Published in final edited form as:

Crit Care Med. 2020 January ; 48(1): 10–21. doi:10.1097/CCM.0000000000004087.

Critical Care Management of Toxicities Associated with Targeted Agents and Immunotherapies for Cancer

Cristina Gutierrez, MD¹ [Assistant Professor of Medicine], Colleen McEvoy, MD² [Assistant Professor of Medicine], Laveena Munshi, MD MSc FRCP³ [Assistant Professor of Medicine], R. Scott Stephens, MD⁴ [Director, Oncology and Bone Marrow Transplant Critical Care and Assistant Professor of Medicine], Michael E. Detsky, MD⁵ [Assistant Professor of Medicine], Joseph L Nates, MD, MBA, MCCM⁶ [Director, Surgical and Medical Intensive Care Units; and Professor and Deputy Chair], Stephen M Pastores, MD, FCCM⁷ [Program Director, Critical Care Medicine, Vice Chair of Education]

¹Department of Critical Care, The University of Texas M.D. Anderson Cancer Center, Houston, TX

²Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, MO

³Interdepartmental Division of Critical Care Medicine, Toronto General Hospital, Toronto, Ontario, Canada

⁴Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, MD

⁵Interdepartmental Division of Critical Care Medicine, Mount Sinai Hospital, Toronto, ON, Canada

⁶Division of Anesthesiology and Critical Care, Department of Critical Care, The University of Texas M.D. Anderson Cancer Center, Houston, TX

⁷Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; and Professor of Medicine and Anesthesiology, Weill Cornell Medical College, New York, NY

Abstract

Objective: To describe the most common serious adverse effects and organ toxicities associated with emerging therapies for cancer that may necessitate admission to the ICU.

Data Sources and Study Selection: PubMed and Medline search of relevant articles in English on the management of adverse effects of immunotherapy for cancer.

Data extraction and Data Synthesis: Targeted immunotherapies including tyrosine kinase inhibitors, monoclonal antibodies, checkpoint inhibitors, and immune effector cell therapy have improved the outcome and quality of life of patients with cancer. However, severe and life-

Corresponding author: Stephen M. Pastores, MD, FCCM, Program Director, Critical Care Medicine, Vice Chair of Education, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue C-1179, New York, NY 10065, pastores@mskcc.org.

Copyright form disclosure: Drs. Gutierrez, McEvoy, Stephens, and Pastores disclosed off-label product use of siltuximab for use in cytokine release syndrome and neurotoxicity related to chimeric antigen receptor T cells. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Disclosures: The authors report no financial conflict of interest.

threatening side effects can occur. These toxicities include infusion or hypersensitivity reactions, cytokine release syndrome, pulmonary, cardiac, renal, hepatic, and neurologic toxicities, hemophagocytic lymphohistiocytosis, opportunistic infections, and endocrinopathies. Cytokine release syndrome is the most common serious toxicity after administration of monoclonal antibodies and immune effector cell therapies. Most of the adverse events from immunotherapy results from an exaggerated T-cell response directed against normal tissue, resulting in the generation of high levels of proinflammatory cytokines. Toxicities from targeted therapies are usually secondary to “on target toxicities”. Management is largely supportive and may include discontinuation of the specific agent corticosteroids and other immune-suppressing agents for severe (grade 3 or 4) immune-related adverse events like neurotoxicity and pneumonitis.

Conclusions: The complexity of toxicities associated with modern targeted and immunotherapeutic agents for cancer require a multidisciplinary approach among ICU staff, oncologists, and organ specialists and adoption of standardized treatment protocols to ensure the best possible patient outcomes.

Keywords

Cancer; immunotherapy; adverse events; toxicities; chimeric antigen receptor cell therapy; cytokine release syndrome; neurotoxicity; intensive care unit

Introduction

The treatment of cancer has evolved significantly in the last two decades with the development of tyrosine kinase inhibitors (TKIs), monoclonal antibodies (mAbs), immune checkpoint inhibitors (ICIs), and immune effector cell (IEC) therapy. These approaches have improved the outcome and quality of life of patients with cancer. However, severe and life-threatening side effects can occur necessitating admission to the intensive care unit (ICU) (Table 1). As oncologic patients get increasingly exposed to these novel therapies, it is paramount for clinicians to recognize their toxicities and institute rapid and effective treatments. In this first of a two-part review of oncologic critical care, we will focus on the most common organ toxicities associated with new and emerging therapies for cancer and their management.

Novel Agents and Toxicity Profiles

Tyrosine kinase inhibitors block the action of tyrosine kinases, vital for tumor cell signaling, proliferation, and metabolism (1). Severe adverse events with TKIs include cardiomyopathy, pneumonitis, pulmonary hypertension and thromboembolism, neurotoxicity, and hemorrhagic complications (Table 2) (1–3).

Monoclonal antibodies (mAbs) are designed to bind to specific tumoral antigens, inflammatory cytokines and their receptors, or to endothelial and epithelial growth factors (3–6). Adverse events are diverse ranging from severe infusion reactions to pulmonary toxicities (Table 3). The toxicity spectrum varies depending on the mechanism of action of the mAb.

Immune checkpoint inhibitors, are mAbs that bind to programmed cell death (PD)-1/programmed death ligand (PDL)-1 and cytotoxic T-lymphocyte antigen 4 (CTLA4) to block T-cell inhibition, thereby upregulating T-cells and enhancing their anti-tumor immunity (7). Most toxicities from ICIs arise from immune-mediated inflammatory responses that lead to organ toxicity (4, 8, 9). Severe toxicities may affect different organ systems and manifest with pneumonitis, neurotoxicity, cardiomyopathy, renal failure or hepatitis (Table 4).

Immune effector cell (IEC) therapies include chimeric antigen receptors (CARs) and T-cell receptors (TCRs). CARs are autologous cells modified to express a single chain antibody that recognizes a tumoral antigen (e.g., CD19 CAR T-cells recognize CD19 in B-cell malignancies)(10, 11). TCRs are autologous T-cells with a modified T-cell receptor that recognize the major histocompatibility complex of a specific tumoral antigen (12). Toxicities of CARs are secondary to the exaggerated inflammatory response caused by their activation leading to shock, hypoxic respiratory failure, and/or neurotoxicity (10, 13). In the case of TCRs, adverse events due to their proliferation are minimal, but “off-target” toxicities exist. CARs are a promising treatment for chemotherapy-refractory B-cell malignancies, but more than 30–40% of patients who receive this therapy require ICU admission (14, 15).

Toxicity Profiles

Infusion reactions

Infusion reactions due to mAbs, are divided into immediate and delayed (4). Immediate infusion reactions may reflect hypersensitivity reactions (anaphylaxis), reactions due to immunogenicity to non-specific proteins of the mAbs (anaphylactoid) and cytokine release syndrome (CRS). Anaphylaxis is IgE mediated and occurs within minutes to 1 hour of infusion following repeat exposure to the mAb (4, 9, 16, 17). Anaphylactoid reactions are non-IgE mediated and usually have a milder clinical presentation (16, 18). Cytokine release syndrome, which is T-cell mediated, has a myriad of clinical symptoms and will be discussed in detail in the next section. Monoclonal antibodies associated with severe infusion reactions include rituximab (anti-CD20), brentuximab (anti-CD30), alemtuzumab (anti-CD52), trastuzumab and pertuzumab (anti-HER2), bevacizumab (anti-vascular endothelial growth factor [VEGF]), and cetuximab (anti-epithelial growth factor receptor [EGFR])(4, 9, 16, 17, 19). Infusion reactions are extremely rare for checkpoint inhibitors (<1%), except for avelumab (20%) (7, 19).

Signs and symptoms of anaphylaxis include angioedema, bronchospasm, hypotension, or anaphylactic shock (16, 19). Initial non-specific protein-related reactions may also present with hypotension and fever but are usually milder, self-limited and are unlikely to require an ICU admission (16, 18). Treatment of infusion reactions includes immediate interruption of the infusion and supportive care with epinephrine (in anaphylaxis), antihistamines, and corticosteroids (4). Vasopressor support and mechanical ventilation may be required. In the case of a severe infusion reaction, desensitization, premedication with antihistamines and corticosteroids, and re-challenging with a lower rate and dose of the infusion may minimize the risk of subsequent reactions (4, 16, 19).

