuricemia results from the rapid release and catabolism of intracellular nucleic acids either spontaneously or in response to chemotherapy in patients with a high tumor burden. Patients who are considered high risk for TLS should receive rasburicase over allopurinol (Table 10) [25].

Table 8 Oncologic considerations for bleeding in the ICU

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
Aminocaproic acid [64, 113]	DAH, oral bleeding with thrombocytopenia	**Dosing** **DAH:** IV: 4 g over 1 h, followed by continuous infusion at 1 g/h **Topical for oral bleeding with thrombocytopenia:** Rinse with hydrogen peroxide, then rinse with saline, followed by a third rinse with 5 ml (1.25 g) aminocaproic acid syrup for 30 sec. Repeat q4h until bleeding controlled **Administration** Rapid IV administration can result in hypotension, bradycardia, and/or arrhythmias	**Monitoring** CPK, heart rate agranulocytosis, signs and symptoms of VTE **AE/toxicities** Bradycardia, arrhythmias, VTE		• May accumulate in renal failure. Specific guidelines for dosage adjustments are unavailable; dose should be modified based on clinical response and degree of renal impairment
Tranexamic acid [62, 105, 123]	DAH, thrombocytopenia-related bleeding	**Dosing** Minimal dosing recommendations *We recommend* IV/PO/PT: TXA 10–15 mg/kg q8-12 h *Alternate dosing regimens*: *Hemoptysis*: 250–500 mg TXA in 500 mg/5 mL solution nebulized via facemask over 15 min **Administration** Hypotension can occur when infusion rates exceed 100 mg/min	**AE/toxicities** VTE, abdominal pain, back pain, musculoskeletal pain, myalgia		• Accumulates in renal failure. Dose adjustment needed. See package insert.
Factor VIIa, recombinant [12, 63, 95, 100, 133]	Refractory bleeding	**Dosing** *Life-threatening bleeding*: IV: 35–120 mcg/kg q2h up to 4 doses per day. Usual starting dose was 75 mcg/kg	**Monitoring** aPTT, DIC **AE/toxicities** Thromboembolism		

DAH diffuse alveolar hemorrhage, *IV* intravenous, *PO* oral, *CPK* creatinine protein kinase, *VTE* venous thromboembolism, *TXA* tranexamic acid, *aPTT* activated partial thromboplastin time, *PTT* partial thromboplastin time, *DIC* disseminated intravascular coagulation, *PT* Prothrombin time

Table 9 Oncologic considerations for thrombolytics

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
Defibrotide [69, 117]	Hepatic SOS (VOD)	**Dosing** IV: 6.25 mg/kg q6h for at least 21 days and a maximum of 60 days (until SOS resolution or hospital discharge) Utilize baseline (dry) weight prior to stem cell transplant or initiation of chemotherapy **Administration** Administer over 2 h using 0.2 micron in-line filter via a dedicated line	**Monitoring** Platelets, INR, Fibrinogen **AE/Toxicities** Hemorrhage, Hypersensitivity reaction **CI** Active bleeding, hemodynamic instability requiring vasopressor support	Co-administration with systemic anticoagulation or fibrinolytic therapy is contraindicated	• For invasive procedures – discontinue defibrotide at least 2 h prior to procedure; resume treatment once the procedure-related risk of bleeding is resolved • Maintain platelets >30,000, INR <1.5, Fibrinogen >150 to decrease bleeding risk

SOS Sinusoidal obstruction syndrome, *VOD* Veno-occlusive disease, *IV* intravenous, *INR* International normalized ratio, *AE*: adverse effects, *CI* Contraindications

Hypercalcemia of Malignancy/ Hypercalcemia Management

All patients presenting with hypercalcemia of malignancy should be given IV crystalloids at 1–2 ml/kg/h to restore intravascular volume and promote calciuresis. For patients that are fluid restricted due to other co-morbidities (e.g., heart failure), consider concomitant diuresis with a loop diuretic if necessary. Symptomatic patients presenting with abdominal pain, confusion, weakness, and electrocardiogram (EKG) changes may require a bisphosphonate +/− calcitonin. Critical care practitioners should be cognizant of all prior therapy given in order to avoid duplicating therapy and the potential development of hypocalcemia (e.g., recent bisphosphonate or denosumab administration) (Table 11).

Interleukin-6 Receptor Antagonists

Chimeric antigen receptor (CAR) T-cell therapy induces rapid and durable clinical responses in many types of cancer but is associated with unique, acute toxicities that can be fatal. This includes both cytokine release syndrome (CRS) and cytokine-related encephalopathy syndrome (CRES). IL-6 therapy may be warranted in patients exhibiting signs and symptoms of toxicity, particularly those requiring ICU care. IL-6 receptor antagonists are indicated in patients with grade 2 and greater CRES and grade 3 and 4 CRS, and may be considered in those with grade 1 CRES and/or persistent grade 1 or 2 CRS [91]. See Table 12 for considerations for IL-6 therapy for CRS or CRES.

Growth Factors

Colony stimulating factors (CSF) are recommended to be administered in a prophylactic manner when the risk of febrile neutropenia (FN) with a given chemotherapy regimen is 20% or higher [127]. The American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) recommend primary prophylaxis for FN with CSFs based on factors associated with the disease, chemotherapy regimen, patient risk, and treatment intent (curative vs. palliative). Secondary prophylaxis may be warranted in patients who have FN or a dose-

Table 10 Oncologic considerations for uric acid reduction

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
Allopurinol [144]	Prevention of hyperuricemia in TLS	**Dosing** PO/PT: 600–800 mg daily in one to three divided doses. IV: 200–400 mg/m^2 daily **Administration** Initiate 1–2 days before chemotherapy	**Monitoring** Serum uric acid levels, BUN, SCr HLA-B*5801 testing in high-risk patients (not typically feasible in acute setting) **AE/Toxicities** Dermatologic toxicities Hepatotoxicity (increased alkaline phosphatase) Nephrotoxicity	6-mercaptopurine, azathioprine, cyclophosphamide, thiazide, and loop diuretics, warfarin	• Preferred in patients with known G6PD deficiency • Does not lower existing uric acid levels • May require up to 72 h to effectively decrease uric acid levels • Does not warrant dose reductions in acute management of TLS • Caution in hypoxanthine/xanthine nephropathy
Rasburicase [20, 121]	Hyperuricemia associated with malignancy	**Dosing** IV: 3–6 mg x 1, may repeat **Administration** Infuse over 30 min to avoid reaction, dose 4 h prior to chemotherapy if possible	**Monitoring** Serum uric acid levels **AE/toxicities** Anaphylaxis CI: Patients with known hemolytic anemia, methemoglobinemia, and G6PD deficiency* *due to time sensitive administration, G6PD screening should not preclude administration of rasburicase acutely	N/A	• Initiate in patients with pre-existing hyperuricemia (Uric acid >7.5 mg/dL) or high-risk patients regardless of baseline uric acid levels • Achieves target uric acid lowering in ~ 4 h in most patients • Enzymatic degradation of uric acid in blood specimen will occur if left at room temperature; collect samples on ice and assay within 4 h

