Complications and Toxicities Associated with Cancer Therapies in the Intensive Care Unit

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Abstract

Advances in the management of hematologic malignancies and solid tumors have given rise to diverse modalities to treat cancer other than cytotoxic chemotherapy, including targeted therapies, immunotherapies, and cellular therapies. Currently, there are over 175 FDA-approved antineoplastic agents in the United States, many with a diverse and profound toxicity profile. Complications of antineoplastic therapy may result in the need for intensive care unit (ICU) admission to provide acute symptom management. Accordingly, ICU providers caring for cancer patients should have a working knowledge of the toxicities and complications associated with antineoplastic therapy.

Keywords

Chemotherapy · Immunotherapy · Cancer · Toxicity · Oncology · Critical care · Intensive care · Complications · Adverse effects · Antineoplastic agents

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J. L. Nates, K. J. Price (eds.), *Oncologic Critical Care*,
https://doi.org/10.1007/978-3-319-74588-6_21

Introduction

The prevalence of cancer has grown tremendously and with that so has the need for new or repurposed anticancer therapies. Advances in the management of hematologic malignancies and solid tumors have given rise to diverse modalities to treat cancer other than cytotoxic chemotherapy, including targeted therapies, immunotherapies, and cellular therapies. There are over 175 approved antineoplastic agents in the United States and more in development with unique toxicity profiles [163]. This has created a unique opportunity for critical care specialists to manage complications of critically ill cancer patients receiving anticancer therapies.

Toxicities of Anticancer Therapy

Tables 1A–H provides a list of antineoplastic agents and toxicities that may necessitate a higher level of care and/or impact care within the intensive care unit (ICU). These tables are not all-inclusive of every minor adverse effect of each agent. Instead, they focus on toxicities that are considered severe/life-threatening complications or clinically relevant (e.g., grade 3 or 4 adverse effects). Agents that did not meet the criteria for addition to Tables 1A–H include the following: azacitidine, cladarabine, decitabine, elotuzumab, hydroxyurea, ixazomib, lomustine, olaratumab, omacetaxine, procarbazine, talimogene, valrubicin, and venetoclax.

Table 1A

	Neuro		Cardiac						Pulmonary						Renal			GI				Endocrine				Miscellaneous						Notes
	Encephalopathy	Seizures	Heart failure	Thromboembolism	Arrhythmias	QT prolongation	Pericardial effusions	Severe hypertension	Pneumonitis	Pulmonary edema	Pulmonary hypertension	Pleural effusions	Organizing pneumonia	Diffuse alveolar hemorrhage	SIADH – hyponatremia	Renal failure	Hemorrhagic cystitis	Bowel perforation	Neutropenic colitis	Pancreatitis	Hepatotoxicity	Adrenal insufficiency	Hypophysitis	Hyperglycemia	Thyroid disorders	Cytokine release syndrome	Differentiation syndrome	Opportunistic infections	Bleeding (severe)	Rhabdomyolysis	Stevens – Johnson syndrome or Toxic epidermal necrolysis	
5-Fluorouracil (5-FU)	X	X	X		X					X																				X	See Note 1
Abemaciclib				X																	X										See Note 2
Acalabrutinib					X	X																						X	X		See Note 3
Ado-trastuzumab	X		X						X												X								X		See Note 4
Afatinib			X						X							X					X									X	See Note 5
Aflibercept	X			X				X								X		X											X		See Note 6
Aldesleukin	X				X					X						X					X			X							See Note 7
Alectinib					X				X							X					X		X								See Note 8
Alemtuzumab																											X				See Note 9

[1]Cases of hyperammonemic encephalopathy have occurred within 72 h of infusion initiation. Most cases of hyperammonemic encephalopathy are treated with ammonia lowering therapies. Cases of acute cerebellar syndrome have also been reported. Higher incidence of cardiac toxicity with infusion vs bolus dosing of 5FU [60, 149, 151, 238]

[2]Delayed hepatotoxicity (ALT and AST elevations of grade 3 or greater) with median onset 2–6 months, generally resolving to less than grade 3 in 2 weeks with dose interruption, reduction, discontinuation, or delay [137, 225]

[3]Atrial fibrillation and flutter can occur. PJP prophylaxis and CMV monitoring are recommended. Major hemorrhage has been reported with BTK inhibitors. Consider withholding 3–7 days prior to procedures depending on risk of bleeding [13, 41]

[4]GI, CNS, and pulmonary bleeding have occurred in trials with some fatalities. Higher risk in patients on anticoagulants or antiplatelet therapy. Liver failure, hepatic encephalopathy, idiopathic noncirrhotic portal hypertension, and death have been reported [82]

[5]Hepatic impairment is rare but fatalities have been reported. Diarrhea can be severe and may lead to dehydration and subsequent renal failure [31]

[6]Hypertension onset is generally within the first two cycles. Proteinuria, nephrotic syndrome, and TMA have been associated with ziv-aflibercept [210]

[7]High-dose IL-2 has a black box warning for capillary leak syndrome, CNS toxicity, and increased risk for disseminated infection. Use should be restricted to patients with normal cardiac and pulmonary function. IL-2 should only be administered under the supervision of an experienced cancer chemotherapy physician in a facility with ICU facilities available. Consensus guidelines are available to provide criteria for safe administration and toxicity management [66, 196]

[8]Symptomatic bradycardia can occur. When treating hypertension use caution when administering antihypertensive agents that can cause bradycardia. Severe renal events are rare but fatal cases have been reported. The majority of hepatotoxicity occurs within the first 3 months of therapy. Monitor CPK and for signs or symptoms of muscle pain or weakness. Median time to grade 3 CPK elevations 14 days [86]

[9]PJP and HSV prophylaxis is recommended from initiation of treatment until 2 months following last dose or until CD4+ >200/mm^3 [91]

Table 1B

	Neuro		Cardiac						Pulmonary						Renal			GI				Endocrine				Miscellaneous						Notes
	Encephalopathy	Seizures	Heart failure	Thromboembolism	Arrhythmias	QT prolongation	Pericardial effusions	Severe hypertension	Pneumonitis	Pulmonary edema	Pulmonary hypertension	Pleural effusions	Organizing pneumonia	Diffuse alveolar hemorrhage	SIADH – hyponatremia	Renal failure	Hemorrhagic cystitis	Bowel perforation	Neutropenic colitis	Pancreatitis	Hepatotoxicity	Adrenal insufficiency	Hypophysitis	Hyperglycemia	Thyroid disorders	Cytokine release syndrome	Differentiation syndrome	Opportunistic infections	Bleeding (severe)	Rhabdomyolysis	Stevens – Johnson syndrome or Toxic epidermal necrolysis	
Arsenic trioxide						X				X						X															See Note 10
Asparaginase Erwinia chrysanthemi	X			X																X	X			X							See Note 11
Atezolizumab	X		X						X						X	X				X	X	X	X	X	X				X	X	See Note 12
Avelumab	X						X		X						X	X				X	X	X	X	X	X					X	See Note 13
Axicabtagene ciloleucel	X	X	X		X				X							X					X					X		X			See Note 14
Axitinib	X		X	X				X							X			X			X			X	X				X		See Note 15
Belinostat						X																									See Note 16
Bendamustine																														X	See Note 17
Bevacizumab	X		X	X				X	X					X		X		X											X		See Note 18
Bexarotene																				X	X				X						See Note 19
Bleomycin									X				X																		See Note 20
Blinatumomab	X	X																		X	X					X					See Note 21
Bortezomib	X		X						X		X										X										See Note 22
Bosutinib												X				X															See Note 23
Brentuximab vedotin									X									X	X	X								X		X	See Note 24
Brigatinib					X			X	X											X				X							See Note 25
Busulfan		X							X				X								X										See Note 26
Cabazitaxel									X							X	X	X	X												See Note 27
Cabozantinib	X			X				X										X		X					X				X		See Note 28