Infusion reactions from mAbs can be similar in presentation to CRS. However, the following are differentiating features: 1) CRS typically occurs with the first dose administered and more than 2 hours post-infusion, while hypersensitivity infusion reactions occur immediately and after at least one uneventful dose has been administered; and 2) CRS is T-cell and cytokine-mediated while hypersensitivity reactions are IgE mediated and lead to mast cell activation, release of histamines, leukotrienes and prostaglandins (16, 19). It is important to note that exceptions can occur; anaphylaxis due to cetuximab is observed with the first dose due to preformed IgE antibodies (4, 17).

Delayed serious infusion reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, are rare and limited to case reports with rituximab and cetuximab (4, 21, 22), and with ICIs (23).

Cytokine Release Syndrome due to Immune Effector Cell Therapy

Cytokine release syndrome (CRS) is the most common toxicity with CARs (60–94% of patients), with 13–20% requiring high doses vasopressors (24–27). The incidence and severity of CRS increases with large tumor burden and higher cell dosing (14, 24). A recent consensus group defined CRS related to IECs as “a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T-cells and/or other immune effector cells”(28). The inflammatory response during CRS is associated with marked elevations of inflammatory cytokines (e.g.; IL-6, IL-8, IL-10, INF- γ) and endothelial activation markers such as von-Willebrand factor and angiopoietin-2 (29–31).

CRS symptoms usually occur within the first 7–14 days of CAR T-cell infusion depending on the construct (25, 27, 32). The hallmark symptoms are fever, hypotension, and hypoxemia. A consensus was recently reached for CRS grading (Figure 1) (28). As the syndrome evolves, various organ systems may be affected leading to multisystem organ failure. Cardiac toxicity manifests as tachycardia, arrhythmias, heart blocks, hypotension and shock. Decreased left ventricular ejection is also observed. Hypoxemic respiratory failure can rapidly progress from capillary leak syndrome and non-cardiogenic pulmonary edema to acute respiratory distress syndrome (ARDS). Renal failure, hepatotoxicity, disseminated intravascular coagulopathy and skin lesions can also occur.

Treatment of grade 2 CRS includes anti-IL-6 therapy with tocilizumab and siltuximab, and corticosteroids to suppress inflammation and CAR proliferation (14, 33) (Figure 1). Recent data suggest anti-IL-1 receptor anakinra, anti-granulocyte macrophage colony stimulating factor, and JAK1 and 2 inhibition with ruxolitinib are successful in suppressing CRS in animal models (34–36). Since the clinical presentation of CRS may mimic sepsis, alternative causes of fever, hypotension and hypoxemia, need to be simultaneously investigated.

The clinical presentation of CRS caused by mAbs is similar to that observed with IECs. High tumor burden, rapid infusion, and high doses of the mAbs can increase the risk and severity of CRS (17, 20). Treatment for mAb-induced CRS includes acetaminophen, antihistamines, tocilizumab, and corticosteroids (4, 17). Supportive care of specific organ failure should be similar to that of IECs.

Pulmonary toxicities

The incidence of ICI-related pneumonitis ranges between 1–10% and is more common with anti-PD-1/PD-L1 agents and with combination therapy (37–42). Acute pneumonitis typically presents 3 months (2–24 months) following treatment initiation but may occur earlier with dual agent therapy (40, 41). Non-specific clinical symptoms and radiographic patterns have been described (40). Due to their low specificity, a meticulous approach to rule out infection is necessary during the work-up of respiratory failure in this population. Computed tomography of the chest and early fiberoptic bronchoscopy and bronchoalveolar lavage to rule out infectious etiologies, while empirically treating, is recommended.

Treatment strategies for severe pneumonitis include permanent discontinuation of the ICI and initiation of IV methylprednisolone 1–2 mg/kg/day (39, 43). Corticosteroid taper should be performed over 4–6 weeks (43, 44). Most adverse events from ICIs resolve within weeks to months of initiation of corticosteroid therapy(44), although mortality related to ICI pneumonitis is seen in 14% of patients (45). Additional treatments to consider in refractory patients include infliximab, mycophenolate mofetil (MMF), cyclophosphamide and intravenous immunoglobulin (IVIg) (39).

Cytokine release syndrome can cause acute respiratory distress syndrome (ARDS) as a direct consequence of capillary leak leading to non-hydrostatic pulmonary edema. Hydrostatic pulmonary edema may result from CRS-associated acute dilated cardiomyopathy. Excessive fluid administration could further exacerbate respiratory failure. Besides close monitoring for signs of respiratory failure and utilizing lung protective ventilation, infectious causes should be ruled out(46, 47). Treatment with anti-IL-6 therapy and corticosteroids is recommended (Figure 1) (14, 33).

Drugs targeting angiogenesis inhibition such as bevacizumab and aflibercept and TKIs (dasatinib, ponatinib and axitinib) are associated with pulmonary thromboembolic complications (6). Interstitial pneumonitis and interstitial lung disease has been reported with rituximab (8–20%) (48, 49) and time to onset varies from 2 weeks to 3 months after initiation of treatment (48, 49). Treatment consists of cessation of the antibody and glucocorticoids. TKIs have also been associated with other pulmonary complications such as pneumonitis, pleural effusions, and pulmonary hypertension (6, 50, 51). Pulmonary hypertension (pHTN) is usually observed with dasatinib in less than 1% of patients, and has also been reported with the use of imatinib(50, 51). While it is recommended to screen patients for cardiopulmonary disease prior to their use, pHTN usually resolves after discontinuation of the medication (50, 51). Pneumonitis has been observed in <10% of patients treated with dasatinib and <1% with imatinib, and discontinuation of the medication usually leads to resolution of the symptoms(50, 51). Its incidence increases when combining therapy with TKIs (afatinib, erlotinib, gefitinib, osimertinib) and ICIs (nivolumab)(53).

Neurotoxicity

Neurological complications vary significantly in presentation, and treatment can be challenging. CAR-associated neurotoxicity, now referred to as Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) presents in 70–80% of patients receiving

CARs and 30–40% of cases are severe (13–15, 33). ICANS may occur either within 7 days of CAR-T cell infusion with or without CRS, or after resolution of CRS (1–2 weeks after infusion). The syndrome is usually reversible, but can be severe and lead to death if left unrecognized(54). Mild presentations include tremors, headache, mild aphasia, confusion and dysgraphia (14, 28, 33, 55) (Figure 2A). As symptoms evolve, global aphasia, seizures, status epilepticus, coma, paresis and cerebral edema can occur (14, 28, 33, 55). Similar to CRS, a consensus was recently reached for ICANS grading that includes the use of the Immune Effector Cell-Associated Encephalopathy (ICE) assessment tool (Figure 2A and 2B) (28). The pathophysiology of ICANS includes local central nervous system (CNS) inflammation, endothelial dysfunction of the blood-brain barrier (BBB) and cell trafficking of CARs into the CNS(13, 55). Management of seizures, status epilepticus and cerebral edema is vital (14). Corticosteroids reverse symptoms in many cases and are recommended in patients with severe (grade 3 and 4) neurotoxicity associated with the axicabtagene-ciloleucel CAR construct (Figure 2A) (14, 55). Use of corticosteroids for other CARs, such as tisagenlecleucel, is not routinely recommended and can be considered for severe persistent symptoms. Thus, due to the variability between cell products, the use of corticosteroids should be carefully discussed with the oncologist balancing the patient's clinical condition versus the risk of affecting CAR replication.

With ICIs, neurologic toxicities can present within 1 week of infusion and have significant morbidity and mortality (45, 56). Neurologic toxicities are more common with anti-PD-1/PDL-1 antibodies and combination therapy (43). Both Guillain-Barre syndrome and myasthenia gravis have been described with ICIs and sunitinib (2, 3, 44, 56, 57) (Table 4). While the presentation can be typical, a significant number of patients present with variants associated to severe myositis and polyradiculoneuropathies (56, 57). Diagnosis includes a comprehensive clinical exam, cerebrospinal fluid (CSF) studies demonstrating pleocytosis and elevated protein, electromyography and nerve conduction studies(23, 43). Creatine kinase levels should be monitored (8, 45, 57). Acetylcholine antibodies, while helpful, are not always positive and should not guide treatment (56, 57). Treatment for both Guillain-Barre syndrome and myasthenia gravis include corticosteroids, plasmapheresis and IVIg (3, 23, 43, 56, 57). Since many cases present with concurrent severe myositis, corticosteroid-sparing treatments such as rituximab and infliximab can be considered.(44, 56, 58).