TLS tumor lysis syndrome, *PO* oral, *IV* intravenous, *AE* adverse events, *G6PD* glucose-6 phosphate dehydrogenase deficiency, *CI* contraindicated in, *N/A* not available

Table 11 Oncologic considerations for hypercalcemia of malignancy

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
Calcitonin [55, 90, 132]	Acute treatment for hypercalcemia of malignancy	**Dosing** SQ: 4–8 units/kg q12h Skin test should be performed in patients with sensitivity to salmon calcitonin	**AE/toxicities** Hypocalcemia, facial flushing, local injection site edema		• Onset within 2–4 h. Tachyphylaxis develops within 48–72 h • Not to be used as single agent • Bisphosphonate therapy can be prescribed on day 1 of calcitonin (overlap therapy to compensate for slow onset of bisphosphonate)
Pamidronate [13, 26, 55, 132]	Hypercalcemia of malignancy	**Dosing** IVPB: 60–90 mg x1 Dose can be repeated x1 after 7 days if inadequate response to initial treatment, then do not give more than once every 28 days due to risk of renal failure **Administration** Infuse over 2–24 h	**AE/toxicities** Hypocalcemia, nephrotoxicity Flu-like symptoms (fever, chills) Bone pain Osteonecrosis of the jaw (rare)		• Onset of action 2–4 days with response duration of 1–3 weeks • Not recommended in renal dysfunction. Dosage should be modified depending on degree of renal impairment and response, but no quantitative recommendations are available. Dose reduction generally not warranted unless SCr severely elevated >4.5 mg/dL
Zoledronic acid [26, 55, 94, 132]	Hypercalcemia of malignancy	**Dosing** 4 mg IVPB x1 Dose can be repeated x1 after 7 days if inadequate response to initial treatment, then do not give more than once every 28 days due to risk of renal failure **Administration** Can be infused over 15–30 min	**AE/toxicities** Hypocalcemia, nephrotoxicity Flu-like symptoms (fever, chills) Bone pain Osteonecrosis of the jaw (rare)		• Convenience of administration (IVPB over 15–30 min) for outpatients • Onset of action 2–4 days with response duration of 1–3 weeks • Not recommended in renal dysfunction. Dosage should be modified depending on degree of renal impairment, but no quantitative recommendations are available. Dose reduction generally not warranted unless SCr severely elevated >4.5 mg/dL
Denosumab [4, 55, 132]	Hypercalcemia refractory to bisphosphonates	**Dosing** 120 mg SQ weekly x4 weeks, then every 28 days **Administration** Denosumab should only be administered via the SQ route. Do not administer IV, IM, or ID	**AE/toxicities** Hypocalcemia Osteonecrosis of the jaw		• Onset of action 2–4 days. Terminal half-life of 25.4 days after single-dose administration

SQ subcutaneous, *AE* adverse effects, *IVPB* intravenous piggy back, *SCr* serum creatinine, *IV* intravenous, *IM* intramuscular, *ID* intradermal

Table 12 Oncologic considerations for treatment of cytokine release syndrome or cytokine related encephalopathy syndrome

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
Tocilizumab [48]	CRS CRES	**Dosing** IV: 8 mg/kg for up to 3 doses in a 24-h period (max 800 mg/dose) **Administration** Infuse over 1 h No premedications needed Have emergency medications immediately available in the event of hypersensitivity reaction	**Monitoring prior to therapy** Latent TB,CBC with diff, LFTs, lipid panel **AE/Toxicities** Infection, infusion reaction, anaphylaxis, GI perforation, CNS demyelinating disorders, increased cholesterol, increased LFTs, infusion reactions, neutropenia, thrombocytopenia	Theoretical increased metabolism of CYP 450 substrates	• May consider re-dosing in patients not responding or with worsening grade toxicities within 4 h.
Siltuximab [68]	CRS CRES	**Dosing** IV: 11 mg/kg once **Administration** Infuse over 1 h; complete infusion within 4 h of reconstitution No premedications needed Have emergency medications immediately available in the event of hypersensitivity reaction	**Monitoring prior to therapy** CBC prior to first dose **AE/Toxicities** Infection, infusion reaction, anaphylaxis, GI perforation, peripheral edema, fatigue (long-term exposure), pruritus, skin rash, weight gain, hyperuricemia, diarrhea, abdominal pain, arthralgia, URI, thrombocytopenia, hypertriglyceridemia	Theoretical increased metabolism of CYP 450 substrates	• Do not re-dose within 21 days • Consider in patients who fail to respond to 1–2 doses of tocilizumab

CRS cytokine release syndrome, *CRES* cytokine related encephalopathy syndrome, *IV* intravenous, *TB* tuberculosis, *CBC* complete blood count, *diff* differential, *LFTs* liver function tests, *AE* adverse effects, *GI* gastrointestinal, *CNS* cerebral nervous system, *CBC*: complete blood count, *URI* upper respiratory infection

limiting neutropenic event [31, 127]. Additionally, CSFs may be used to reduce the length of hospitalization and time to neutrophil recovery, for HCT mobilization, and to reduce the risk of infection in patients with intermittent/persistent neutropenia status post HCT. Of note, the medical record of oncology patients admitted to the ICU should be evaluated for prior CSF administration as such therapy my confound interpretation of leukocytosis (Table 13).

Thrombopoietin and thrombopoietin mimetics are FDA approved for the treatment of chronic immune thrombocytopenia; these agents may also be helpful off label to increase the platelet count in patients with thrombocytopenic disorders [66, 74, 76]. The management of thrombocytopenia in patients with increased bleeding risk (e.g., post-surgical), chemotherapy-induce thrombocytopenia, and/or promotion of platelet engraftment after HCT are

Table 13 Oncologic considerations for growth factors in the ICU

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
Filgrastim [6]	Increase WBC	**Dosing** 5 mcg/kg/day IV/SQ	**Monitoring** CBC with differential **AE/toxicities** Common: fatigue, bone/joint pain, peripheral edema/ capillary leak syndrome, thrombocytopenia, headache, splenomegaly Serious: ARDS, pulmonary infiltrates, splenic rupture	N/A	• Higher doses may be used during mobilization for HCT • Onset of action, 24 h • Duration: Counts return to baseline within 4 days • Do not administer within 24 h (before or after) of cytotoxic chemotherapy
Pegfilgrastim [5]	Increase WBC	**Dosing** 6 mg SQ once per chemotherapy cycle, beginning at least 24 h after completion of chemotherapy	**Monitoring** CBC with differential **AE/toxicities** Common: bone/joint/ muscle pain Serious: ARDS, pulmonary infiltrates, splenic rupture	N/A	• Onset of action is 96 h(delayed compared to filgrastim) • Pegylated formulation allows for prolonged duration of action (half-life 15–80 h) • Do not administer within 14 days before or 24 h after cytotoxic chemotherapy
Romiplostim [3]	Increase platelets in chronic ITP	**Dosing** 1 mcg/kg SQ once weekly; increasing by 1 mcg/kg/week increments to achieve platelet count $\geq$50,000/mm^3 (Max dose: 10 mcg/kg/ week)	**Monitoring** CBC with differential **AE/toxicities** Common: headache, dizziness, abdominal pain, arthralgia, myalgia, increased circulating myeloblasts (MDA patients) Serious: angioedema, marrow fibrosis, VTE, hematology malignancy risk		• Onset of action between 4–9 days • Should be discontinued after 4 weeks if no response • Upon discontinuation of therapy, may see rebound thrombocytopenia and increased bleeding risk • May be used off label to increase platelet count if high risk for bleeding or for CIT