[10]Differentiation syndrome usually occurs during the first cycle of arsenic, median onset 17 days (7–24 days) and is commonly associated with the development of hyperleukocytosis, pulmonary edema, generalized edema, headache, bone pain, and renal failure. Management includes steroids and/or discontinuation of arsenic depending on severity. Although QT prolongation is well described, clinically significant arrhythmias are rare when appropriately monitored and managed – maintain serum potassium levels above 4 mEq/L and magnesium levels above 1.8 mg/dL [201, 215]

[11]Similar to the other asparaginase formulations, pancreatitis, abnormal transaminases, coagulation abnormalities including thrombosis and hemorrhage, and hyperglycemia can occur [115]

[12]May cause severe immune-mediated adverse events including pneumonitis, median onset 3 months (3 days to 18.7 months) and median duration 2–6 weeks, up to 12.6 months or longer; severe diarrhea, median onset 3–7 weeks (12 days to 3.4 months); hepatitis, median onset 1 month; hypothyroidism, median onset 5 months (15 days to 31 months); hypophysitis, rare, two

case reports, onset 12–13 months. May aggravate underlying autoimmune disorders. Management includes holding therapy, systemic corticosteroids, +/− additional immunosuppressants (e.g., infliximab, mycophenolate, and vedolizumab). Consider PJP prophylaxis in patients with prolonged corticosteroid exposure [33, 89, 122, 160]

[13]May cause severe immune-mediated adverse events including pneumonitis, median onset 2.5 months (3 days to 11 month); hepatitis, median onset 3.2 months (7 days to 15 months); colitis, median onset 2.1 months (2 days to 11 months); adrenal insufficiency, median onset 2.5 months; immune-mediated thyroid disorders, median onset for 2.8 months (2 weeks to 13 months). May aggravate underlying autoimmune disorders. Management includes holding therapy, systemic corticosteroids, +/− additional immunosuppressants (e.g., infliximab, mycophenolate, and vedolizumab). Consider PJP prophylaxis in patients with prolonged corticosteroid exposure [33, 73]

[14]ICANS: Median onset 4 days (1–43 days); median duration of neurologic toxicities 17 days. Most common neurological toxicities: encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia, and anxiety. Fatal and serious cases of cerebral edema have occurred. Other serious events included leukoencephalopathy and seizures

CRS: Median onset 2 days (1–12 days); median duration 7 days (2–58 days). Key manifestations of CRS: fever, hypotension, tachycardia, hypoxia, and chills

Management of CRS depends on grading or severity but includes supportive care, interleukin-2 receptor antagonist tocilizumab, and/or systemic corticosteroids

Grade 2 or higher ICANS without CRS should be treated with supportive care and/or systemic corticosteroids as there is insufficient data with tocilizumab in this setting. Consider anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any grade 2 or higher neurologic toxicities

Cardiac arrhythmias (e.g., atrial fibrillation, ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, HLH/MAS can occur

Hypogammaglobulinemia secondary to B-cell aplasia may persist for up to 13 months and increase the risk for infections. PJP and HSV prophylaxis is recommended for at least 1 year after CAR-T cell therapy [128, 161, 221]

[15]Wound healing complications – hold for at least 24 h prior to surgery and restart when wound healed. RPLS is rare but serious. Monitor for headache, seizure, lethargy, and hypertension [187]

[16]QT prolongation is a class effect of HDAC inhibitors, although the incidence may be lower than initially reported. Optimize serum potassium and magnesium levels [205, 228]

[17]Severe cutaneous reactions including SJS, TEN, DRESS, and bullous pemphigoid have been reported [45, 131, 239]

[18]RPLS: onset of symptoms from 16 h to 1 year after the first dose. Monitor for headache, seizure, lethargy, and hypertension. Wound healing: if possible wait at least 4 weeks after bevacizumab discontinuation for major surgical procedures and do not restart for at least 4 weeks after surgery or until wound is fully healed. Cases of TMA have been reported. Higher incidence of GI perforation in patients with previous pelvic irradiation. Severe pulmonary hemorrhage reported in NSCLC [30, 75, 87, 107, 197, 218]

[19]Bexarotene induces significant lipid abnormalities, usually occurring within 2–4 weeks. Pancreatitis associated with hypertriglyceridemia has been reported. Interrupt treatment and evaluate if pancreatitis is suspected; triglycerides should be maintained <400 mg/dL utilizing HMG-CoA reductase inhibitors or fenofibrate. Gemfibrozil is not recommended due to increased bexarotene and triglyceride levels. Bexarotene rapidly suppresses TSH levels by directly inhibiting TSH secretion and thyroid hormone metabolism [98, 236]

[20]Bleomycin may cause pneumonitis leading to pulmonary fibrosis. Risk factors include age > 70 years, cumulative lifetime dose > 450 units, prior mantle radiation, renal impairment, oxygen exposure, smoking, and granulocyte-colony stimulating factor use [16, 37]

[21]Neurotoxicities include tremors, confusion, encephalopathy, aphasia, and seizures, which are reversible in most cases. Onset of symptoms usually occurs around day 7 of the first cycle of treatment. Management includes treatment with dexamethasone, with or without blinatumomab interruption, and anti-seizure medication as indicated. CRS is managed with dexamethasone, with or without blinatumomab interruption, and tocilizumab as indicated. Hepatotoxicity can present alone or in association with CRS [7, 242, 243]

[22]New onset or exacerbation of HF, pneumonitis, and pulmonary hypertension may occur. Acute liver failure and RPLS have been reported rarely with bortezomib. HSV/VZV prophylaxis is required during therapy due to risk of reactivation [150]

[23]Most common toxicities are GI (i.e., diarrhea, nausea, and vomiting). Pleural effusions may develop in patients with a prior history of pleural effusions and dasatinib exposure [125]

[24]Serious and fatal cases of GI complications (i.e., acute pancreatitis, hemorrhage, obstruction, perforation) and hepatotoxicity have been reported, with higher incidence in patients with GI or liver disease involvement. Cases of PML and death due to JC virus infection have occurred with median onset of 7 weeks after initiation (3–34 weeks) ([48], Seattle [217])

[25]Symptomatic bradycardia can occur. When treating hypertension, use caution when administering with antihypertensive agents that can cause bradycardia. Higher incidence and earlier onset of pneumonitis compared to other ALK inhibitors. ILD/pneumonitis typically occurs within 9 days of initiation – higher incidence with 180 mg/day vs 90 mg/day. Monitor CPK at baseline and periodically for signs or symptoms of muscle pain or weakness [9, 127].

[26]Anti-seizure prophylaxis required with administration of busulfan. VOD is a risk among patients receiving busulfan, but the incidence has decreased since the transition in standard of care from oral to IV busulfan and the use of PK for dosing. Avoid use of acetaminophen, metronidazole, or introduction of any medication that may inhibit/induce CYPA3A4 for at least 72 h before, during, and for 72 h after busulfan administration as these are major drug interactions that will affect PK dosing [52, 181]

[27]Case reports of hemorrhagic cystitis, which may be due to radiation recall in patients with history of pelvic irradiation. High rates of grade 3/4 neutropenia in clinical trials [97, 141, 213]

[28]RPLS has occurred rarely in trials. Monitor for headache, seizure, lethargy, and hypertension. Can impair wound healing – hold 28 days prior to surgery and resume once wound has healed [76]