Posterior reversible encephalopathy syndrome (PRES) is common with mAbs, ICIs, and TKIs (Tables 2, 3, 4)(2, 3, 9). In the case of anti-angiogenic therapies, PRES is triggered by acute endothelial injury with breakdown of the blood-brain barrier and subsequent cerebral edema (2). However, with ICIs and other mAbs the pathophysiology is unclear (56). The main features are altered mental status, headache, visual disturbances, and seizures. Typical findings on magnetic resonance imaging (MRI) are symmetric T2 or fluid-attenuated inversion recovery imaging (FLAIR) hyperintensities located in the occipital and parietal regions (2). (9, 56). Lowering of high blood pressure and discontinuation of the agent are the mainstays of treatment (2, 56).

Aseptic meningitis, encephalitis and encephalopathy may present in patients treated with mAbs and ICIs (2, 44, 57, 59) (Tables 3 and 4). Infectious causes should be ruled out and treated concomitantly until a definite diagnosis is made. MRI findings and CSF studies vary

significantly; however, a CSF with lymphocytic pleocytosis may suggest an immune-related process (23, 43, 60). Treatment includes corticosteroids, IVIg and rituximab(23, 56, 60). Responses to treatment vary significantly and relapses can be observed, therefore a corticosteroid taper over 4–8 weeks is recommended (43, 56). Encephalopathy caused by blinatumomab, a bispecific mAb, is very similar to ICANS and can be severe in 13% of patients(2, 6). Treatment includes discontinuation of the medication, corticosteroids and supportive care(2, 6).

Seizures present with TKIs and ICIs (2, 3). Treatment include antiepileptic drugs, corticosteroids, IVIg and apheresis in refractory cases (2, 3, 56, 57). Transverse myelitis is described with ipilimumab and reversed after high dose corticosteroids (2, 56). Cerebral edema can occur with nivolumab and the BRAF inhibitors vemurafenib and dabrafenib (3). Anti-angiogenic agents, either mAbs (bevacizumab, ramucirumab) or TKIs (imatinib, dasatinib, lenvatinib mesylate, sunitinib, sorafenib, ibrutinib) are associated with intracranial hemorrhage (0.3%–3.3%) and ischemic cerebral events (1.3–1.9%) (2, 3, 6, 17). Hemorrhagic presentations include intraparenchymal hemorrhages independent of CNS lesions, subarachnoid hemorrhage and subdural hematomas (2, 3). In the case of ibrutinib, dasatinib, and imatinib, bleeding has been attributed to inhibition of platelet aggregation via inhibition of cyclooxygenase, kinases vital to platelet aggregation or collagen dependent aggregation (3, 61). In these patients, the utility of platelet transfusions should be discussed with the hematology and oncology teams. Relapse of autoimmune disorders such as multiple sclerosis has been described with the use of ipilimumab(3).

Cardiac toxicities

The cardiovascular symptoms of CRS associated to both CARs and mAbs can range from tachycardia to life threatening complications such as dysrhythmias, impaired left ventricular ejection fraction and vasodilatory shock requiring high dose vasopressors(14, 17, 31, 33, 62, 63). Treatment is largely supportive and include corticosteroids and IL-6 antagonists (14, 33). Initial investigations should include electrocardiography, continuous telemetry and echocardiography to identify the potential dysrhythmias and ejection fraction, respectively.

Cardiovascular toxicities from mAbs vary significantly (Table 3). Infusion of mAbs, such as rituximab and bevacizumab can cause significant dysrhythmias and cardiomyopathy independent of cardiovascular risk factors(64, 65). Classic acute coronary syndromes such as vasospastic angina and stent thrombosis are reported with bevacizumab, trastuzumab and ranibizumab(66). A more specific coronary syndrome associated with mAbs (rituximab, infliximab, cetuximab and alemtuzumab) is Kounis Syndrome(66–68). Kounis syndrome is defined by the presence of mast cell degranulation, cross bridging of platelets and secondary allergic thrombosis (67). Any allergic reaction can cause Kounis syndrome, but in this case antibodies directed against the mAbs lead to mast cell activation(68). Opiates such as morphine should be administered with extreme caution in patients with Kounis syndrome, since this can induce massive mast cell degranulation and aggravate the allergic reaction(67). Management is limited to case reports that suggest treatment of both an anaphylactic reaction and acute coronary syndrome simultaneously. The use of epinephrine can be considered both helpful and harmful(69).

The incidence ICI-associated myocarditis is low (<1%) but comprises 22% of the fatalities associated with ICIs (7, 45, 70). Symptoms usually start 30 days after starting therapy(70). As soon as myocarditis is recognized, stopping the agent and starting high dose corticosteroids is recommended (71). In refractory cases, infliximab, anti-thymocyte globulin and mycophenolate mesylate (MMF) can be considered(43).

QTc prolongation and increased cardiovascular ischemic events are reported with nilotinib (72, 73). In patients with pre-existing cardiovascular risk factors, ponatinib increases the risk of cardiac ischemic events(72, 73). Screening for underlying coronary artery disease is recommended for patients who will receive TKIs known to cause cardiovascular toxicity.

Renal failure

Acute kidney injury (AKI) can occur in 10–20% of patients treated with ICIs (74, 75). Patients develop pyuria, proteinuria and typical pathological features of an acute lymphocytic tubulointerstitial nephritis (76–80). Nephrotic syndrome can also occur (79). AKI occurs at a median of 3 months after initiation of ICIs and more than 2 months after the last dose (76, 80). Treatment and prognostic data are limited, but in addition to discontinuation of the ICI, the use of corticosteroids can be considered (75, 76, 80). Other treatments such as rituximab, infliximab, MMF and plasmapheresis are described (80). Experimental models suggest that patients receiving ICIs are more susceptible to AKI due to sepsis and shock (81).

Anti-vascular endothelial growth factors (VEGF) antibodies (e.g., bevacizumab) and anti-VEGF TKIs such as sunitinib and sorafenib can cause a variety of kidney injuries as high levels of VEGF are expressed in the normal kidney (79, 82, 83). The most serious of these are interstitial nephritis and thrombotic microangiopathy (79, 82, 83). Other TKIs (bortezomib and carfilzomib) can also cause thrombotic microangiopathy (79, 84–86).

Tumor lysis syndrome can cause AKI after treatment with mAbs (e.g. rituximab, obinutuzumab), TKIs (e.g. alvocidib, ibrutinib, nilotinib, dasatinib) and CARs (87–89). Management of TLS should not differ from that described for cytotoxic agents(88, 89). AKI due to CRS occurs after treatment with CARs and mAbs (29, 90–92). The mechanism of AKI is multifactorial: hypoperfusion from hemodynamic instability and fluid shifts, and direct injury from cytokines (91, 92). Management should be supportive and treating the underlying CRS with corticosteroids and anti-IL-6 therapy. The AKI associated with TLS after CARs can be difficult to differentiate from CRS, especially since it can present concomitantly with CRS. Therefore, supportive treatment for TLS should be considered in patients with high tumor burden before and after infusion of CARs.

Other Considerations

Secondary hemophagocytic lymphohistiocytosis (HLH) was described in patients receiving CAR T-cells, ICIs (pembrolizumab) and blinatumomab (93–95). Its presentation can mimic other conditions such as CRS and sepsis, making its diagnosis challenging. Signs and symptoms include fever with multi-organ dysfunction (e.g., altered mental status/seizure, respiratory distress syndrome, hypotension/shock, severe liver dysfunction), hepato/

splenomegaly, anemia, thrombocytopenia, and hypertriglyceridemia. LDH, ferritin and IL-2R levels are markedly elevated and bone marrow aspirates show hemophagocytosis (93, 95). Diagnostic criteria and recommendations have been made in the CAR-T population, but further data are required to evaluate their sensitivity and specificity (96–98). The treatment of HLH in patients with concurrent CRS includes corticosteroids and anti-IL-6 therapy, with consideration of etoposide if there is no clinical improvement (33, 99).