WBC white blood cell, *IV* intravenous, *SQ* subcutaneous, *CBC* complete blood count, *AE* adverse effects, *ARDS* acute respiratory distress syndrome, *ITP* idiopathic thrombocytopenia purpura, *VTE* venous thromboembolism, *CIT* chemotherapy-induced thrombocytopenia

Table 14 Antidotes for critically Ill oncologic patients

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
Sodium bicarbonate or sodium acetate [65]	Urinary alkalinization for methotrexate toxicity	**Dosing** **Dose**: IV: 50 meq/L to maximally tolerated rate (≥3 L/m^2 per day) to maximize urine output and keep urine pH > 7	**AE/Toxicities** Metabolic alkalosis		• Limited compatibility with many other IV medications
Amifostine [122]	Cisplatin toxicity	**Dosing** **Dose**: IV: 910 mg/m^2 over 15 min once daily given 30 min prior to chemotherapy. Chemotherapy should be started 15 min after completion of amifostine infusion.	**Monitoring** BP every 3–5 min during infusion and decrease dose for severe decrease in SBP (see dosage adjustments from package insert). If full dose cannot be administered prior to cisplatin therapy, reduce amifostine dose to 740 mg/m^2 for subsequent cycles **AE/Toxicities** Hypotension, N/V	Patients should have antihypertensive therapy interrupted 24 h before receiving amifostine	• Cytoprotective detoxicant. Reduces ototoxicity, nephrotoxicity, and possible decrease in severity of peripheral neuropathy • Premedicate with antiemetics including dexamethasone and a serotonin $5HT_3$ receptor antagonist
Dexrazoxane [107]	Extravasation Doxorubicin toxicity	**Dosing** First infusion should be started within 6 h after extravasation IV: Day 1: 1,000 mg/m2 (max 2000 mg/day) Day 2: 1,000 mg/m2 (Max: 2000 mg) Day 3: 500 mg/m2 (Max 1000 mg) Infusions on day 2 and 3 should start at the same hour (± 3 h) as on the first day	**AE/Toxicities** myelosuppression		• Remove cooling procedures (e.g., ice packs) from area at least 15 min prior to administration to allow sufficient blood flow to area
Leucovorin [65]	Primary therapy for MTX toxicity	**Dosing** IV, IM, or PO: Initially 15 mg (10 mg/m^2), then 15 mg (10 mg/m^2) q6h until serum MTX <0.05 uM/L. Subsequent dosing based on follow-up MTX levels [65] If SCr ≥ 50% baseline 24 h post MTX, or if serum MTX > 5 uM/L, increase leucovorin to 100 mg/m^2 IV or q3h until serum MTX < 0.05 uM/L.	**AE/Toxicities** Dehydration, diarrhea		• Do *not* administer within 2 h before or after glucarpidase • Do not exceed infusion rate of 160 mg of leucovorin per minute due to calcium content of solution

(*continued*)

Table 14 (continued)

Drug	Primary role in therapy	Dosing and administration	Monitoring, adverse events, and toxicities	Drug-drug interactions	Clinical pearls
Glucarpidase [65]	MTX toxicity in patients with renal dysfunction	**Dosing** IV: 50 U/g over 5 min	**Monitoring** Serum MTX reduced by ≥97% within 15 min of dose administration		• MTX TDM is unreliable for at least 48 h following glucarpidase administration • No effect on intracellular MTX concentrations. Must be administered with high-dose leucovorin
Levocarnitine [15]	Pegaspargase-induced hepatotoxicity	**Dosing** IV LD: 50 mg/kg, followed by 50 mg/kg/day divided in six daily doses	**AE/Toxicities** Diarrhea, hypertension	Patients who are on antidiabetic agents may need dose adjustments for hypoglycemia	• Use with caution in patients with history of seizures
Methylene blue [103, 115]	Ifosfamide-induced neurotoxicity	**Dosing** IV: 50 mg infused up to six times daily	**AE/Toxicities** Contraindicated in patients with G6PD deficiency Dysgeusia, hot flashes	Avoid concomitant use with SSRIs, SNRIs, and MAOI therapy due to risk of serotonin syndrome	• Urine discoloration (blue or green) can occur due to oxidation when exposed to air
Thiamine [46, 61, 73, 131]	Ifosfamide toxicity Beriberi Wernicke's Encephalopathy	**Dosing** Limited data: IV: Ifosfamide toxicity: 100 mg q4h Beriberi: IV: 100 mg/day x7 days, followed by 10 mg/day orally until complete recovery Wernicke's Encephalopathy: IV: 200 mg TID x 5–7 days or until no further improvement in symptoms			• Consider thiamine for Wernicke in the malnourished and confused oncologic patient

IV intravenous, *AE* adverse effects, *BP* blood pressure, *SBP* systolic blood pressure, *N/V* nausea and vomiting, *MTX* methotrexate, *IM* intramuscular, *PO* by mouth, *q3h* every three hours, *TDM* therapeutic drug monitoring, *LD* loading dose, *TID* three times daily

some examples of off-label uses for thrombopoietin agents, such as romiplostim (Table 13) [83, 86, 96, 128].

Antidotes

The toxicity profiles of chemotherapy regimens are often severe and adversely affect patients' quality of life. Although most symptoms can be managed with supportive care (see Table 1 in ▶ Chap. 16, "Complications and Toxicities Associated with Cancer Therapies in the Intensive Care Unit"), there are times when treatment interruptions or reversal are necessary.

For reversal of toxicities or overdose, infusion of antidote should be started as soon as possible (Table 14).