Table 1C

	Neuro		Cardiac						Pulmonary						Renal			GI				Endocrine				Miscellaneous						Notes
	Encephalopathy	Seizures	Heart failure	Thromboembolism	Arrhythmias	QT prolongation	Pericardial effusions	Severe hypertension	Pneumonitis	Pulmonary edema	Pulmonary hypertension	Pleural effusions	Organizing pneumonia	Diffuse alveolar hemorrhage	SIADH – hyponatremia	Renal failure	Hemorrhagic cystitis	Bowel perforation	Neutropenic colitis	Pancreatitis	Hepatotoxicity	Adrenal insufficiency	Hypophysitis	Hyperglycemia	Thyroid disorders	Cytokine release syndrome	Differentiation syndrome	Opportunistic infections	Bleeding (severe)	Rhabdomyolysis	Stevens – Johnson syndrome or Toxic epidermal necrolysis	
Capecitabine	X	X	X	X	X		X									X		X	X		X										X	See Note 29
Carboplatin	X														X				X													See Note 30
Carfilzomib	X		X	X				X	X			X				X													X			See Note 31
Carmustine									X																							See Note 32
Ceritinib					X	X	X	X	X											X	X			X								See Note 33
Cetuximab									X																						X	See Note 34
Chlorambucil		X																													X	See Note 35
Cisplatin	X	X		X											X	X			X													See Note 36
Clofarabine																X					X							X	X	X	X	See Note 37
Cobimetinib			X					X										X											X	X		See Note 38
Copanlisib								X	X															X			X					See Note 39
Crizotinib					X	X			X												X			X								See Note 40
Cyclophosphamide			X		X		X		X						X		X				X											See Note 41
Cytarabine	X									X			X																			See Note 42
Dabrafenib			X	X		X			X															X					X			See Note 43
Dacarbazine																					X											See Note 44
Dactinomycin									X												X										X	See Note 45
Daratumumab									X	X																						See Note 46
Dasatinib					X	X	X		X		X	X																	X		X	See Note 47
Daunorubicin			X																													See Note 48
Daunorubicin and cytarabine (liposomal)			X																													See Note 49

[29]Cardiotoxicity: lower incidence than 5FU, mechanism thought to be due to coronary vasospasm. Higher risk in patients with cardiac or renal comorbidities. Bowel perforation: higher incidence in colon/rectal cancer but cases also reported in breast cancer patients [57, 85, 207]

[30]Incidence of hypersensitivity reactions increases with repeated exposure. Rate of reactions increased from 1% to 27% in women with ovarian cancer who received >7 cycles. Desensitization may require ICU admission [109, 142]

[31]New onset or worsening HF, restrictive cardiomyopathy, pulmonary hypertension, myocardial ischemia, and infarction, including fatalities, may occur. Patients with prior cardiovascular disease or advanced age (>75 years of age) are at an increased risk. Acute kidney injury may be associated with progressive myeloma although prerenal insults, tumor lysis-like syndrome, ATN, and TMA have occurred. Acute liver failure and RPLS have been reported rarely with carfilzomib. Monitor for headache, seizure, lethargy, and hypertension. Thromboembolism and hemorrhage risks are thought to be associated with disease-related processes or combination regimens containing immunomodulatory agents. Anticoagulation or antiplatelet therapy is not required for patients receiving carfilzomib monotherapy. HSV/VZV prophylaxis is required during therapy due to risk of reactivation [63, 178, 250]

[32]Black box warning for dose-related pulmonary toxicity, especially in patients receiving >1400 mg/m^2 cumulative dose. Pulmonary fibrosis may have delayed onset, occurring years after treatment, especially in children. Other risk factors, aside from cumulative dose, include history of lung disease and baseline FVC or DLCO <70% [101, 253]

[33]Symptomatic bradycardia can occur. When treating hypertension, use caution when administering antihypertensive agents that can cause bradycardia. Cases of grade 3 and 4 pancreatitis have been reported, including fatal ones. Monitor amylase/lipase at baseline, periodically during therapy and when clinically necessary [15, 167, 227]

[34]Cardiopulmonary arrest and/or sudden death in 2–3% of patients with squamous cell carcinoma of the head and neck treated with cetuximab-based therapy [69]

[35]Patients with a history of nephrotic syndrome and receiving high pulse doses of chlorambucil are at an increased risk of seizures [195, 208]

[36]RPLS has been reported. Monitor for headache, seizure, lethargy, and hypertension. Renal toxicity is dose-related and becomes more prolonged and severe with repeated courses. Hypocalcemia and hypomagnesemia-related tetany have been reported. Incidence of hypersensitivity reactions increases with repeated exposure, peaking after six cycles. Desensitization may require ICU admission [38, 229]

[37]Older age may correlate with decreased metabolic clearance of clofarabine or possibly decreased nonrenal excretion of the drug. Clofarabine may cause a capillary leak syndrome that can be prevented and managed with steroids. Consider PJP and fungal prophylaxis. Serious and fatal hemorrhage, including cerebral, GI, and pulmonary hemorrhage have occurred [77, 186]

[38]Risk of GI perforation 0.3%. Median first onset of LVEF decline was 4 months (23 days to 13 months). Rhabdomyolysis: median time to first occurrence of grade 3 or 4 CPK elevations 16 days (12 days to 11 months) [84]

[39]PJP and noninfectious pneumonitis have been reported. PJP prophylaxis is recommended in patients with prior PJP infection or lymphopenia. Infusion-related hyperglycemia and hypertension have also occurred. Serum glucose levels typically peak at 5–8 h post infusion, whereas systolic and diastolic blood pressure peak 2 h post infusion [23]

[40]Symptomatic bradycardia can occur. When treating hypertension, use caution when administering with antihypertensive agents that can cause bradycardia. Pneumonitis onset is generally within 3 months of treatment initiation. Severe cases of liver injury have been reported during the first 6 weeks of therapy. Fatal cases of ketoacidosis have been reported [190, 203, 223]

[41]Cardiotoxicity is related to endothelial capillary damage. Risk is increased with higher doses, advanced age, prior radiation to the cardiac region, and/or prior use of other cardiotoxic agents. Reported cardiotoxicities include arrhythmias (atrial fibrillation, atrial flutter, and ventricular arrhythmias), HF, heart block, myocarditis (including hemorrhagic), pericarditis, and pericardial effusion (including cardiac tamponade). Late-onset pneumonitis (> 6 months) is associated with increased mortality. Hyperhydration plus/minus MESNA are utilized to help prevent hemorrhagic cystitis during the infusion of cyclophosphamide. VOD has been described with high doses of cyclophosphamide in combination with other agents, such as TBI or busulfan as part of a conditioning regimen for stem cell transplant [21, 62]

[42]Doses ≥3 g/m^2 every 12 h have been reported to cause an acute cerebellar syndrome in 10–25% of patients. Patients >40 years of age who have abnormal liver or renal function, underlying neurologic dysfunction, or who receive a total dose of >30 g, are particularly vulnerable to developing cerebellar toxicity [19, 102, 118, 226]

[43]Median onset of cardiomyopathy is 4 months when used alone or 8 months if used concurrently with trametinib. Fever is common with dabrafenib and trametinib and can lead to hypotension, dizziness, and kidney dysfunction if dehydration occurs [171, 255]

[44]Hepatotoxicity may be accompanied by hepatic vein thrombosis and hepatocellular necrosis [11]

[45]Increased risk of VOD in children <4 years of age [182]

[46]Infusion-related reactions including bronchospasm, pneumonitis, and pulmonary edema may occur. Combination regimens with corticosteroids and premedication with antihistamines and antipyretics have helped alleviate symptoms, although patients may still be at risk for delayed infusion reactions. Consider bronchodilators in patients with a history of COPD or $FEV_1 < 80\%$. HSV prophylaxis should start within 1 week of initiation and continue for 3 months following treatment. May result in a false-positive Indirect Coombs test that may persist for up to 6 months after the last infusion [111]

[47]Optimize serum potassium and magnesium levels prior to and during therapy to reduce risk of cardiotoxicity. Pleural effusions can occur. Management of pleural effusions consists of temporary dose interruption, dose reductions, diuretics, and/or corticosteroids. Pulmonary arterial hypertension typically occurs after 8–48 months of exposure. Increased risk of bleeding in those with advanced disease and thrombocytopenia [28, 39, 55, 134, 152, 194, 220]