Hepatotoxicity has been described with ICIs. This is usually manifested with transient elevation in transaminases although fulminant liver failure has been reported (58, 74, 100). Hepatitis occurs in 5%–10% of patients treated with ipilimumab, nivolumab, and pembrolizumab (58, 101–106). Corticosteroids are the treatment of choice for grade 3 or 4 liver toxicity (43). Elevation in transaminases can also occur during CRS following treatment with CAR-T cells and blinatumomab (90, 92, 107).

A recent international consensus document concluded that targeted therapies do not intrinsically increase the incidence of serious infections (109). Nevertheless, opportunistic infections including *Aspergillus fumigatus* pneumonia, cytomegalovirus hepatitis, and *Pneumocystis jirovecii* pneumonia in patients receiving ipilimumab and pembrolizumab and CARs have been reported (110–113). The use of corticosteroids and other immune suppressing agents for the treatment of AEs due to immunotherapy likely renders these patients at higher risk of opportunistic infections (114). Thus, for cancer patients receiving immunotherapy who require 20 mg of prednisone daily or the equivalent for at least 4 weeks, *Pneumocystis jirovecii* prophylaxis is recommended (115). Viral hepatitis reactivation can occur with targeted cancer therapies, particularly rituximab, sometimes with fulminant results (116–118).

Endocrinopathies are described with ICIs (Table 1). Both hyperthyroidism and hypothyroidism can develop in 1–10% of cases and increase to 20% with combination therapy (7, 43, 44). Hypophysitis can also occur, and while rare with anti-PD-1/PDL-1, rates of 16% are observed with anti-CTLA-4 or combination of anti-CTLA-4 and anti-PD-1 therapy (43, 44). Patients may be asymptomatic or can present with headache, visual disturbances or other endocrine-related syndromes. Magnetic resonance imaging of the brain is important to exclude secondary meningeal or parenchymal lesions. Levels of thyroid stimulating hormone, adrenocorticotropin hormone and cortisol should be monitored regularly in patients receiving ICIs (23, 43). In patients recently treated with ICIs, suspicion of adrenal insufficiency and hypo/hyperthyroidism should lead to immediate workup and use of corticosteroids and hormone replacement, if indicated. For all moderate-to-severe endocrinopathies, anti-PD-1/PD-L1 agents should be held until the patient is stable on hormone-replacement therapy or the endocrinopathy resolves.

Summary

Novel immunotherapeutic agents for cancer have led to a decreased overall death rate but can be associated with severe and life-threatening complications requiring ICU admission. The complexity of toxicities associated with these therapies require a multidisciplinary

approach among ICU staff, oncologists, and organ specialists and adoption of standardized treatment protocols to ensure the best possible patient outcomes.

References:

1. Shah DR, Shah RR, Morganroth J. Tyrosine kinase inhibitors: their on-target toxicities as potential indicators of efficacy. *Drug Saf* 2013; 36: 413–426. [PubMed: 23620170]
2. Forst DA, Wen PY. Neurological Complications of Targeted Therapies. In: Schiff D, Arrillaga I, Wen PY, editors. *Cancer Neurology in Clinical Practice*: Springer, Cham; 2017 p. 311–333.
3. Zukas AM, Schiff D. Neurological complications of new chemotherapy agents. *Neuro Oncol* 2018; 20: 24–36. [PubMed: 28992326]
4. Picard M, Galvao VR. Current Knowledge and Management of Hypersensitivity Reactions to Monoclonal Antibodies. *J Allergy Clin Immunol Pract* 2017; 5: 600–609. [PubMed: 28110056]
5. Baldo BA. Adverse events to monoclonal antibodies used for cancer therapy: Focus on hypersensitivity responses. *Oncoimmunology* 2013; 2: e26333. [PubMed: 24251081]
6. Kroschinsky F, Stölzel F, von Bonin S, et al.; Intensive Care in Hematological and Oncological Patients (iCHOP) Collaborative Group. New drugs, new toxicities: severe side effects of modern targeted and immunotherapy of cancer and their management. *Crit Care* 2017; 21: 89. [PubMed: 28407743]
7. Johnson DB, Chandra S, Sosman JA. Immune Checkpoint Inhibitor Toxicity in 2018. *JAMA* 2018; 320: 1702–1703. [PubMed: 30286224]
8. Gelao L, Criscitiello C, Esposito A, Goldhirsch A, Curigliano G. Immune checkpoint blockade in cancer treatment: a double-edged sword cross-targeting the host as an “innocent bystander”. *Toxins (Basel)* 2014; 6: 914–933. [PubMed: 24594636]
9. Meisel K, Rizvi S. Complications of monoclonal antibody therapy. *Med Health R I* 2011; 94: 317–319. [PubMed: 22204093]
10. Corrigan-Curay J, Kiem HP, Baltimore D, et al. T-cell immunotherapy: looking forward. *Mol Ther* 2014; 22: 1564–1574. [PubMed: 25186558]
11. Jackson HJ, Rafiq S, Brentjens RJ. Driving CAR T-cells forward. *Nat Rev Clin Oncol* 2016; 13: 370–383. [PubMed: 27000958]
12. Linette GP, Stadtmauer EA, Maus MV, et al. Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma. *Blood* 2013; 122: 863–871. [PubMed: 23770775]
13. Gust J, Hay KA, Hanafi LA, et al. Endothelial Activation and Blood-Brain Barrier Disruption in Neurotoxicity after Adoptive Immunotherapy with CD19 CAR-T Cells. *Cancer Discov* 2017; 7: 1404–1419. [PubMed: 29025771]
14. Gutierrez C, McEvoy C, Mead E, et al. Management of the Critically Ill Adult Chimeric Antigen Receptor-T Cell Therapy Patient: A Critical Care Perspective. *Crit Care Med* 2018;46(9):1402–1410. [PubMed: 29939878]
15. Locke FL, Neelapu SS, Bartlett NL, et al. Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. *Mol Ther* 2017; 25: 285–295. [PubMed: 28129122]
16. Asselin B. Immunology of infusion reactions in the treatment of patients with acute lymphoblastic leukemia. *Future Oncol* 2016; 12: 1609–1621. [PubMed: 27086555]
17. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. *Nat Rev Drug Discov* 2010; 9: 325–338. [PubMed: 20305665]
18. Doessegger L, Banholzer ML. Clinical development methodology for infusion-related reactions with monoclonal antibodies. *Clin Transl Immunology* 2015; 4: e39.
19. Rosello S, Blasco I, Garcia Fabregat L, Cervantes A, Jordan K; ESMO Guidelines Committee. Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines. *Ann Oncol* 2017; 28: iv100–iv118.