References

1. Abouelnasr A, Roy J, Cohen S, Kiss T, Lachance S. Defining the role of sirolimus in the management of graft-versus-host disease: from prophylaxis to treatment. Biol Blood Marrow Transplant. 2013;19(1):12–21. https://doi.org/10.1016/j.bbmt.2012.06.020.
2. Afessa B, Tefferi A, Litzow MR, Peters SG. Outcome of diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. Am J Respir Crit Care Med. 2002;166(10):1364–8. https://doi.org/10.1164/rccm.200208-792OC.
3. Amgen Inc. Nplate (romiplostim) [package insert]. Thousand Oaks; 2008.
4. Amgen Inc. Xgeva (denosumab) [package insert]. Thousand Oaks; 2013.
5. Amgen Inc. Neulasta (pegfilgrastim) [package insert]. Thousand Oaks; 2015a.
6. Amgen Inc. Neupogen (filgrastim) [package insert]. Thousand Oaks; 2015b.
7. Antun AG, Gleason S, Arellano M, Langston AA, McLemore ML, Gaddh M, el Rassi F, Bernal-Mizrachi L, Galipeau J, Heffner LT Jr, Winton EF, Khoury HJ. Epsilon aminocaproic acid prevents bleeding in severely thrombocytopenic patients with hematological malignancies. Cancer. 2013;119(21):3784–7. https://doi.org/10.1002/cncr.28253.
8. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother. 2014;69(5):1162–76. https://doi.org/10.1093/jac/dkt508.
9. Astellas Pharma. Prograf (tacrolimus) [package insert]. Deerfield; 2012.
10. Astellas Pharma. Cresemba (Isavuconazonium sulfate) [package insert]. Northbrook; 2015.
11. Baden LR, Swaminathan S, Almyroudis NG, Angarone M, Blouin G, Camins BC, Cooper B, Dubberke ER, Engemann AM, Freifeld AG, Greene JN, Gregg K, Hakim H, Ito. IJ, Lustberg ME, Mones JV, Pergam S, Rolston K, Satyanarayana G, Schulz L, Seo SK, Shoham S, Taplitz R, Topal J, Wilson JW. Prevention and treatment of cancer-related infections, Version 1.2018. NCCN Clinical Practice Guidelines in Oncology; 2018.
12. Baker MS, Diab KJ, Carlos WG, Mathur P. Intrapulmonary recombinant factor VII as an effective treatment for diffuse alveolar hemorrhage: a case series. J Bronchol Intervent Pulmonol. 2016;23(3):255–8. https://doi.org/10.1097/lbr.0000000000000286.
13. Ben Venue Laboratories I. Aredia (pamidronate) [package insert]. Bedford; 2009.
14. Blackburn LM, Tverdek FP, Hernandez M, Bruno JJ. First-dose pharmacokinetics of aminoglycosides in critically ill haematological malignancy patients. Int J Antimicrob Agents. 2015;45(1):46–53. https://doi.org/10.1016/j.ijantimicag.2014.09.006.
15. Blackman A, Boutin A, Shimanovsky A, Baker WJ, Forcello N. Levocarnitine and vitamin B complex for the treatment of pegaspargase-induced hepatotoxicity: a case report and review of the literature. J Oncol Pharm Pract. 2017; https://doi.org/10.1177/1078155217710714.
16. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. Blood. 2009;113(23):5711–9. https://doi.org/10.1182/blood-2008-10-143560.
17. Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: cause for concern? Epilepsia. 2013;54(1):11–27. https://doi.org/10.1111/j.1528-1167.2012.03671.x.
18. Brody SR, Humphreys MH, Gambertoglio JG, Schoenfeld P, Cundy KC, Aweeka FT. Pharmacokinetics of cidofovir in renal insufficiency and in continuous ambulatory peritoneal dialysis or high-flux hemodialysis. Clin Pharmacol Ther. 1999;65(1):21–8. https://doi.org/10.1016/s0009-9236(99)70118-9.
19. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, Laroche SM, Riviello JJ Jr, Shutter L, Sperling MR, Treiman DM, Vespa PM. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17(1):3–23. https://doi.org/10.1007/s12028-012-9695-z.
20. Cairo MS, Coiffier B, Reiter A, Younes A. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases:

an expert TLS panel consensus. Br J Haematol. 2010;149(4):578–86. https://doi.org/10.1111/j.1365-2141.2010.08143.x.
21. Casper C, Englund J, Boeckh M. How I treat influenza in patients with hematologic malignancies. Blood. 2010;115(7):1331–42. https://doi.org/10.1182/blood-2009-11-255455.
22. Chemaly RF, Aitken SL, Wolfe CR, Jain R, Boeckh MJ. Aerosolized ribavirin: the most expensive drug for pneumonia. Transpl Infect Dis. 2016;18(4):634–6. https://doi.org/10.1111/tid.12551.
23. Chemaly RF, Shah DP, Boeckh MJ. Management of respiratory viral infections in hematopoietic cell transplant recipients and patients with hematologic malignancies. Clin Infect Dis. 2014;59(Suppl 5):S344–51. https://doi.org/10.1093/cid/ciu623.
24. Cho SY, Lee DG, Choi SM, Park C, Chun HS, Park YJ, Choi JK, Lee HJ, Park SH, Choi JH, Yoo JH. Stenotrophomonas maltophilia bloodstream infection in patients with hematologic malignancies: a retrospective study and in vitro activities of antimicrobial combinations. BMC Infect Dis. 2015;15:69. https://doi.org/10.1186/s12879-015-0801-7.
25. Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26(16):2767–78. https://doi.org/10.1200/jco.2007.15.0177.
26. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J. Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2014;25(Suppl 3):iii124–37. https://doi.org/10.1093/annonc/mdu103.
27. Coppell JA, Richardson PG, Soiffer R, Martin PL, Kernan NA, Chen A, Guinan E, Vogelsang G, Krishnan A, Giralt S, Revta C, Carreau NA, Iacobelli M, Carreras E, Ruutu T, Barbui T, Antin JH, Niederwieser D. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant. 2010;16(2):157–68. https://doi.org/10.1016/j.bbmt.2009.08.024.
28. Cornely OA, Arikan-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, Lanternier F, Pagano L, Skiada A, Akova M, Arendrup MC, Boekhout T, Chowdhary A, Cuenca-Estrella M, Freiberger T, Guinea J, Guarro J, de Hoog S, Hope W, Johnson E, Kathuria S, Lackner M, Lass-Florl C, Lortholary O, Meis JF, Meletiadis J, Munoz P, Richardson M, Roilides E, Tortorano AM, Ullmann AJ, van Diepeningen A, Verweij P, Petrikkos G. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin Microbiol Infect. 2014;20(Suppl 3):5–26. https://doi.org/10.1111/1469-0691.12371.
29. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, Helfgott D, Holowiecki J, Stockelberg D, Goh YT, Petrini M, Hardalo C, Suresh R, Angulo-Gonzalez D. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356(4):348–59. https://doi.org/10.1056/NEJMoa061094.
30. Corp. MSD. Prevymis (letermovir) [package insert]. Whitehouse Station; 2017.
31. Crawford J, Becker PS, Armitage JO, Blayney DW, Chavez J, Curtin P, Dinner S, Fynan T, Gojo I, Griffiths EA, Hough S, Kloth DD, Kuter DJ, Lyman GH, Mably M, Mukherjee S, Patel S, Perez LE, Poust A, Rampal R, Roy V, Rugo HS, Saad AA, Schwartzberg LS, Shayani S, Talbott M, Vadhan-Raj S, Vasu S, Wadleigh M, Westervelt P, Burns JL, Pluchino L. Myeloid growth factors, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw. 2017;15(12):1520–41. https://doi.org/10.6004/jnccn.2017.0175.
32. Crothers K, Furrer H, Helweg-Larsen J, Huang L, Kovacs J, Miller R, Morris A (2017) Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed 19 Apr 2018.
33. Cruciani M, Rampazzo R, Malena M, Lazzarini L, Todeschini G, Messori A, Concia E. Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis. Clin Infect Dis. 1996;23(4):795–805.
34. Crumpacker C, Zhang J. Cytomegalovirus. In: Mandell G, Bennett J, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 7th ed. Philadelphia: Elsevier; 2010. p. 1971–87.
35. Cutler C, Stevenson K, Kim HT, Richardson P, Ho VT, Linden E, Revta C, Ebert R, Warren D, Choi S, Koreth J, Armand P, Alyea E, Carter S, Horowitz M, Antin JH, Soiffer R. Sirolimus is associated with veno-occlusive disease of the liver after myeloablative allogeneic stem cell transplantation. Blood. 2008;112(12):4425–31. https://doi.org/10.1182/blood-2008-07-169342.
36. Dalle JH, Giralt SA. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: risk factors and stratification, prophylaxis, and treatment. Biol Blood Marrow Transplant. 2016;22(3):400–9. https://doi.org/10.1016/j.bbmt.2015.09.024.
37. Diri R, Anwer F, Yeager A, Krishnadasan R, McBride A. Retrospective review of intravenous pentamidine for Pneumocystis pneumonia prophylaxis in allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis. 2016;18(1):63–9. https://doi.org/10.1111/tid.12486.