[48]Onset of cardiotoxic effects of anthracyclines can occur during or immediately after infusion (acute onset), within 1 year of exposure (early onset), and from 1–20 years (late onset) after initial exposure. Factors increasing the risk of cardiac toxicity include the extent of anthracycline exposure, higher doses, older age, pre-existing cardiac disease, concurrent or previous mediastinal radiation therapy, and concomitant administration of cardiotoxic chemotherapy regimens such as paclitaxel or trastuzumab. The incidence of cardiac toxicity increases after a total cumulative dose exceeding 400–550 mg/m^2 in adults, 300 mg/m^2 in children more than 2 years of age, or 10 mg/kg in children less than 2 years of age [27]

[49]Cardiotoxicity may occur due to the anthracycline component (daunorubicin) of the formulation. Observe the same risk factors for cardiotoxicity as with conventional anthracyclines. This formulation is not interchangeable with other formulations of daunorubicin and cytarabine [114, 132]

Table 1D

	Neuro		Cardiac						Pulmonary						Renal			GI				Endocrine				Miscellaneous						Notes
	Encephalopathy	Seizures	Heart failure	Thromboembolism	Arrhythmias	QT prolongation	Pericardial effusions	Severe hypertension	Pneumonitis	Pulmonary edema	Pulmonary hypertension	Pleural effusions	Organizing pneumonia	Diffuse alveolar hemorrhage	SIADH – hyponatremia	Renal failure	Hemorrhagic cystitis	Bowel perforation	Neutropenic colitis	Pancreatitis	Hepatotoxicity	Adrenal insufficiency	Hypophysitis	Hyperglycemia	Thyroid disorders	Cytokine release syndrome	Differentiation syndrome	Opportunistic infections	Bleeding (severe)	Rhabdomyolysis	Stevens – Johnson syndrome or Toxic epidermal necrolysis	
Dinutuximab	X														X	X					X			X					X			See Note 50
Docetaxel		X	X						X	X		X						X	X		X										X	See Note 51
Doxorubicin			X						X				X																			See Note 52
Doxorubicin liposomal			X						X				X																			See Note 53
Durvalumab			X						X						X	X				X	X	X	X	X	X					X		See Note 54
Enasidenib																											X					See Note 55
Epirubicin			X																													See Note 56
Erlotinib				X					X							X		X			X										X	See Note 57
Etoposide	X	X							X																						X	See Note 58
Everolimus	X						X		X			X		X		X								X				X				See Note 59
Fludarabine	X	X							X																			X				See Note 60
Gefitinib									X									X			X										X	See Note 61
Gemcitabine	X								X	X				X		X					X										X	See Note 62
Gemtuzumab ozogamicin						X															X								X			See Note 63
Ibritumomab																															X	See Note 64
Ibrutinib					X	X																						X	X			See Note 65
Idarubicin			X																													See Note 66
Idelalisib									X				X					X			X							X			X	See Note 67

[50]Can cause capillary leak syndrome with hypotension, severe hypokalemia and hyponatremia, HUS, and subsequent renal failure. RPLS can occur – monitor for headache, seizure, lethargy, and hypertension [245]

[51]Fluid retention, due to capillary leakage, can lead to non-cardiogenic pulmonary edema or pleural effusions. Diuretics recommended for treatment [162, 199, 212]

[52]Onset of cardiotoxic effects of anthracyclines can occur during or immediately after infusion (acute onset), within 1 year of exposure (early onset), and from 1–20 years (late onset) after initial exposure. Factors increasing the risk of cardiac toxicity include the extent of anthracycline exposure, higher doses, older age, pre-existing cardiac disease, concurrent or previous mediastinal radiation therapy, and concomitant administration of cardiotoxic chemotherapy regimens such as paclitaxel or trastuzumab. Risk of cardiomyopathy is proportional to the cumulative exposure with incidences from 1% to 20% for cumulative doses of 300 mg/m^2–500 mg/m^2. At a cumulative dose of 400 mg/m^2, the risk of developing HF is 5% [26, 258]

[53]Onset of cardiotoxic effects of anthracyclines can occur during or immediately after infusion (acute onset), within 1 year of exposure (early onset), and from 1–20 years (late onset) after initial exposure. Factors increasing the risk of cardiac toxicity include the extent of anthracycline exposure, higher doses, older age, pre-existing cardiac disease, concurrent or previous mediastinal radiation therapy, and concomitant administration of cardiotoxic chemotherapy regimens such as paclitaxel or trastuzumab. Risk of cardiac toxicity has been reported to be 11% with cumulative doses between 450 and 550 mg/m^2 [113]

[54]May cause severe immune-mediated adverse events including pneumonitis, median onset 1.8 months; hepatitis, median onset ~52 days (2–45 weeks); and immune-mediated thyroid disorders, median onset 3 months (range: 2 weeks to 13 months). May aggravate underlying autoimmune disorders. Management includes holding therapy, systemic corticosteroids, +/– additional immunosuppressants (e.g., infliximab, mycophenolate and vedolizumab). Consider PJP prophylaxis in patients with prolonged corticosteroid exposure [12, 33]

[55]Differentiation syndrome is commonly associated with the development of hyperleukocytosis, pulmonary edema, generalized edema, headache, bone pain, and renal failure, with a median onset of 48 days (10–340 days). Management includes steroids and/or discontinuation of enasidenib depending on severity. For management, please refer to the package insert. Patients with leukocytosis can be managed with hydroxyurea [230]

[56]Onset of cardiotoxic effects of anthracyclines can occur during or immediately after infusion (acute onset), within 1 year of exposure (early onset), and from 1–20 years (late onset) after initial exposure. Factors increasing the risk of cardiac toxicity include the extent of anthracycline exposure, higher doses, older age, pre-existing cardiac disease, concurrent or previous mediastinal radiation therapy, and concomitant administration of cardiotoxic chemotherapy regimens such as paclitaxel or trastuzumab. Risk of cardiomyopathy is proportional to the cumulative exposure with incidences from 0.9% to 3.3% for cumulative doses from 550 mg/m^2–900 mg/m^2 [144]

[57]The risk of CVA is increased in patients with pancreatic cancer, with a higher incidence found in those receiving erlotinib + gemcitabine (2.5%) versus gemcitabine alone. Median onset of ILD symptoms is 39 days (5 days to more than 9 months) after initiating therapy. Renal failure may arise from exacerbation of underlying baseline hepatic impairment or severe dehydration. Rare incidence of renal failure in monotherapy (0.5%) and 1.4% when combined with gemcitabine [79, 180]

[58][2, 202]

[59]Noninfectious pneumonitis, PJP, and invasive fungal and viral infections have been reported. Administer prophylaxis for PJP when concomitant use of corticosteroids or other immunosuppressive agents are required [120, 164]

[60]Incidence of pulmonary toxicity 8.6%, more likely with CLL. Pneumonitis occurs days to weeks after therapy and may occur following the first cycle; management includes systemic corticosteroids. Fludarabine can also cause autoimmune hemolytic anemia (AIHA). Serious and sometimes fatal infections including opportunistic and reactivation of latent viral infections such as VZV, EBV, and JC virus have been reported [100, 231, 246]

[61]Median onset of ILD symptoms 3–6 weeks, with fatalities reported. Serum hepatic enzyme elevations typically occur after 4–12 weeks of treatment with a hepatocellular pattern [17]

[62]Associated with a range of pulmonary toxicities: interstitial pneumonitis, capillary leak, non-cardiogenic pulmonary edema, and pulmonary fibrosis; onset can be up to 2 weeks following the last dose. Potential for radiation recall. HUS has been reported, including fatalities or need for dialysis due to renal failure. Capillary leak syndrome and RPLS have been reported [46, 72, 206, 244]

[63]Optimize potassium and magnesium prior to and during therapy to reduce risk of cardiotoxicity. Increased risk for VOD. Median onset of hyperbilirubinemia and increases in AST and ALT 8 days and median duration 20 days following initiation of therapy [145, 224, 249]