20. Bugelski PJ, Achuthanandam R, Capocasale RJ, Treacy G, Bouman-Thio E. Monoclonal antibody-induced cytokine-release syndrome. *Expert Rev Clin Immunol* 2009; 5: 499–521. [PubMed: 20477639]
21. Lin WL, Lin WC, Yang JY, et al. Fatal toxic epidermal necrolysis associated with cetuximab in a patient with colon cancer. *J Clin Oncol* 2008; 26: 2779–2780. [PubMed: 18509187]
22. Lowndes S, Darby A, Mead G, Lister A. Stevens-Johnson syndrome after treatment with rituximab. *Ann Oncol* 2002;13:1948–1950. [PubMed: 12453865]
23. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the Immune-Related Adverse Effects of Immune Checkpoint Inhibitors: A Review. *JAMA Oncol* 2016; 2: 1346–1353. [PubMed: 27367787]
24. Hay KA, Hanafi LA, Li D, et al. Kinetics and Biomarkers of Severe Cytokine Release Syndrome after CD19 Chimeric Antigen Receptor-modified T Cell Therapy. *Blood* 2017;130(21):2295–2306. [PubMed: 28924019]
25. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med* 2017; 377: 2531–2544. [PubMed: 29226797]
26. Park JH, Riviere I, Gonen M, et al. Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. *N Engl J Med* 2018; 378: 449–459. [PubMed: 29385376]
27. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. *N Engl J Med* 2017; 377: 2545–2554. [PubMed: 29226764]
28. Lee DW, Santomasso BD, Locke FL, et al. ASBMT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant* 2019;25(4):625–638. [PubMed: 30592986]
29. Wang Z, Han W. Biomarkers of Cytokine Release Syndrome and neurotoxicity related to CAR-T cell Therapy. *Biomark Res* 2018;6:4. [PubMed: 29387417]
30. Xu XJ, Tang YM. Cytokine release syndrome in cancer immunotherapy with chimeric antigen receptor engineered T cells. *Cancer Lett* 2014; 343: 172–178. [PubMed: 24141191]
31. Kochenderfer JN, Dudley ME, Feldman SA, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. *Blood* 2012; 119: 2709–2720. [PubMed: 22160384]
32. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014; 124: 188–195. [PubMed: 24876563]
33. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol* 2018; 15: 47–62. [PubMed: 28925994]
34. Norelli M, Camisa B, Barbiera G, et al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. *Nat Med* 2018; 24: 739–748. [PubMed: 29808007]
35. Sterner RM, Sakemura R, Cox MJ, et al. GM-CSF inhibition reduces cytokine release syndrome and neuroinflammation but enhances CAR-T cell function in xenografts. *Blood* 2018.
36. Frey N, Porter D. Cytokine Release Syndrome with Chimeric Antigen Receptor T Cell Therapy. *Biol Blood Marrow Transplant* 2019;25(4):e123–e127. [PubMed: 30586620]
37. Chuzy S, Tavora F, Cruz M, et al. Clinical features, diagnostic challenges, and management strategies in checkpoint inhibitor-related pneumonitis. *Cancer Manag Res* 2017; 9: 207–213. [PubMed: 28652812]
38. Barjaktarevic IZ, Qadir N, Suri A, Santamauro JT, Stover D. Organizing pneumonia as a side effect of ipilimumab treatment of melanoma. *Chest* 2013; 143: 858–861. [PubMed: 23460165]
39. Brahmer JR, Lacchetti C, Schneider BJ, et al.; National Comprehensive Cancer Network. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2018; 36: 1714–1768. [PubMed: 29442540]
40. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. *J Clin Oncol* 2017; 35: 709–717. [PubMed: 27646942]

41. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS. Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in Patients With Advanced Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol* 2016; 2: 1607–1616. [PubMed: 27540850]
42. Tirumani SH, Ramaiya NH, Keraliya A, et al. Radiographic Profiling of Immune-Related Adverse Events in Advanced Melanoma Patients Treated with Ipilimumab. *Cancer Immunol Res* 2015; 3: 1185–1192. [PubMed: 26100356]
43. Haanen J, Carbone F, Robert C, et al.; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; 28: iv119–iv142.
44. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. *N Engl J Med* 2018; 378: 158–168. [PubMed: 29320654]
45. Wang DY, Salem JE, Cohen JV, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. *JAMA Oncol* 2018; 4: 1721–1728. [PubMed: 30242316]
46. Fan E, Del Sorbo L, Goligher EC, et al.; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2017; 195: 1253–1263. [PubMed: 28459336]
47. Pastores SM, Voigt LP. Acute Respiratory Failure in the Patient with Cancer: Diagnostic and Management Strategies. *Critical Care Clinics Intensive Care of the Cancer Patient*; 2010 p. 21–40.
48. Bitzan M, Anselmo M, Carpineta L. Rituximab (B-cell depleting antibody) associated lung injury (RALI): a pediatric case and systematic review of the literature. *Pediatr Pulmonol* 2009; 44: 922–934. [PubMed: 19681063]
49. Keefer K, Bender R, Liao J, Sivik J, Van de Louw A. Characteristics of pulmonary complications in non-Hodgkin's lymphoma patients treated with rituximab-containing chemotherapy and impact on survival. *Ann Hematol* 2018; 97: 2373–2380. [PubMed: 30030570]
50. Medeiros BC, Possick J, Fradley M. Cardiovascular, pulmonary, and metabolic toxicities complicating tyrosine kinase inhibitor therapy in chronic myeloid leukemia: Strategies for monitoring, detecting, and managing. *Blood Rev* 2018; 32: 289–299. [PubMed: 29454474]
51. Shah NP, Wallis N, Farber HW, et al. Clinical features of pulmonary arterial hypertension in patients receiving dasatinib. *Am J Hematol* 2015; 90: 1060–1064. [PubMed: 26284693]
52. Ozgur Yurttas N, Eskazan AE. Dasatinib-induced pulmonary arterial hypertension. *Br J Clin Pharmacol* 2018; 84: 835–845. [PubMed: 29334406]
53. Oshima Y, Tanimoto T, Yuji K, Tojo A. EGFR-TKI-Associated Interstitial Pneumonitis in Nivolumab-Treated Patients With Non-Small Cell Lung Cancer. *JAMA Oncol* 2018; 4: 1112–1115. [PubMed: 29327061]
54. Abbasi K Connections with death. *J R Soc Med* 2007; 100: 205. [PubMed: 17470919]
55. Santomaso BD, Park JH, Salloum D, et al. Clinical and Biological Correlates of Neurotoxicity Associated with CAR T-cell Therapy in Patients with B-cell Acute Lymphoblastic Leukemia. *Cancer Discov* 2018; 8: 958–971. [PubMed: 29880584]
56. Gill C, Rouse S, Jacobson RD. Neurological Complications of Therapeutic Monoclonal Antibodies: Trends from Oncology to Rheumatology. *Curr Neurol Neurosci Rep* 2017; 17: 75. [PubMed: 28819716]
57. Zimmer L, Goldinger SM, Hofmann L, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Cancer* 2016; 60: 210–225. [PubMed: 27084345]
58. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of Immunotherapy for the Practitioner. *J Clin Oncol* 2015; 33: 2092–2099. [PubMed: 25918278]
59. Spain L, Walls G, Julve M, et al. Neurotoxicity from immune-checkpoint inhibition in the treatment of melanoma: a single centre experience and review of the literature. *Ann Oncol* 2017; 28: 377–385. [PubMed: 28426103]