38. El Chaer F, Shah DP, Chemaly RF. How I treat resistant cytomegalovirus infection in hematopoietic cell transplantation recipients. Blood. 2016;128(23):2624–36. https://doi.org/10.1182/blood-2016-06-688432.
39. Escuissato DL, Warszawiak D, Marchiori E. Differential diagnosis of diffuse alveolar haemorrhage in immunocompromised patients. Curr Opin Infect Dis. 2015;28(4):337–42. https://doi.org/10.1097/qco.0000000000000181.
40. Exela Pharma Sciences. Ganciclovir [package insert]. Lenoir; 2017.
41. Falci DR, Pasqualotto AC. Profile of isavuconazole and its potential in the treatment of severe invasive fungal infections. Infect Drug Resist. 2013;6:163–74. https://doi.org/10.2147/idr.S51340.
42. Foolad F, Aitken S, Shigle T. Use of oral ribavirin for the treatment of RSV Infections in Hematopoietic Cell Transplant Recipients. Paper presented at the ID Week; 2017.
43. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2011;52(4):e56–93. https://doi.org/10.1093/cid/cir073.
44. Fresenius Kabi. Decadron (dexamethasone sodium phosphate) [package insert]. Lake Zurich; 2014.
45. Fukuda T, Hackman RC, Guthrie KA, Sandmaier BM, Boeckh M, Maris MB, Maloney DG, Deeg HJ, Martin PJ, Storb RF, Madtes DK. Risks and outcomes of idiopathic pneumonia syndrome after nonmyeloablative and conventional conditioning regimens for allogeneic hematopoietic stem cell transplantation. Blood. 2003;102(8):2777–85. https://doi.org/10.1182/blood-2003-05-1597.
46. Galvin R, Brathen G, Ivashynka A, Hillbom M, Tanasescu R, Leone MA. EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. Eur J Neurol. 2010;17(12):1408–18. https://doi.org/10.1111/j.1468-1331.2010.03153.x.
47. Garnacho-Montero J, Diaz-Martin A, Canton-Bulnes-L, Ramirez P, Sierra R, Arias-Verdu D, Rodriguez-Delgado M, Loza-Vazquez A, Rodriguez-Gomez J, Gordon M, Estella A, Garcia-Garmendia JL. Initial antifungal strategy reduces mortality in critically ill patients with candidemia: a propensity score-adjusted analysis of a multicenter study. Crit Care Med. 2018;46(3):384–93. https://doi.org/10.1097/ccm.0000000000002867.
48. Genentech I. Actemra (tocilizumab) [package insert]. South San Francisco: Genentech, Inc; 2018.
49. Genentech USA I. Copegus (ribavirin) [package insert]. South San Francisco; 2011.
50. Gerber B, Guggenberger R, Fasler D, Nair G, Manz MG, Stussi G, Schanz U. Reversible skeletal disease and high fluoride serum levels in hematologic patients receiving voriconazole. Blood. 2012;120(12):2390–4. https://doi.org/10.1182/blood-2012-01-403030.
51. Gilbert D. Aminoglycosides. In: Mandell GLBJ, Dolin R, editors. Principles and practice of infectious diseases. 5th ed. New York: Churchill Livingston; 2000. p. 307–35.
52. Gilead Sciences I. Tamiflu (oseltamivir phosphate) [package insert]. Foster City; 2008.
53. Gilead Sciences I. Vistide (cidofovir injection) [package insert]. Foster City; 2010.
54. GlaxoSmithKline. Zovirax (acyclovir) [package insert]. Research Triangle Park; 2003.
55. Goldner W. Cancer-related hypercalcemia. J Oncol Pract. 2016;12(5):426–32. https://doi.org/10.1200/jop.2016.011155.
56. Greenberg RN, Mullane K, van Burik JA, Raad I, Abzug MJ, Anstead G, Herbrecht R, Langston A, Marr KA, Schiller G, Schuster M, Wingard JR, Gonzalez CE, Revankar SG, Corcoran G, Kryscio RJ, Hare R. Posaconazole as salvage therapy for zygomycosis. Antimicrob Agents Chemother. 2006;50(1):126–33. https://doi.org/10.1128/aac.50.1.126-133.2006.
57. Grewal J, Grewal HK, Forman AD. Seizures and epilepsy in cancer: etiologies, evaluation, and management. Curr Oncol Rep. 2008;10(1):63–71.
58. Gupta SK, Kantesaria B, Glue P. Pharmacokinetics, safety, and tolerability of ribavirin in hemodialysis-dependent patients. Eur J Clin Pharmacol. 2012;68(4):415–8. https://doi.org/10.1007/s00228-011-1137-x.
59. Gupta SK, Kantesaria B, Glue P. Pharmacokinetics and safety of single-dose ribavirin in patients with chronic renal impairment. Drug Discov Ther. 2013;7(4):158–63.
60. Gupta SK, Kantesaria B, Glue P. Exploring the influence of renal dysfunction on the pharmacokinetics of ribavirin after oral and intravenous dosing. Drug Discoveries & Therapeutics. 2014;8(2):89–95.
61. Hamadani M, Awan F. Role of thiamine in managing ifosfamide-induced encephalopathy. J Oncol Pharm Pract. 2006;12(4):237–9. https://doi.org/10.1177/1078155206073553.
62. Hankerson MJ, Raffetto B, Mallon WK, Shoenberger JM. Nebulized tranexamic acid as a noninvasive therapy for cancer-related hemoptysis. J Palliat Med. 2015;18(12):1060–2. https://doi.org/10.1089/jpm.2015.0167.
63. Holly P, Lisa L, Plamenova I, Dobrotova M, Kubisz P. Recombinant activated factor VII as an additional agent in the management of bleeding in patients with chemotherapy-induced thrombocytopenia. Blood transfus. 2013;11(3):466–8. https://doi.org/10.2450/2012.0077-12.
64. Hospira Inc. Amicar (aminocaproic acid) [package insert]. Lake Forest; 2017.

65. Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and managing toxicities of high-dose methotrexate. Oncologist. 2016;21(12):1471–82. https://doi.org/10.1634/theoncologist.2015-0164.
66. Imbach P, Crowther M. Thrombopoietin-receptor agonists for primary immune thrombocytopenia. N Engl J Med. 2011;365(8):734–41. https://doi.org/10.1056/NEJMct1014202.
67. Jaksic B, Martinelli G, Perez-Oteyza J, Hartman CS, Leonard LB, Tack KJ. Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. Clin Infect Dis. 2006;42(5):597–607. https://doi.org/10.1086/500139.
68. Janssen Biotech I. Sylvant (siltuximab) [package insert]. Horsham; 2017.
69. Jazz Pharmaceuticals I. Defitelio (defibrotide) [package insert]. Palo Alto; 2016.
70. Kantrow SP, Hackman RC, Boeckh M, Myerson D, Crawford SW. Idiopathic pneumonia syndrome: changing spectrum of lung injury after marrow transplantation. Transplantation. 1997;63(8):1079–86.
71. Kim S-H, Kwon J-C, Choi S-M, Lee D-G, Park SH, Choi J-H, Yoo J-H, Cho B-S, Eom K-S, Kim Y-J, Kim H-J, Lee S, Min C-K, Cho S-G, Kim D-W, Lee J-W, Min W-S. Escherichia coli and Klebsiella pneumoniae bacteremia in patients with neutropenic fever: factors associated with extended-spectrum β-lactamase production and its impact on outcome. Ann Hematol. 2013;92(4):533–41. https://doi.org/10.1007/s00277-012-1631-y.
72. Kostakou E, Rovina N, Kyriakopoulou M, Koulouris NG, Koutsoukou A. Critically ill cancer patient in intensive care unit: issues that arise. J Crit Care. 2014;29(5):817–22. https://doi.org/10.1016/j.jcrc.2014.04.007.
73. Kuo SH, Debnam JM, Fuller GN, de Groot J. Wernicke's encephalopathy: an underrecognized and reversible cause of confusional state in cancer patients. Oncology. 2009;76(1):10–8. https://doi.org/10.1159/000174951.
74. Kuter DJ. Thrombopoietin and thrombopoietin mimetics in the treatment of thrombocytopenia. Annu Rev Med. 2009;60:193–206.
75. Kuter DJ. Managing thrombocytopenia associated with cancer chemotherapy. Oncology (Williston Park). 2015;29(4):282–94.
76. Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Gernsheimer TB, Senecal FM, Aledort LM, George JN, Kessler CM, Sanz MA, Liebman HA, Slovick FT, de Wolf JT, Bourgeois E, Guthrie TH Jr, Newland A, Wasser JS, Hamburg SI, Grande C, Lefrere F, Lichtin AE, Tarantino MD, Terebelo HR, Viallard JF, Cuevas FJ, Go RS, Henry DH, Redner RL, Rice L, Schipperus MR, Guo DM, Nichol JL. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet (London, England). 2008;371(9610):395–403. https://doi.org/10.1016/s0140-6736(08)60203-2.
77. Lara AR, Schwarz MI. Diffuse alveolar hemorrhage. Chest. 2010;137(5):1164–71. https://doi.org/10.1378/chest.08-2084.
78. Leibovici L, Paul M, Cullen M, Bucaneve G, Gafter-Gvili A, Fraser A, Kern WV. Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. Cancer. 2006;107(8):1743–51. https://doi.org/10.1002/cncr.22205.
79. Lewis ID, DeFor T, Weisdorf DJ. Increasing incidence of diffuse alveolar hemorrhage following allogeneic bone marrow transplantation: cryptic etiology and uncertain therapy. Bone Marrow Transplant. 2000;26(5):539–43. https://doi.org/10.1038/sj.bmt.1702546.
80. Lindemans CA, Leen AM, Boelens JJ. How I treat adenovirus in hematopoietic stem cell transplant recipients. Blood. 2010;116(25):5476–85. https://doi.org/10.1182/blood-2010-04-259291.
81. Loblaw DA, Perry J, Chambers A, Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. J Clin Oncol. 2005;23(9):2028–37. https://doi.org/10.1200/jco.2005.00.067.
82. Ltd. CH. Foscavir (foscarnet sodium) [package insert]. DE14 2WW, UK; 2011.
83. Marshall AL, Goodarzi K, Kuter DJ. Romiplostim in the management of the thrombocytopenic surgical patient. Transfusion. 2015;55(10):2505–10. https://doi.org/10.1111/trf.13181.
84. Marty FM, Ljungman P, Chemaly RF, Maertens J, Dadwal SS, Duarte RF, Haider S, Ullmann AJ, Katayama Y, Brown J, Mullane KM, Boeckh M, Blumberg EA, Einsele H, Snydman DR, Kanda Y, DiNubile MJ, Teal VL, Wan H, Murata Y, Kartsonis NA, Leavitt RY, Badshah C. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. N Engl J Med. 2017;377(25):2433–44. https://doi.org/10.1056/NEJMoa1706640.
85. Metcalf JP, Rennard SI, Reed EC, Haire WD, Sisson JH, Walter T, Robbins RA. Corticosteroids as adjunctive therapy for diffuse alveolar hemorrhage associated with bone marrow transplantation. University of Nebraska Medical Center Bone Marrow Transplant Group. Am J Med. 1994;96(4):327–34.
86. Miao J, Leblebjian H, Fowler-Scullion B, Parnes A. Single-center experience with Romiplostim for management of chemotherapy-induced thrombocytopenia (CIT). Blood. 2016;128:530.
87. Mielcarek M, Furlong T, Storer BE, Green ML, McDonald GB, Carpenter PA, Flowers ME, Storb R, Boeckh M, Martin PJ. Effectiveness and safety of lower dose prednisone for initial treatment of acute graft-versus-host disease: a randomized