[64]SJS may occur within days to 4 months following infusion [117]

[65]Arrhythmias (i.e., ventricular arrhythmias, atrial fibrillation, and flutter) have occurred, particularly in patients with cardiac risk factors, hypertension, acute infections, or history of arrhythmias. Cases of PJP have been reported with a median onset of 6 months (2–24 months). Invasive fungal infections (i.e., aspergillosis, cryptococcal, and mucor) have been reported. Consider PJP and fungal prophylaxis in patients with lymphopenia or prolonged corticosteroid exposure. Major hemorrhage (grade 3–4) has been reported with BTK inhibitors. Consider withholding for 3–7 days prior to procedures depending on the risk of bleeding [3, 20, 146, 176, 193, 219]

[66]Onset of cardiotoxic effects of anthracyclines can occur during or immediately after infusion (acute onset), within 1 year of exposure (early onset), and from 1–20 years (late onset) after initial exposure. Factors increasing the risk of cardiac toxicity include the extent of anthracycline exposure, higher doses, older age, pre-existing cardiac disease, concurrent or previous mediastinal radiation therapy, and concomitant administration of cardiotoxic chemotherapy regimens such as paclitaxel or trastuzumab. Estimated incidence of heart failure is 5–18% with doses >90 mg/m^2 [258]

[67]Pneumonitis and organizing pneumonia may occur 1-15 months after initiation of idelalisib and should be managed with corticosteroids. GI perforation typically preceded by moderate to severe diarrhea. Median onset of diarrhea 1.9 months (range, 0.0–29.8 months). Anti-motility drugs such as loperamide are not useful in the management of idelalisib-induced diarrhea, which is best managed with dose interruptions; the median time to resolution of diarrhea can be up to 1 month. Enteric budesonide or systemic corticosteroids may be considered for treatment of severe or unresolved diarrhea, leading to shorter time to resolution compared to interruption alone (1–2 weeks vs. 1 month). Elevations in ALT or AST >5 times ULN have been observed, usually occurring within the first 12 weeks of treatment. Most transaminase elevations were reversible with dose interruption. Median time to PJP event 4.5 months after initiation. Consider PJP prophylaxis and CMV monitoring [93]

Table 1E

	Neuro		Cardiac						Pulmonary						Renal			GI				Endocrine				Miscellaneous						Notes
	Encephalopathy	Seizures	Heart failure	Thromboembolism	Arrhythmias	QT prolongation	Pericardial effusions	Severe hypertension	Pneumonitis	Pulmonary edema	Pulmonary hypertension	Pleural effusions	Organizing pneumonia	Diffuse alveolar hemorrhage	SIADH – hyponatremia	Renal failure	Hemorrhagic cystitis	Bowel perforation	Neutropenic colitis	Pancreatitis	Hepatotoxicity	Adrenal insufficiency	Hypophysitis	Hyperglycemia	Thyroid disorders	Cytokine release syndrome	Differentiation syndrome	Opportunistic infections	Bleeding (severe)	Rhabdomyolysis	Stevens – Johnson syndrome or Toxic epidermal necrolysis	
Ifosfamide	X	X	X		X			X							X	X	X				X											See Note 68
Imatinib			X									X						X			X								X		X	See Note 69
Inotuzumab ozogamicin																					X											See Note 70
Ipilimumab	X		X						X				X			X		X		X	X	X	X		X						X	See Note 71
Irinotecan				X					X			X				X		X														See Note 72
Ixabepilone			X																		X											See Note 73
L-Asparaginase	X			X																X	X			X								See Note 74
Lapatinib			X			X		X	X												X										X	See Note 75
Lenalidomide				X					X												X				X						X	See Note 76
Lenvatinib	X		X	X		X		X								X		X		X	X				X			X				See Note 77
Lisocabtagene maraleucel	X	X	X		X				X							X					X					X		X				See Note 78
Mechlorethamine																											X					See Note 79
Melphalan									X						X						X											See Note 80
Methotrexate	X								X				X			X		X			X						X			X		See Note 81
Midostaurin									X														X									See Note 82
Mitomycin-C									X							X																See Note 83
Mitoxantrone									X																							See Note 84
Nab-paclitaxel				X					X																							See Note 85
Necitumumab			X	X																												See Note 86
Nelarabine	X	X																														See Note 87

[68]Ifosfamide encephalopathy (ranging from mild somnolence to confusion and hallucinations to coma) may occur within hours to days after a dose. Risk factors for CNS toxicity include hypoalbuminemia, pre-existing renal dysfunction, concomitant use of aprepitant, and prior cisplatin exposure. IV albumin and thiamine supplementation are recommended for prevention. Encephalopathy typically resolves within 2–3 days after discontinuation; however, IV methylene blue may be considered as a treatment option. Cardiotoxicity including arrhythmias (i.e., SVT, atrial fibrillation, and pulseless ventricular tachycardia), heart failure with congestion and hypotension, pericardial effusion, fibrinous pericarditis, and epicardial fibrosis may occur. VOD has been reported in combination regimens [22, 183]

[69]Heart failure has been reported, although mostly in those with other comorbidities and risk factors, including advanced age and previous cardiac disease. Although rare, it is worth noting the reports of interstitial pneumonia. Median onset 7 weeks (1.5–40 weeks) and presentation includes low-grade fever, dry cough, and progressive dyspnea on exertion, with or without hypoxia. Management includes steroids and/or drug discontinuation of imatinib [175]

[70]VOD can occur during or after treatment. Median onset of VOD was 15 days (range, 3–57 days) for patients receiving stem cell transplant [123, 124]

[71]Pneumonitis: highest incidence when given with nivolumab (5–10% incidence) with median onset of symptoms 2.6 months following therapy initiation. Onset of GI symptoms is typically 6 weeks or more after initiating therapy. Moderate to severe endocrine disorders: median onset 2.2–2.5 months. Immune-mediated hepatitis (grade 3 or 4): median onset 2 months. Treat toxicities by holding ipilimumab and administering corticosteroids. Consider PJP and fungal prophylaxis in patients with prolonged corticosteroid exposure. Although rare, lethal myocarditis accompanied by myositis in patients treated with a combination of nivolumab and ipilimumab has been reported [34, 40, 42]

[72]Pulmonary toxicity more common with irinotecan than topotecan. Higher risk in patients with pre-existing lung disease, prior thoracic radiation, use of pneumotoxic drugs, and colony-stimulating factors. Severe/fatal diarrhea can occur with irinotecan. Early diarrhea (within 24 hrs) is accompanied by anticholinergic symptoms. Late diarrhea can occur more than 24 hrs following dose administration. Cases of megacolon and bowel perforation have been reported [192]

[73]MI and ventricular dysfunction have been reported [35]

[74]Noted complications typically occur after several weeks of treatment and often during the induction phase. Encephalopathy may be related to hyperammonemia and RPLS. Serious thrombotic events, including sagittal sinus thrombosis, have been reported [5, 78, 99, 126]

[75]Decreases in LVEF have been reported, usually within the first 3 months of treatment. Optimize serum potassium and magnesium levels prior to and during therapy. Case reports describe serious or fatal hepatotoxicity, usually 1–3 months following treatment initiation [165, 184, 185]

[76]Thromboprophylaxis with either aspirin or a LMWH should be considered for patients receiving lenalidomide in combination with chemotherapy and/or dexamethasone [140, 241]

[77]RPLS has been reported. Monitor for headache, seizure, lethargy, and hypertension. Median time to onset of new or worsening hypertension is 16–35 days. Can impair wound healing; should be held at least 6 days prior to surgical procedures [67]