60. Laserna A, Tummala S, Patel N, El Hamouda DEM, Gutierrez C. Atezolizumab-related encephalitis in the intensive care unit: Case report and review of the literature. *SAGE Open Med Case Rep* 2018; 6: 2050313X18792422.
61. Quintas-Cardama A, Han X, Kantarjian H, Cortes J. Tyrosine kinase inhibitor-induced platelet dysfunction in patients with chronic myeloid leukemia. *Blood* 2009; 114: 261–263. [PubMed: 19414863]
62. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood* 2016; 127: 3321–3330. [PubMed: 27207799]
63. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. *Lancet* 2015; 385: 517–528. [PubMed: 25319501]
64. Poterucha JT, Westberg M, Nerheim P, Lovell JP. Rituximab-induced polymorphic ventricular tachycardia. *Tex Heart Inst J* 2010; 37: 218–220. [PubMed: 20401299]
65. Stopeck AT, Unger JM, Rimsza LM, et al. A phase 2 trial of standard-dose cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) and rituximab plus bevacizumab for patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: SWOG 0515. *Blood* 2012; 120: 1210–1217. [PubMed: 22734071]
66. Kounis NG, Soufras GD, Tsigkas G, Hahalis G. Adverse cardiac events to monoclonal antibodies used for cancer therapy: The risk of Kounis syndrome. *Oncoimmunology* 2014; 3: e27987. [PubMed: 25340003]
67. Kounis NG. Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. *Clin Chem Lab Med* 2016; 54: 1545–1559. [PubMed: 26966931]
68. Kounis NG, Kounis GN, Soufras GD, Tsigkas G, Hahalis G. Attention to Infliximab adverse events: chimeric monoclonal antibodies can induce anti chimeric antibodies that may result in Kounis hypersensitivity associated acute coronary syndrome. *Eur Rev Med Pharmacol Sci* 2014; 18: 3735–3736. [PubMed: 25555859]
69. Omri M, Kraiem H, Mejri O, Naija M, Chebili N. Management of Kounis syndrome: two case reports. *J Med Case Rep* 2017; 11: 145. [PubMed: 28532437]
70. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. *J Am Coll Cardiol* 2018; 71: 1755–1764. [PubMed: 29567210]
71. Neilan TG, Rothenberg ML, Amiri-Kordestani L, et al.; Checkpoint Inhibitor Safety Working Group. Myocarditis Associated with Immune Checkpoint Inhibitors: An Expert Consensus on Data Gaps and a Call to Action. *Oncologist* 2018; 23: 874–878. [PubMed: 29802220]
72. Moslehi JJ, Deininger M. Tyrosine Kinase Inhibitor-Associated Cardiovascular Toxicity in Chronic Myeloid Leukemia. *J Clin Oncol* 2015; 33: 4210–4218. [PubMed: 26371140]
73. Aghel N, Delgado DH, Lipton JH. Cardiovascular toxicities of BCR-ABL tyrosine kinase inhibitors in chronic myeloid leukemia: preventive strategies and cardiovascular surveillance. *Vasc Health Risk Manag* 2017; 13: 293–303. [PubMed: 28831263]
74. Sukari A, Nagasaka M, Alhasan R, et al. Cancer Site and Adverse Events Induced by Immune Checkpoint Inhibitors: A Retrospective Analysis of Real-life Experience at a Single Institution. *Anticancer Res* 2019; 39: 781–790. [PubMed: 30711957]
75. Wanchoo R, Karam S, Uppal NN, et al.; Cancer, Kidney International Network Workgroup on Immune Checkpoint I. Adverse Renal Effects of Immune Checkpoint Inhibitors: A Narrative Review. *Am J Nephrol* 2017; 45: 160–169. [PubMed: 28076863]
76. Cortazar FB, Marrone KA, Troxell ML, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. *Kidney Int* 2016; 90: 638–647. [PubMed: 27282937]
77. Shirali AC, Perazella MA, Gettinger S. Association of Acute Interstitial Nephritis With Programmed Cell Death 1 Inhibitor Therapy in Lung Cancer Patients. *Am J Kidney Dis* 2016; 68: 287–291. [PubMed: 27113507]
78. Jolly EC, Clatworthy MR, Lawrence C, Nathan PD, Farrington K. Anti-CTLA-4 (CD 152) monoclonal antibody-induced autoimmune interstitial nephritis. *NDT Plus* 2009; 2: 300–302. [PubMed: 25984021]

79. Lefebvre J, Glezerman IG. Kidney Toxicities Associated With Novel Cancer Therapies. *Adv Chronic Kidney Dis* 2017; 24: 233–240. [PubMed: 28778363]
80. Mamlouk O, Selamet U, Machado S, et al. Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: single-center experience. *J Immunother Cancer* 2019; 7: 2. [PubMed: 30612580]
81. Jaworska K, Ratajczak J, Huang L, et al. Both PD-1 ligands protect the kidney from ischemia reperfusion injury. *J Immunol* 2015; 194: 325–333. [PubMed: 25404361]
82. Eremina V, Jefferson JA, Kowalewska J, et al. VEGF inhibition and renal thrombotic microangiopathy. *N Engl J Med* 2008; 358: 1129–1136. [PubMed: 18337603]
83. Launay-Vacher V, Aapro M, De Castro G Jr., et al. Renal effects of molecular targeted therapies in oncology: a review by the Cancer and the Kidney International Network (C-KIN). *Ann Oncol* 2015; 26: 1677–1684. [PubMed: 25735315]
84. Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood* 2012; 120: 2817–2825. [PubMed: 22833546]
85. Jhaveri KD, Chidella S, Varghese J, Mailloux L, Devoe C. Carfilzomib-related acute kidney injury. *Clin Adv Hematol Oncol* 2013; 11: 604–605. [PubMed: 24518527]
86. Chan KL, Filshie R, Nandurkar H, Quach H. Thrombotic microangiopathy complicating bortezomib-based therapy for multiple myeloma. *Leuk Lymphoma* 2015; 56: 2185–2186. [PubMed: 25547654]
87. Kasi PM, Tawbi HA, Oddis CV, Kulkarni HS. Clinical review: Serious adverse events associated with the use of rituximab - a critical care perspective. *Crit Care* 2012; 16: 231. [PubMed: 22967460]
88. Cheson BD, Heitner Enschede S, Cerri E, et al. Tumor Lysis Syndrome in Chronic Lymphocytic Leukemia with Novel Targeted Agents. *Oncologist* 2017; 22: 1283–1291. [PubMed: 28851760]
89. Howard SC, Trifilio S, Gregory TK, Baxter N, McBride A. Tumor lysis syndrome in the era of novel and targeted agents in patients with hematologic malignancies: a systematic review. *Ann Hematol* 2016; 95: 563–573. [PubMed: 26758269]
90. Jhaveri KD, Rosner MH. Chimeric Antigen Receptor T Cell Therapy and the Kidney.: What the Nephrologist Needs to Know. *CJASN* 2018;13(5):796–798. [PubMed: 29523675]
91. Perazella MA, Shirali AC. Nephrotoxicity of Cancer Immunotherapies: Past, Present and Future. *J Am Soc Nephrol* 2018; 29: 2039–2052. [PubMed: 29959196]
92. Fitzgerald JC, Weiss SL, Maude SL, et al. Cytokine Release Syndrome After Chimeric Antigen Receptor T Cell Therapy for Acute Lymphoblastic Leukemia. *Crit Care Med* 2017; 45: e124–e131. [PubMed: 27632680]
93. Shah AR, Muzzafar T, Assi R, et al. Hemophagocytic lymphohistiocytosis in adults: An under recognized entity. *BBA Clin* 2017; 7: 36–40. [PubMed: 28070498]
94. Neelapu SS, Locke FL, Bartlett NL, et al. Kte-C19 (anti-CD19 CAR T Cells) Induces Complete Remissions in Patients with Refractory Diffuse Large B-Cell Lymphoma (DLBCL): Results from the Pivotal Phase 2 Zuma-1. *Blood* 2016; 128: LBA-6.
95. Daver N, McClain K, Allen CE, et al. A consensus review on malignancy-associated hemophagocytic lymphohistiocytosis in adults. *Cancer* 2017; 123: 3229–3240. [PubMed: 28621800]
96. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol* 2018;15(1):47–62. [PubMed: 28925994]
97. Henter JI, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; 48: 124–131. [PubMed: 16937360]
98. Henter JI, Samuelsson-Horne A, Arico M, et al.; Histocyte S. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood* 2002; 100: 2367–2373. [PubMed: 12239144]
99. Teachey DT, Rheingold SR, Maude SL, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. *Blood* 2013; 121: 5154–5157. [PubMed: 23678006]