controlled trial. Haematologica. 2015;100(6):842–8. https://doi.org/10.3324/haematol.2014.118471.
88. Mintzer S, Mattson RT. Should enzyme-inducing antiepileptic drugs be considered first-line agents? Epilepsia. 2009;50(Suppl 8):42–50. https://doi.org/10.1111/j.1528-1167.2009.02235.x.
89. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis. 1987;155(1):93–9.
90. Mylan Institutional LLC. Miacalcin (calcitonin) [product insert]. Rockford; 2016.
91. Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, Komanduri KV, Lin Y, Jain N, Daver N, Westin J, Gulbis AM, Loghin ME, de Groot JF, Adkins S, Davis SE, Rezvani K, Hwu P, Shpall EJ. Chimeric antigen receptor T-cell therapy – assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15(1):47–62. https://doi.org/10.1038/nrclinonc.2017.148.
92. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother. 1995;39(3):650–5.
93. Novartis Pharmaceuticals Corporation. Sandimmune (cyclosporine capsules, oral solution, injection) [package insert]. East Hanover; 2015.
94. Novartis Pharmaceuticals Corporation. Zometa (zoledronic acid) [package insert]. East Hanover; 2016.
95. Novo Nordisk Inc. NovoSeven (coagulation factor VIIa) [package insert]. Princeton; 2006.
96. Ojeda E, Carca-Marco JA, Navarro B, Delalglesia A, Fores R, Bautista G, Krsnik I, Sanchez-Guerrero A, Sanjuan I, Regidor C, Gonzalo-Daganzo R, Martin-Donaire T, Sanchez R, Bravo G, Claros N, Cabero M, Beltran P, Cabrera JR. Use of romiplostim to facilitate platelet engraftment in allogeneic hematopoietic transplantation. Blood. 2011;118:1947.
97. Pagkalis S, Mantadakis E, Mavros MN, Ammari C, Falagas ME. Pharmacological considerations for the proper clinical use of aminoglycosides. Drugs. 2011;71(17):2277–94. https://doi.org/10.2165/11597020-000000000-00000.
98. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. Clinical Practice Guideline for the Management of Candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1–50. https://doi.org/10.1093/cid/civ933.
99. Paquette F, Bernier-Jean A, Brunette V, Ammann H, Lavergne V, Pichette V, Troyanov S, Bouchard J. Acute kidney injury and renal recovery with the use of aminoglycosides: a large retrospective study. Nephron. 2015;131(3):153–60. https://doi.org/10.1159/000440867.
100. Pathak V, Kuhn J, Gabriel D, Barrow J, Jennette JC, Henke DC. Use of activated factor VII in patients with diffuse alveolar hemorrhage: a 10 years institutional experience. Lung. 2015;193(3):375–9. https://doi.org/10.1007/s00408-015-9720-z.
101. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal BH, Steinbach WJ, Stevens DA, Walsh TJ, Wingard JR, Young JA, Bennett JE. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63(4):e1–e60. https://doi.org/10.1093/cid/ciw326.
102. Paul M, Yahav D, Fraser A, Leibovici L. Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2006;57(2):176–89. https://doi.org/10.1093/jac/dki448.
103. Pelgrims J, De Vos F, Van den Brande J, Schrijvers D, Prove A, Vermorken JB. Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. Br J Cancer. 2000;82(2):291–4. https://doi.org/10.1054/bjoc.1999.0917.
104. Pennington CA, Park JM. Sublingual tacrolimus as an alternative to oral administration for solid organ transplant recipients. Am J Health Syst Pharm. 2015;72(4):277–84. https://doi.org/10.2146/ajhp140322.
105. Pfizer. Cyklokapron (tranexamic acid) [package insert]. New York; 2011a.
106. Pfizer. Solu-Medrol (methylprednisolone sodium succinate for injection) [package insert]. New York; 2011b.
107. Pfizer. Zinecard (dexrazoxane for injection) [package insert]. New York; 2012.
108. Pfizer Inc. Rapamune (sirolimus) [package insert]. Philadelphia; 2011.
109. Pharmacia & Upjohn Co. Zyvox (linezolid) [package insert]. New York; 2018.
110. Posteraro B, De Pascale G, Tumbarello M, Torelli R, Pennisi MA, Bello G, Maviglia R, Fadda G, Sanguinetti M, Antonelli M. Early diagnosis of candidemia in intensive care unit patients with sepsis: a prospective comparison of (1–>3)-beta-D-glucan assay, Candida score, and colonization index. Crit Care. 2011;15(5):R249. https://doi.org/10.1186/cc10507.
111. Radigan EA, Gilchrist NA, Miller MA. Management of aminoglycosides in the intensive care unit. J Intensive Care Med. 2010;25(6):327–42. https://doi.org/10.1177/0885066610377968.
112. Raptis A, Mavroudis D, Suffredini A, Molldrem J, Rhee FV, Childs R, Phang S, Barrett A. High-dose corticosteroid therapy for diffuse alveolar hemorrhage in allogeneic bone marrow stem cell transplant recipients. Bone Marrow Transplant.

1999;24(8):879–83. https://doi.org/10.1038/sj.bmt.1701995.
113. Rathi NK, Tanner AR, Dinh A, Dong W, Feng L, Ensor J, Wallace SK, Haque SA, Rondon G, Price KJ, Popat U, Nates JL. Low-, medium- and high-dose steroids with or without aminocaproic acid in adult hematopoietic SCT patients with diffuse alveolar hemorrhage. Bone Marrow Transplant. 2015;50(3):420–6. https://doi.org/10.1038/bmt.2014.287.
114. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45(3):486–552. https://doi.org/10.1097/ccm.0000000000002255.
115. Richards A, Marshall H, McQuary A. Evaluation of methylene blue, thiamine, and/or albumin in the prevention of ifosfamide-related neurotoxicity. J Oncol Pharm Pract. 2011;17(4):372–80. https://doi.org/10.1177/1078155210385159.
116. Richardson PG, Ho VT, Giralt S, Arai S, Mineishi S, Cutler C, Antin JH, Stavitzski N, Niederwieser D, Holler E, Carreras E, Soiffer R. Safety and efficacy of defibrotide for the treatment of severe hepatic veno-occlusive disease. Ther Adv Hematol. 2012;3(4):253–65. https://doi.org/10.1177/2040620712441943.
117. Richardson PG, Riches ML, Kernan NA, Brochstein JA, Mineishi S, Termuhlen AM, Arai S, Grupp SA, Guinan EC, Martin PL, Steinbach G, Krishnan A, Nemecek ER, Giralt S, Rodriguez T, Duerst R, Doyle J, Antin JH, Smith A, Lehmann L, Champlin R, Gillio A, Bajwa R, D'Agostino RB Sr, Massaro J, Warren D, Miloslavsky M, Hume RL, Iacobelli M, Nejadnik B, Hannah AL, Soiffer RJ. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. Blood. 2016;127(13):1656–65. https://doi.org/10.1182/blood-2015-10-676924.
118. Roberts I, Coats T, Edwards P, Gilmore I, Jairath V, Ker K, Manno D, Shakur H, Stanworth S, Veitch A. HALT-IT–tranexamic acid for the treatment of gastrointestinal bleeding: study protocol for a randomised controlled trial. Trials. 2014;15:450. https://doi.org/10.1186/1745-6215-15-450.
119. Rybak JM, Marx KR, Nishimoto AT, Rogers PD. Isavuconazole: pharmacology, pharmacodynamics, and current clinical experience with a new triazole antifungal agent. Pharmacotherapy. 2015;35(11):1037–51. https://doi.org/10.1002/phar.1652.
120. Sandherr M, Maschmeyer G. Pharmacology and metabolism of voriconazole and Posaconazole in the treatment of invasive aspergillosis: review of the literature. Eur J Med Res. 2011;16(4):139–44.
121. Sanofi-Aventis. Elitek (rasburicase) [package insert]. Bridgewater; 2017.
122. Santabarbara G, Maione P, Rossi A, Gridelli C. Pharmacotherapeutic options for treating adverse effects of Cisplatin chemotherapy. Expert Opin Pharmacother. 2016;17(4):561–70. https://doi.org/10.1517/14656566.2016.1122757.
123. Segrelles Calvo G, De Granda-Orive I, Lopez Padilla D. Inhaled tranexamic acid as an alternative for hemoptysis treatment. Chest. 2016;149(2):604. https://doi.org/10.1016/j.chest.2015.10.016.
124. Shimabukuro-Vornhagen A, Boll B, Kochanek M, Azoulay E, von Bergwelt-Baildon MS. Critical care of patients with cancer. CA Cancer J Clin. 2016; https://doi.org/10.3322/caac.21351.
125. Skiada A, Lanternier F, Groll AH, Pagano L, Zimmerli S, Herbrecht R, Lortholary O, Petrikkos GL. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). Haematologica. 2013;98(4):492–504. https://doi.org/10.3324/haematol.2012.065110.
126. Smith PF, Birmingham MC, Noskin GA, Meagher AK, Forrest A, Rayner CR, Schentag JJ. Safety, efficacy and pharmacokinetics of linezolid for treatment of resistant Gram-positive infections in cancer patients with neutropenia. Ann Oncol. 2003;14(5):795–801.
127. Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, Goldberg JM, Khatcheressian JL, Leighl NB, Perkins CL, Somlo G, Wade JL, Wozniak AJ, Armitage JO. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline update. J Clin Oncol. 2015;33(28):3199–212. https://doi.org/10.1200/jco.2015.62.3488.
128. Soff GA, Miao Y, Devlin SM, Mantha S, Mones JV, Li VJ, Abou-Alfa GK, Cercek A, Kemeny N, Parameswara R. Romiplostim for chemotherapy-induced thrombcytopenia (CIT). Results of a phase 2 trial. Blood. 2017;130:289.
129. Soubani AO, Pandya CM. The spectrum of non-infectious pulmonary complications following hematopoietic stem cell transplantation. Hematol Oncol Stem Cell Ther. 2010;3(3):143–57.
130. Staras SA, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of