[78]Lisocabtagene maraleucel is a CAR T-cell therapy undergoing FDA approval. Latest available data revealed a 1% incidence of severe CRS (35% any grade CRS) and 12% incidence of severe ICANS (19% any grade ICANS). Management of CRS and/or ICANS is grading dependent but may include supportive care, tocilizumab, and/or systemic corticosteroids. Anti-seizure, PJP, and HSV prophylaxis similar to other CAR T-cell therapies should be considered [119]

[79]PJP and CMV pneumonia have occurred due to severe and prolonged neutropenia. Consider PJP prophylaxis and CMV monitoring [43]

[80]GI toxicity, including grade 3/4 mucositis, has been reported with high-dose melphalan. Cryotherapy may help prevent/reduce mucositis severity [95]

[81]Glucarpidase may be considered for patients receiving high-dose methotrexate (HDMTX) with delayed clearance (serum methotrexate levels $>$ 1 μmol/L beyond 42 h after the start of HDMTX infusion) and renal dysfunction (serum creatinine $>$1.3 mg/dL or $>$ 50% increase from baseline). Leucovorin calcium should not be administered within 2 h of glucarpidase due to competing binding sites. Intrathecal methotrexate is commonly associated with aseptic meningitis characterized by fever, headache, and vomiting that can last several days. Generalized and focal seizures have been reported. Methotrexate may increase the risk of developing life-threatening opportunistic infections. Do not initiate penicillins, fluoroquinolones, sulfonamide antibiotics, nonsteroidal anti-inflammatory drugs, or proton pump inhibitors until methotrexate has cleared [80, 129]

[82]Fatal events involving pulmonary toxicity have occurred [232]

[83]Infrequent but severe pulmonary toxicity (e.g., ARDS) has been reported. HUS and subsequent renal failure have been reported. Dose-related pulmonary toxicity ($>$20 mg/m^2) [138, 177, 234, 248]

[84]Onset of cardiotoxic effects of anthracyclines can occur during or immediately after infusion (acute onset), within 1 year of exposure (early onset), and from 1–20 years (late onset) after initial exposure. Factors increasing the risk of cardiac toxicity include the extent of anthracycline exposure, higher doses, older age, pre-existing cardiac disease, concurrent or previous mediastinal radiation therapy, and concomitant administration of cardiotoxic chemotherapy regimens such as paclitaxel or trastuzumab. Estimated risk of CHF is 2.6% for doses up to 140 mg/m^2 [74]

[85][1]

[86]Cardiopulmonary arrest and/or sudden death has been reported in patients treated with necitumumab in combination with gemcitabine and cisplatin. Severe hypomagnesemia is common in those treated with necitumumab, gemcitabine, and cisplatin, with a median onset of 6 weeks. Optimize serum potassium, magnesium, and calcium during and for at least 8 weeks following administration. Cerebral stroke and MI have also been reported [68, 240]

[87]Most neurologic toxicities occur within 12 days of infusion or after successive cycles of therapy. The most common grade 3/4 neurologic adverse events reported include confusion, malaise, somnolence, ataxia, muscle weakness, and peripheral neuropathies [121, 130]

Table 1F

	Neuro		Cardiac						Pulmonary						Renal			GI				Endocrine				Miscellaneous						Notes
	Encephalopathy	Seizures	Heart failure	Thromboembolism	Arrhythmias	QT prolongation	Pericardial effusions	Severe hypertension	Pneumonitis	Pulmonary edema	Pulmonary hypertension	Pleural effusions	Organizing pneumonia	Diffuse alveolar hemorrhage	SIADH – hyponatremia	Renal failure	Hemorrhagic cystitis	Bowel perforation	Neutropenic colitis	Pancreatitis	Hepatotoxicity	Adrenal insufficiency	Hypophysitis	Hyperglycemia	Thyroid disorders	Cytokine release syndrome	Differentiation syndrome	Opportunistic infections	Bleeding (severe)	Rhabdomyolysis	Stevens – Johnson syndrome or Toxic epidermal necrolysis	
Nilotinib						X	X			X		X								X	X			X				X		X	See Note 88
Niraparib								X																							See Note 89
Nivolumab	X								X						X	X				X	X	X	X	X	X				X	X	See Note 90
Obinutuzumab																												X			X	See Note 91
Ofatumumab																												X			X	See Note 92
Olaparib				X					X			X																				See Note 93
Osimertinib			X			X			X																							See Note 94
Oxaliplatin	X	X			X	X			X				X	X							X									X		See Note 95
Paclitaxel		X							X																						X	See Note 96
Palbociclib				X																												See Note 97
Panitumumab				X					X																						X	See Note 98
Panobinostat					X	X																										See Note 99
Pazopanib	X		X	X		X		X	X									X			X				X				X		X	See Note 100
PEG-asparaginase	X			X																X	X			X								See Note 101
Pembrolizumab	X								X				X		X	X				X	X	X	X	X	X						X	See Note 102
Pemetrexed									X							X															X	See Note 103
Pentostatin																X					X							X				See Note 104
Pertuzumab			X					X																								See Note 105
Pomalidomide				X					X												X				X						X	See Note 106
Ponatinib			X	X	X	X	X	X												X	X								X			See Note 107
Pralatrexate																					X										X	See Note 108

[88]Risk of QT prolongation warrants a baseline 12-lead EKG with repeat assessment after 7 days of therapy, following any dose change, and regularly during treatment. Optimize serum potassium and magnesium levels prior to and during therapy. Biochemical abnormalities are common (i.e., increased lipase, glucose, total bilirubin, ALT) [4, 94, 103, 135, 172, 198]

[89]Hypertensive crisis has been reported [237]

[90]May cause severe immune-mediated adverse events including pneumonitis, median onset 1.6–3.5 months (1 day to 22.3 months); nephritis, 2.7–4.6 months (9 days to 12.3 months); hepatitis, 2.1–3.3 months (6 days to 11 months); colitis, 1.6–5.3 months (2 days to 21 months); adrenal insufficiency (across several clinical trials), 3–4.3 months (15 days to 21 months);

hyperthyroidism, 23 days to 1.5 months (1 day to 14.2 months); hypothyroidism, 2–3 months (1 day to 16.6 months); and hypophysitis, 4.9 months (1.4–11 months). May aggravate underlying autoimmune disorders. Management includes holding therapy, systemic corticosteroids, and +/− additional immunosuppressants (e.g., infliximab, mycophenolate, and vedolizumab). Consider PJP prophylaxis in patients with prolonged corticosteroid exposure. Although rare, lethal myocarditis accompanied by myositis in patients treated with a combination of nivolumab and ipilimumab has been reported [33, 36, 116, 133, 159, 160]

[91]HBV reactivation may occur during and up to 24 months after discontinuation of anti-CD20 antibodies. Patients on antiviral prophylaxis should continue for 6–12 months after completing treatment. JC virus infection resulting in PML has been reported [32, 106]

[92]HBV reactivation may occur during and up to 24 months after discontinuation of anti-CD20 antibodies. Patients on antiviral prophylaxis should continue for 6–12 months after completing treatment. Fatal cases of PML have been reported [32, 106]

[93][14, 64]

[94][18]

[95]Ventricular arrhythmias, including fatal Torsades de Pointes, have been reported. Optimize potassium and magnesium prior to and during therapy. Cases of pulmonary fibrosis, including fatal events, have been reported. RPLS has been reported. Monitor for headache, seizure, lethargy, and hypertension [154, 204, 211, 222]

[96][29, 162]

[97][191]

[98]Monitor for hypomagnesemia and hypocalcemia prior to, during and up to 8 weeks after therapy. Severe dermatologic complications may effect up to 15% of patients and can lead to life-threatening infectious complications such as necrotizing fasciitis and abscesses [8, 179]

[99]QT prolongation is a class effect of HDAC inhibitors, although the incidence may be lower than initially reported. Optimize serum potassium and magnesium levels prior to and during therapy [173, 205]