100. Di Giacomo AM, Biagioli M, Maio M. The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. *Semin Oncol* 2010; 37: 499–507. [PubMed: 21074065]
101. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med* 2013; 369: 122–133. [PubMed: 23724867]
102. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet* 2014; 384: 1109–1117. [PubMed: 25034862]
103. Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol* 2012; 30: 2691–2697. [PubMed: 22614989]
104. Weber JS, Dummer R, de Pril V, Lebbe C, Hodi FS, Investigators MDX. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. *Cancer* 2013; 119: 1675–1682. [PubMed: 23400564]
105. Weber JS, Kudchadkar RR, Yu B, et al. Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. *J Clin Oncol* 2013; 31: 4311–4318. [PubMed: 24145345]
106. Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol* 2014; 32: 1020–1030. [PubMed: 24590637]
107. Namuduri M, Brentjens RJ. Medical management of side effects related to CAR T cell therapy in hematologic malignancies. *Expert Rev Hematol* 2016; 9: 511–513. [PubMed: 27139507]
108. Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol* 1996; 14: 7–17. [PubMed: 8558223]
109. Redelman-Sidi G, Michielin O, Cervera C, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine-1-phosphate receptor modulators and proteasome inhibitors). *Clin Microbiol Infect* 2018; 24 Suppl 2: S95–S107. [PubMed: 29427804]
110. Arriola E, Wheeler M, Krishnan R, Smart J, Foria V, Ottensmeier C. Immunosuppression for ipilimumab-related toxicity can cause pneumocystis pneumonia but spare antitumor immune control. *Oncoimmunology* 2015; 4: e1040218. [PubMed: 26451305]
111. Kyi C, Hellmann MD, Wolchok JD, Chapman PB, Postow MA. Opportunistic infections in patients treated with immunotherapy for cancer. *J Immunother Cancer* 2014; 2: 19. [PubMed: 24991413]
112. Oltolini C, Ripa M, Andolina A, et al. Invasive Pulmonary Aspergillosis Complicated by Carbapenem-Resistant *Pseudomonas aeruginosa* Infection During Pembrolizumab Immunotherapy for Metastatic Lung Adenocarcinoma: Case Report and Review of the Literature. *Mycopathologia* 2018.
113. Uslu U, Agaimy A, Hundorfean G, Harrer T, Schuler G, Heinzerling L. Autoimmune Colitis and Subsequent CMV-induced Hepatitis After Treatment With Ipilimumab. *J Immunother* 2015; 38: 212–215. [PubMed: 25962110]
114. Del Castillo M, Romero FA, Arguello E, Kyi C, Postow MA, Redelman-Sidi G. The Spectrum of Serious Infections Among Patients Receiving Immune Checkpoint Blockade for the Treatment of Melanoma. *Clin Infect Dis* 2016; 63: 1490–1493. [PubMed: 27501841]
115. Network NCC. Prevention and treatment of cancer related infections, version 1.2018. [serial online] 2017
116. Yazici O, Sendur MA, Aksoy S. Hepatitis C virus reactivation in cancer patients in the era of targeted therapies. *World J Gastroenterol* 2014; 20: 6716–6724. [PubMed: 24944464]
117. Dervite I, Hober D, Morel P. Acute hepatitis B in a patient with antibodies to hepatitis B surface antigen who was receiving rituximab. *N Engl J Med* 2001; 344: 68–69.
118. Yeo W, Chan TC, Leung NW, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol* 2009; 27: 605–611. [PubMed: 19075267]

119. Chu F, Cao J, Neelapu SS. Versatile CAR T-cells for cancer immunotherapy. *Contemp Oncol (Pozn)* 2018; 22: 73–80. [PubMed: 29628798]
120. Gargett T, Brown MP. The inducible caspase-9 suicide gene system as a “safety switch” to limit on-target, off-tumor toxicities of chimeric antigen receptor T cells. *Front Pharmacol* 2014; 5: 235. [PubMed: 25389405]
121. Kao RL, Truscott LC, Chiou TT, Tsai W, Wu AM, De Oliveira SN. A Cetuximab-Mediated Suicide System in Chimeric Antigen Receptor-Modified Hematopoietic Stem Cells for Cancer Therapy. *Hum Gene Ther* 2019; 30: 413–428. [PubMed: 30860401]
122. Minagawa K, Jamil MO, Al-Obaidi M, et al. In Vitro Pre-Clinical Validation of Suicide Gene Modified Anti-CD33 Redirected Chimeric Antigen Receptor T-Cells for Acute Myeloid Leukemia. *PLoS One* 2016; 11: e0166891. [PubMed: 27907031]

Figure 1. CRS Grading and Management Considerations Associated with Immune Effector Cell Therapy

The major clinical manifestations of CRS are fever, hypotension, and hypoxia. The CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. The mainstays of treatment of grade 2 CRS are anti-IL-6 monoclonal antibodies (tocilizumab) and corticosteroids. Recommended dose of corticosteroids can vary among institutions and within protocols. Suicide and elimination genes are still experimental (119–122).

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (unarousable and unable to perform)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor Findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/Local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's Triad
Supportive Care	<ul style="list-style-type: none"> - Frequent neurologic examination - Imaging (CT brain or MRI) and EEG - Consider seizure prophylaxis - Consider and treat other causes of encephalopathy 	<ul style="list-style-type: none"> - Frequent neurologic examination - Imaging (CT brain or MRI) and EEG - Consider seizure prophylaxis - Consider and treat other causes of encephalopathy - Lumbar puncture if no contraindication 	<ul style="list-style-type: none"> - Transfer to ICU - Frequent neurologic examination with prevention and close monitoring for signs of elevated ICP - Imaging: (CT or MRI Brain) and EEG - Treatment of seizures including benzodiazepines, levetiracetam or other antiepileptic drugs - Neurosurgical consultation - Lumbar puncture if no contraindication - Consider and treat other causes of encephalopathy 	<ul style="list-style-type: none"> - ICU supportive care (airway and hemodynamic management) - Frequent neurologic examination and close monitoring for signs of elevated ICP - Imaging: (CT or MRI Brain) and EEG - Management of cerebral edema per institution guidelines - Management of status epilepticus per institution guidelines - Consider and treat other cause of encephalopathy - Neurosurgical consultation
Treatment	Close monitoring for progression**	Consider corticosteroids if symptoms are persistent	Corticosteroids: dexamethasone 10 mg IV q6 hr or equivalent to methylprednisolone	<ul style="list-style-type: none"> - Consider high dose corticosteroids (methylprednisolone IV 1 g/day) - Consider cyclophosphamide, other immunosuppressive agents or anakinra*** - Consider suicide/elimination gene activation for refractory symptoms when available (experimental¹⁹)

ICE = Immune Effector Cell-Associated Encephalopathy; CT = computed tomography; MRI = magnetic resonance imaging; EEG = electroencephalogram

**Tocilizumab or siltuximab is not indicated if there is no concurrent CRS

***No data available for their use, however can be considered in patients with refractory toxicity or concerns of worsening cerebral edema or refractory seizures

Figure 2A. ICANS Grading and Treatment Considerations

The grading of ICANS is determined by the most severe events (ICE score, level of consciousness, motor symptoms, seizures, and signs of elevated ICP/cerebral edema) not attributable to any other cause. Patients with grade 3 and 4 neurotoxicity should be monitored and managed in the ICU. Frequent neurologic examination and treatment of seizures and cerebral edema require close collaboration with neurology and neurosurgical consult services. Corticosteroids are indicated in patients with grade 3 and 4 neurotoxicity. Suicide and elimination genes are still experimental (119–122).

- Evaluation should be performed at least twice a day and should be repeated as needed if there is evidence of deterioration or to assess patient's response to treatment
- ICE assessment should not replace a complete neurological exam to further assess for motor deficits, clinical signs suggesting non-convulsive seizures and elevated intracranial pressure
- Maximum ICE score is 10/10 and a minimum is 0/10

Orientation: patient should state the year, month, city and hospital. **4 points**

Naming objects: Patient should name 3 objects that are pointed to during the evaluation. **3 points**

Commands: Able to follow simple commands such as "close eyes" or "show two fingers." **1 point**

Writing: Ability to write a sentence* (e.g.: "our national bird is a bald eagle"). **1 point**

Attention: Ability to count backwards from 100 by 10. **1 point**

* The same sentence should be used during each evaluation. A comparison to prior handwriting should be performed to assess changes. If using non-Latin alphabet, a translator might be required to evaluate.

Figure 2B.