cytomegalovirus infection in the United States, 1988–1994. Clin Infect Dis. 2006;43(9):1143–51. https://doi.org/10.1086/508173.
131. Steinberg A, Gorman E, Tannenbaum J. Thiamine deficiency in stem cell transplant patients: a case series with an accompanying review of the literature. Clin Lymphoma Myeloma Leuk. 2014;14(Suppl): S111–3. https://doi.org/10.1016/j.clml.2014.06.009.
132. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. N Engl J Med. 2005;352(4):373–9. https://doi.org/10.1056/NEJMcp042806.
133. Tang Y, Wu Q, Wu X, Qiu H, Sun A, Ruan C, Wu D, Han Y. Use of recombinant factor VIIa in uncontrolled gastrointestinal bleeding after hematopoietic stem cell transplantation among patients with thrombocytopenia. Pak J Med Sci. 2015;31(6):1389–93. https://doi.org/10.12669/pjms.316.8357.
134. Thachil J, Falanga A, Levi M, Liebman H, Di Nisio M. Management of cancer-associated disseminated intravascular coagulation: guidance from the SSC of the ISTH. J Thromb Haemost. 2015;13(4):671–5. https://doi.org/10.1111/jth.12838.
135. Tizon R, Frey N, Heitjan DF, Tan KS, Goldstein SC, Hexner EO, Loren A, Luger SM, Reshef R, Tsai D, Vogl D, Davis J, Vozniak M, Fuchs B, Stadtmauer EA, Porter DL. High-dose corticosteroids with or without etanercept for the treatment of idiopathic pneumonia syndrome after allo-SCT. Bone Marrow Transplant. 2012;47(10):1332–7. https://doi.org/10.1038/bmt.2011.260.
136. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, Wingard JR, Young J-A, Boeckh MJ. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. Bone Marrow Transplant. 2009;44(8):453–558.
137. Turner RB, Cumpston A, Sweet M, Briggs F, Slain D, Wen S, Craig M, Hamadani M, Petros W. Prospective, controlled study of acyclovir pharmacokinetics in obese patients. Antimicrob Agents Chemother. 2016;60(3):1830–3. https://doi.org/10.1128/aac.02010-15.
138. UCB I. Keppra (levetiracetam) [package insert]. Smyrna; 2017.
139. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, Greinix H, Morais de Azevedo W, Reddy V, Boparai N, Pedicone L, Patino H, Durrant S. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med. 2007;356(4):335–47. https://doi.org/10.1056/NEJMoa061098.
140. Van Lint MT, Uderzo C, Locasciulli A, Majolino I, Scime R, Locatelli F, Giorgiani G, Arcese W, Iori AP, Falda M, Bosi A, Miniero R, Alessandrino P, Dini G, Rotoli B, Bacigalupo A. Early treatment of acute graft-versus-host disease with high- or low-dose 6-methylprednisolone: a multicenter randomized trial from the Italian Group for Bone Marrow Transplantation. Blood. 1998;92(7):2288–93.
141. Vecht CJ, Haaxma-Reiche H, van Putten WL, de Visser M, Vries EP, Twijnstra A. Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal cord compression. Neurology. 1989;39(9):1255–7.
142. Vecht CJ, van Breemen M. Optimizing therapy of seizures in patients with brain tumors. Neurology. 2006;67(12 Suppl 4):S10–3.
143. Wanko SO, Broadwater G, Folz RJ, Chao NJ. Diffuse alveolar hemorrhage: retrospective review of clinical outcome in allogeneic transplant recipients treated with aminocaproic acid. Biol Blood Marrow Transplant. 2006;12(9):949–53. https://doi.org/10.1016/j.bbmt.2006.05.012.
144. West-Ward Pharmaceuticals. Allopurinol [package insert]. Eatontown; 2015.
145. Wilson DT, Dimondi VP, Johnson SW, Jones TM, Drew RH. Role of isavuconazole in the treatment of invasive fungal infections. Ther Clin Risk Manag. 2016;12:1197–206. https://doi.org/10.2147/tcrm.S90335.
146. Wingard JR, Carter SL, Walsh TJ, Kurtzberg J, Small TN, Baden LR, Gersten ID, Mendizabal AM, Leather HL, Confer DL, Maziarz RT, Stadtmauer EA, Bolanos-Meade J, Brown J, Dipersio JF, Boeckh M, Marr KA. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. Blood. 2010;116(24):5111–8. https://doi.org/10.1182/blood-2010-02-268151.
147. Winter M. Basic and clinical pharmacokinetics. 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2010. p. 263–70.
148. Woo M, Przepiorka D, Ippoliti C, Warkentin D, Khouri I, Fritsche H, Korbling M. Toxicities of tacrolimus and cyclosporin A after allogeneic blood stem cell transplantation. Bone Marrow Transplant. 1997;20(12):1095–8. https://doi.org/10.1038/sj.bmt.1701027.
149. Zeiser R, Blazar BR. Acute graft-versus-host disease – biologic process, prevention, and therapy. N Engl J Med. 2017;377(22):2167–79. https://doi.org/10.1056/NEJMra1609337.
150. Juhl RC, Roddy JVF, Wang TF, Li J, Elefritz JL (2018) Thromboembolic complications following aminocaproic acid use in patients with hematologic malignancies. Leukemia & lymphoma:1–6. https://doi.org/10.1080/10428194.2018.1434882.