[100]RPLS is rare but serious. Monitor for headache, seizure, lethargy, and hypertension. Some fatal cases of hepatotoxicity have been reported. Serum hepatic enzyme elevations generally occur within 4–12 weeks. The most common hemorrhagic events were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage. Rare cases of hypertensive crisis have been reported, most cases of hypertension within first 18 weeks of therapy. TMA including TTP and HUS can occur, generally within 3 months of treatment initiation [136, 158, 166, 209]

[101]Complications typically occur after several weeks of treatment during the induction phase. Clinical symptoms suggestive of pancreatitis have been reported to occur within 15 days of treatment [65]

[102]May cause severe immune-mediated adverse events including pneumonitis median onset 3.3 months (2 days to ~19 months) and is more common with prior thoracic radiation, hepatitis 1.3 months (8 days to 21.4 months), colitis 3.5 months (10 days to 16.2 months), autoimmune nephritis 5.1 months (12 days to 12.8 months), hyperthyroidism 1.4 months (1 day to ~22 months), and hypothyroidism 3.5 months (1 day to 19 months). May aggravate underlying autoimmune disorders. Management includes holding therapy, systemic corticosteroids, and +/− additional immunosuppressants (e.g., infliximab, mycophenolate, and vedolizumab). Consider PJP prophylaxis in patients with prolonged corticosteroid exposure [33, 148, 159, 160]

[103]Prophylactic folic acid and vitamin B12 supplementation should be provided while receiving pemetrexed to reduce the risk of hematologic toxicity. Renal damage ranges from acute to chronic kidney injury due to tubular and interstitial damage [70, 252]

[104]Consider HSV/VZV prophylaxis [105, 142]

[105]Prior anthracycline therapy or chest irradiation may increase the risk for cardiotoxicity (risk is lower than that seen with trastuzumab) [83, 235]

[106]Thromboprophylaxis with either aspirin or a LMWH should be considered for patients receiving pomalidomide in combination with chemotherapy and/or dexamethasone [49, 92].

[107]Vigilant monitoring for vascular events is recommended (i.e., MI, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease). Vascular occlusion/events can occur within weeks of starting therapy and is not dose dependent and requires interruption or permanent discontinuation of therapy. Arrhythmias, such as atrial fibrillation and symptomatic bradycardia, have been reported. Hypertension can be severe and should be managed as clinically indicated. Hepatotoxicity: median onset 3 months (range, less than 1 month to 47 months); may require treatment interruption or discontinuation. Bleeding can occur during therapy, particularly in patients with accelerated or blast phase disease and thrombocytopenia. RPLS has been reported. Monitor for headache, seizure, lethargy, and hypertension [53, 54, 139, 155, 247]

[108]Prophylactic folic acid and vitamin B12 supplementation are necessary to reduce hematologic toxicity [6]

Table 1G

	Neuro		Cardiac						Pulmonary							Renal			GI					Endocrine				Miscellaneous						Notes
	Encephalopathy	Seizures	Heart failure	Thromboembolism	Arrhythmias	QT prolongation	Pericardial effusions	Severe hypertension	Pneumonitis	Pulmonary edema	Pulmonary hypertension	Pleural effusions	Organizing pneumonia	Diffuse alveolar hemorrhage	SIADH – hyponatremia	Renal failure	Hemorrhagic cystitis	Bowel perforation	Neutropenic colitis	Pancreatitis	Hepatotoxicity	Adrenal insufficiency	Hypophysitis	Hyperglycemia	Thyroid disorders	Cytokine release syndrome	Differentiation syndrome	Opportunistic infections	Bleeding (severe)	Rhabdomyolysis	Stevens – Johnson syndrome or Toxic epidermal necrolysis	
Ramucirumab	X			X				X										X			X				X				X				See Note 109
Regorafenib	X							X										X		X	X								X		X		See Note 110
Ribociclib				X		X															X												See Note 111
Rituximab																		X										X			X		See Note 112
Romidepsin					X	X																						X			X		See Note 113
Ruxolitinib																													X				See Note 114
Sipuleucel-T				X																										X			See Note 115
Sonidegib																X								X						X			See Note 116
Sorafenib	X		X	X		X		X	X									X		X	X				X				X		X		See Note 117
Sunitinib	X		X	X		X		X	X											X	X				X				X				See Note 118
Temozolomide																					X							X						See Note 119
Thalidomide		X		X	X				X																X						X		See Note 120
Thiotepa	X																				X										X		See Note 121
Tisagenlecleucel	X	X	X		X				X							X					X					X		X					See Note 122
Topotecan									X										X															See Note 123
Trabectiden			X	X														X			X									X			See Note 124
Trametinib			X	X		X		X	X									X						X					X	X			See Note 125
Trastuzumab			X						X	X		X	X																					See Note 126
Tretinoin (all-trans retinoic acid)					X					X						X					X						X		X					See Note 127

[109]Serious, sometimes fatal, MI, cardiac arrest, and CVA events have occurred in clinical trials. Can impair wound healing; therapy should be held prior to surgical procedures. Rates of hemorrhage or GI perforation unknown in patients on chronic NSAIDs or anticoagulation as many studies excluded these patients; therefore, use cautiously in combination with these agents [10, 71]

[110]Can impair wound healing. Discontinue 2 weeks prior to surgical procedures and resume once wound has healed. RPLS has been reported. Monitor for headache, seizure, lethargy, and hypertension [25, 158]

[111]Monitor and optimize serum potassium, calcium, phosphorus, and magnesium before and during therapy as electrolyte imbalances may occur to reduce risk of cardiotoxicity. Median onset of grade 3 or higher transaminase elevations ~2 months, with median time to resolution to grade 2 or lower of 24 days [104, 169]

[112]Abdominal pain, bowel obstruction, and perforation have been reported, with an average onset of symptoms ~6 days (1–77 days). JC virus infection resulting in PML has been reported. Median time to PML diagnosis 16 months following rituximab initiation and median time from last rituximab dose 5.5 months. HBV reactivation may occur during and up to 24 months after discontinuation of anti-CD20 antibodies. Patients on antiviral prophylaxis should continue for 6–12 months after completing treatment [32, 47, 106]

[113]QT prolongation is a class effect of HDAC inhibitors, although the incidence may be lower than initially reported. Optimize serum potassium, magnesium, and calcium levels prior to and during therapy. Viral reactivation has occurred during and within 30 days of initiation. Consider antiviral prophylaxis for patients with history of EBV or HBV [50, 205]

[114]Bacterial, mycobacterial, fungal, and viral infections have occurred including TB, PML, HSV/VZV and increased HBV viral load. Withdrawal syndrome can occur with abrupt discontinuation of treatment and is characterized by acute relapse of disease symptoms such as accelerated splenomegaly, worsening cytopenias, and sepsis-like syndrome. It can be managed with corticosteroids with a slow taper off [108]

[115]Vascular disorders including MI and stroke have been reported. Acute infusion reactions within 1 day of infusion have been reported [61].