Immune Effector Cell-Associated Encephalopathy (ICE) Score

Table 1.**Targeted Agents and Immunotherapies and their Associated Toxicities**

Type of Therapy	Toxicities
Tyrosine Kinase Inhibitors	<ul style="list-style-type: none"> Renal toxicity (interstitial nephritis, thrombotic microangiopathy, tumor lysis syndrome) Neurotoxicity (PRES, ischemic or hemorrhagic stroke, seizures, Guillain-Barre syndrome, myasthenia gravis, cerebral edema, subdural hematoma) Pulmonary (pneumonitis, pulmonary hypertension, thromboembolism) Cardiac (dysrhythmias, acute coronary syndrome, QT prolongation)
Monoclonal Antibodies	<ul style="list-style-type: none"> Infusion reactions Cytokine Release Syndrome Pulmonary (pneumonitis, thromboembolic events) Neurotoxicity (PRES, ischemic stroke, intracranial hemorrhage, aseptic meningitis, encephalopathy) Renal (interstitial nephritis, thrombotic microangiopathy, tumor lysis syndrome) Cardiac toxicity (Kounis syndrome, cardiomyopathy, dysrhythmias, acute coronary syndrome)
Immune Checkpoint Inhibitors	<ul style="list-style-type: none"> Pneumonitis Cardiac (myocarditis, pericarditis, dysrhythmias) Neurotoxicity (Guillain-Barre syndrome, myasthenia gravis, meningoencephalitis, cerebral edema, seizures, PRES) Nephrotoxicity (interstitial nephritis, glomerulonephritis, tumor lysis syndrome, nephrotic syndrome) Hepatotoxicity Endocrine (hypophysitis, adrenal insufficiency, thyroid dysfunction)
Chimeric Antigen Receptor (CAR) Cell Therapy	<ul style="list-style-type: none"> Cytokine Release Syndrome ICANS

PRES = posterior reversible encephalopathy syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome

Table 2.**Targets and Toxicities Associated with Tyrosine Kinase Inhibitors**

Drug	Target	Indication	Neurotoxicity	Pulmonary Toxicity	Other Toxicities
Sunitinib	VEGFR, PDGFR, c-Kit, RET	Renal cell carcinoma, GIST. Pancreatic neuroendocrine tumor	PRES, ischemic stroke, GBS and MG	Pneumonitis, Alveolar hemorrhage	Renal: Interstitial nephritis, Thrombotic microangiopathy
Vandetanib	VEGFR, EGFR, RET	Medullary thyroid carcinoma	PRES, Ischemic stroke	Pneumonitis	
Ibrutinib	BTK	CLL, mantle cell lymphoma	ICH	Pneumonitis	Renal: Tumor lysis syndrome Cardiac: arrhythmias
Lenvatinib	VEGFR 1, 2, 3, FGFR, RET, KIT, PDGFR- α	Metastatic differentiated thyroid cancer	Ischemic stroke, TIA, ICH, seizures, PRES		Renal toxicity
Sorafenib	VEGFR 2, 3, PDGFR KIT, FLT 3	Renal cell, hepatocellular and thyroid carcinomas	Ischemic stroke	Pneumonitis, Bronchospasm	Renal: interstitial nephritis and thrombotic microangiopathy
Pazopanib	VEGFR, PDGFR, KIT, FGFR	Renal cell carcinoma	Ischemic stroke, TIA, ICH (including SAH), PRES	Pneumonitis	Hepatotoxicity
Axitinib	VEGFR 1, 2, 3	Renal cell carcinoma	Ischemic stroke and PRES	Thromboembolic events, Pneumonitis, Hemoptysis	
Ceritinib	ALK	NSCLC	Seizures	Pneumonitis	
Imatinib	BCR-ABL	ALL, gastrointestinal stromal tumors, MDS	Subdural hematomas and ICH	Pneumonitis	Renal: Interstitial nephritis
Vemurafenib, Dabrafenib	BRAF inhibitor	Metastatic melanoma	Cerebral edema		
Dasatinib	BCR-ABL	ALL, CML	Subdural hematomas and ICH	Thromboembolic events, Pulmonary hypertension, Pneumonitis	Renal: Tumor lysis syndrome Cardiac: bradycardia
Ponatinib	BCR-ABL	CML, Philadelphia (+) ALL		Thromboembolic events	Cardiac: Acute coronary syndrome
Nilotinib	BCR-ABL	CML			Cardiac: Acute coronary syndrome, QT prolongation Renal: Tumor lysis syndrome
Bortezomib Carfilzomib	26S proteasome inhibitor	Multiple myeloma			Renal: Thrombotic microangiopathy

NSCLC = non-small cell lung carcinoma; SCC = squamous cell carcinoma; GIST = gastrointestinal stromal tumor; ICH = intracerebral hemorrhage; TIA (transient ischemic attack); SAH = subarachnoid hemorrhage; PRES = posterior reversible encephalopathy syndrome; GBS = Guillain-Barre Syndrome; MG = myasthenia gravis; ALL = acute lymphoblastic leukemia; MDS = myelodysplastic syndrome; CML = chronic myelogenous leukemia; CLL = chronic lymphocytic leukemia

Table 3.**Specific Targets and Toxicities Associated with Monoclonal Antibodies**

Drug	Target	Indication	Neuro-Toxicity	Pulmonary Toxicity	Other Toxicities
Alemtuzumab	Anti-CD52				Infusion reaction Cardiac: Kounis syndrome
Bevacizumab	VEGF- α	Colorectal, NSCLC, ovarian cancer, cervical cancer, glioblastoma, renal cell carcinoma	ICH, stroke or TIA, PRES	Thromboembolic events, Bronchospasm	Infusion reaction Cardiac: dysrhythmias, cardiomyopathy, acute coronary syndrome Renal: interstitial nephritis and thrombotic microangiopathy
Blinatumomab	CD19/CD3	B-cell ALL	Neurotoxicity similar to ICANS		Hemophagocytic lymphohistiocytosis
Cetuximab	EGFR	Colorectal, SCC head and neck	Aseptic meningitis, PRES	Pneumonitis, Bronchospasm	Infusion reaction, toxic epidermal necrolysis Cardiac: Kounis syndrome
Ramucirumab	VEGFR2	NSCLC	Ischemic stroke		
Trastuzumab	HER 2	Breast, gastric and esophageal cancer	PRES	Pneumonitis, Bronchospasm	Infusion reaction Cardiac: acute coronary syndrome
Brentuximab	Anti-CD30				Infusion reaction
Rituximab	Anti-CD20	Non-Hodgkin lymphoma, DLBCL		Interstitial pneumonitis and interstitial lung disease	Infusion reaction, Stevens- Johnson syndrome Cardiac: dysrhythmias, cardiomyopathy, Kounis syndrome

NSCLC = non-small cell lung carcinoma; SCC = squamous cell carcinoma; GIST = gastrointestinal stromal tumor; ICH = intracerebral hemorrhage; TIA (transient ischemic attack); PRES = posterior reversible encephalopathy syndrome; GBS = Guillain-Barre Syndrome; MG = myasthenia gravis; ALL = acute lymphoblastic leukemia; MDS = myelodysplastic syndrome; CML = chronic myelogenous leukemia; CLL = chronic lymphocytic leukemia; ICANS = Immune Effector Cell-associated Neurotoxicity Syndrome; DLBCL = diffuse large B cell lymphoma

Table 4.**Targets and Toxicities Associated with Immune Checkpoint Inhibitors**

Drug	Target	Indication	Neuro-Toxicity	Pulmonary Toxicity	Other Toxicities
Ipilimumab	CTLA4	Metastatic melanoma	Aseptic meningitis, GBS, MG, myelitis, PRES and MS relapse,	Pneumonitis	Cardiac: pericarditis, myocarditis Endocrine: Hypophysitis, thyroid dysfunction Hepatotoxicity Renal: Interstitial nephritis, glomerulonephritis
Pembrolizumab	PD-1	NSCLC, melanoma, Hodgkin's lymphoma	GBS, MG, seizures, encephalitis	Pneumonitis, alveolar hemorrhage,	Hemophagocytic lymphohistiocytosis Renal: Interstitial nephritis Cardiac: Pericardial effusion, myocarditis, dysrhythmias Hepatotoxicity Renal: Interstitial nephritis, glomerulonephritis Endocrine: Hypophysitis
Nivolumab	PD-1	NSCLC, melanoma, renal cell carcinoma, Hodgkin's lymphoma	GBS, encephalitis, MG, cerebral edema	Pneumonitis	Cardiac: Myocarditis Endocrine: thyroid dysfunction, hypophysitis Hepatotoxicity Renal: Interstitial nephritis, glomerulonephritis, nephrotic syndrome
Atezolizumab	PDL-1	NSCLC, urothelial cancer	Encephalitis, seizures		Endocrine: thyroid dysfunction, hypophysitis Renal: Interstitial nephritis

NSCLC = non-small cell lung carcinoma; PRES = posterior reversible encephalopathy syndrome; GBS = Guillain-Barre Syndrome; MG = myasthenia gravis; MS = multiple sclerosis