[116]CPK elevations > grade 2 occur at a median of 13 weeks. CPK levels should be monitored at baseline and periodically during therapy. Rare cases of rhabdomyolysis have been reported [110, 233]

[117]HF, myocardial ischemia, and/or MI have been reported. Acute liver injury generally occurs a few days to up to 8 weeks after treatment initiation. Possible impaired wound healing. RPLS can rarely occur. Monitor for headache, seizure, lethargy, and hypertension [24, 216]

[118]RPLS can rarely occur. Case reports have occurred 1–34 weeks following treatment initiation. Monitor for headache, seizure, lethargy, and hypertension. Cardiac events including myocardial ischemia, MI, reductions in LVEF, and cardiac failure including death have occurred [56, 156, 158, 189]

[119]PJP prophylaxis is recommended [147]

[120]VTE, including ischemic heart disease, MI, and CVA have occurred in patients receiving thalidomide and dexamethasone. Thromboprophylaxis with either aspirin or a LMWH should be considered for patients receiving thalidomide in combination with chemotherapy and/or dexamethasone. Seizures and bradycardia have been reported in postmarketing data [51]

[121]Parent drug and/or metabolites may be partially excreted through the skin; severe blistering and desquamation can occur. As a result, patients should shower/bathe at least twice daily while receiving treatment and during the 48 h following therapy. Hepatotoxicity refers to VOD, which has been reported when high doses are used in combination with other chemotherapy as part of a conditioning regimen for stem cell transplant [58, 257]

[122]CRS: Median onset 3 days (1–22 days); median duration 8 days (1–36 days). Monitor for signs or symptoms of CRS for at least 4 weeks after treatment. Key manifestations include high fever, hypotension, and shortness of breath and may be associated with hepatic, renal, and cardiac dysfunction and coagulopathy. Risk factors for severe CRS are high pre-infusion tumor burden (>50% blasts in bone marrow), uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy (fludarabine and cyclophosphamide), active infections, and/or inflammatory processes

ICANS: Most neurological toxicities occurred within 8 weeks and generally resolved within 12 days. Most common neurological toxicities include headache, encephalopathy, delirium, anxiety, and tremor. Fatal and serious cases of cerebral edema have occurred; other serious events included leukoencephalopathy and seizures.

Management of CRS with or without ICANS depends on grading or severity but includes supportive care, tocilizumab, and/or systemic corticosteroids. Grade 2 or higher ICANS without CRS should be treated with corticosteroids alone as there is insufficient data with tocilizumab in this setting. Other interleukin antagonists (e.g., siltuximab) and anti-T cell therapies are currently being evaluated.

Hypogammaglobulinemia secondary to B-cell aplasia may persist for up to 13 months and increase the risk for infections. PJP and HSV prophylaxis are recommended for at least 1 year after CAR-T cell therapy [143, 174]

[123]Post-marketing cases of ILD have been reported. Higher risk in patients with baseline interstitial lung disease, pulmonary fibrosis, lung cancer, thoracic exposure to radiation, use of pneumotoxic drugs, and/or colony-stimulating factors [168]

[124]Grade 3 or 4 CPK elevations have been reported with a median onset of 2 months and resolving in ~2 weeks with dose interruption, reduction, discontinuation, or delay. Capillary leak syndrome has been reported [112]

[125]Cardiomyopathy: median onset in melanoma patients for single-agent trametinib ~2 months (2–22 weeks) and ~8 months (~1–25 months) when used in combination with dabrafenib, in patients with NSCLC 6.7 months (1.4–14.1 months). Pneumonitis: median time to initial presentation in melanoma patients ~5 months (2 to ~6 months). Risk of GI perforation is 0.3% when administered with dabrafenib. Grade 3/4 hyperglycemia reported when used in combination with dabrafenib [170]

[126]Highest incidence of cardiomyopathy in patients receiving trastuzumab with an anthracycline. Reversible upon discontinuation of trastuzumab [81, 96]

[127]Differentiation syndrome is commonly associated with the development of hyperleukocytosis, pulmonary edema, generalized edema, headache, bone pain, and renal failure; bimodal with peaks occurring in the first and third weeks after the start of therapy. Management includes steroids, with or without diuretics, and possible discontinuation of tretinoin, depending on severity [59, 153]

Table 1H

	Neuro		Cardiac						Pulmonary						Renal			GI				Endocrine				Miscellaneous						Notes
	Encephalopathy	Seizures	Heart failure	Thromboembolism	Arrhythmias	QT prolongation	Pericardial effusions	Severe hypertension	Pneumonitis	Pulmonary edema	Pulmonary hypertension	Pleural effusions	Organizing pneumonia	Diffuse alveolar hemorrhage	SIADH – hyponatremia	Renal failure	Hemorrhagic cystitis	Bowel perforation	Neutropenic colitis	Pancreatitis	Hepatotoxicity	Adrenal insufficiency	Hypophysitis	Hyperglycemia	Thyroid disorders	Cytokine release syndrome	Differentiation syndrome	Opportunistic infections	Bleeding (severe)	Rhabdomyolysis	Stevens – Johnson syndrome or Toxic epidermal necrolysis	
Vandetanib	X		X			X		X	X									X		X					X				X	X	X	See Note 128
Vemurafenib						X		X								X				X				X						X	X	See Note 129
Vinblastine															X																	See Note 130
Vincristine	X	X													X			X														See Note 131
Vinorelbine	X					X			X						X					X	X											See Note 132
Vismodegib															X															X		See Note 133
Vorinostat				X		X																		X								See Note 134

[128]Ischemic cerebrovascular events have been reported. RPLS has been reported – monitor for headache, seizure, lethargy, and hypertension. Optimize serum potassium, magnesium, and calcium levels prior to and during therapy. Rare cases of GI perforation. Due to long half-life (19 days), adverse reactions, including QT prolongation, may resolve slowly [214, 254]

[129]Optimize serum potassium, magnesium, and calcium levels prior to and during therapy to reduce risk of cardiotoxicity. AIN and ATN have been reported. Hypersensitivity: anaphylaxis and DRESS syndrome have been reported. Pancreatitis generally occurs within 2 weeks of treatment initiation [90, 157, 251, 255, 256]

[130]Paralytic ileus and obstruction may occur, although to a lesser extent than that observed with other vinca alkaloids

[131]Known to affect the cranial nerves resulting in ptosis, diplopia, and facial palsies. Paresthesias involving the hands and feet often occur within weeks of therapy and depending on severity and may require several months to resolve following drug discontinuation. Loss of motor involvement is possible as well (i.e., foot and hand drop, loss of deep tendon reflexes, weakness in the lower and upper extremities). Acute GI symptoms such as constipation and abdominal pain commonly occur within a few days of therapy, with more serious GI toxicities including adynamic ileus and bowel obstruction. SIADH-induced hyponatremia has led to seizures [200]

[132]May cause severe paralytic ileus [44, 188]

[133]May cause CPK elevations; rare occurrence of rhabdomyolysis [88]

[134]QT prolongation is a class effect of HDAC inhibitors, although the incidence may be lower than initially reported. Optimize serum potassium and magnesium levels prior to and during therapy [205]

5-FU, 5-fluorouracil; AIN, acute interstitial nephritis; ALK, anaplastic lymphoma kinase; ALT, alanine transaminase; AST, aspartate aminotransferase; ATN, acute tubular necrosis; BTK, Bruton's tyrosine kinase; CD4, cluster of differentiation 4; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CPK, creatine phosphokinase; CRS, cytokine release syndrome; CVA, cerebrovascular accident; DLCO, diffusing capacity of carbon monoxide; DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein-Barr virus; EKG, electrocardiogram; FVC, forced vital capacity; GI, gastrointestinal; HBV, hepatitis B virus; HDAC, histone deacetylase; HF, heart failure; HLH, hemophagocytic lymphohistiocytosis; HMG-CoA, hydroxymethylglutaryl coenzyme A; HUS, hemolytic uremic syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ILD, interstitial lung disease; IV, intravenous; JC virus, John Cunningham virus; LMWH, low molecular weight heparin; LVEF, left ventricular ejection fraction; MAS, macrophage activation syndrome; MI, myocardial infarction; NSCLC, non-small cell lung cancer; PD-1, programmed cell death 1; PJP, Pneumocystis jiroveci pneumonia; PK, pharmacokinetics; PML, progressive multifocal leukoencephalopathy; REMS, risk evaluation and mitigation strategy; RPLS, reversible posterior leukoencephalopathy syndrome; SJS, Stevens-Johnson syndrome; TB, tuberculosis; TBI, total body irradiation; TEN, toxic epidermal necrolysis; TMA, thrombotic microangiopathy; TSH, thyroid-stimulating hormone; TTP, thrombotic thrombocytopenic purpura; ULN, upper limit of normal; VOD, veno-occlusive disease; VTE, venous thromboembolism; VZV, varicella zoster virus

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