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RELIAS MEDIA

Managing Complications of New-Age Cancer Therapy

Introduction

Cancer therapy has been an area of constant discovery and evolution over the past two centuries, with innovative therapeutic strategies being developed as understanding of the underlying biologic processes increases. This has led to an expansion of treatment options in recent years with newer, more effective, and better-tolerated alternatives developed seemingly daily.

Until the early 20th century, surgical excision of tumors remained the mainstay of cancer therapy. Perhaps the most influential individual to have shaped the surgical approach to cancer was William Halstead (1852-1922) through his advocacy for the en bloc resection of the tumors and enough surrounding tissue to remove all the cancer cells. However, this approach was useful only for solid tumors that had not spread beyond their site of origin. With the discoveries of X-rays by Roentgen and radium by Pierre and Marie Curie, radiation therapy was introduced as a second modality to combat cancer.[1] Nitrogen mustard, used during the first World War as an agent of chemical warfare, was noted to have destructive effects on white blood cells, and subsequently was approved by the U.S. Food and Drug Administration (FDA) as a chemotherapeutic agent against Hodgkin lymphoma.[2] This marked the advent of cancer chemotherapy as an adjuvant to surgery and radiation. Successful trials involving Hodgkin lymphoma and childhood leukemia using regimens such as MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) and prednisone with 6-MP (6-mercaptopurine) introduced the concepts of combination chemotherapy in the 1960s.[3,4] For the next several decades, surgery, radiation, and chemotherapy would remain the mainstays of cancer therapy.

In recent years, a paradigm shift has occurred in cancer therapeutics. A vast number of newer treatment modalities are being used today, including targeted therapies, cancer vaccines, and, most recently, immunotherapy. Since 2006, the FDA has approved more than 130 new cancer drugs and indications for their use.[5]

Such major improvements in the ability to fight cancer have led to a 27% decline in death rates and increased five-year survival rates. Two-thirds of people diagnosed with cancer live at least five years after diagnosis. The projected population living with a cancer diagnosis is expected to grow to nearly 26 million by 2040, with 73% of survivors 65 years of age or older.[5,6] In turn, this increase in survivors will increase the number of emergency department (ED) visits of patients experiencing both acute and chronic complications related to cancer therapy.

EXECUTIVE SUMMARY

- The keys to identifying toxicity from checkpoint inhibitor therapy are knowing the patient has received such therapy and connecting the various symptoms and signs to one cause.
- The toxicity from checkpoint inhibitor therapy resembles autoimmune disorders, with skin, intestinal, endocrine, and pulmonary manifestations appearing in that sequence.
- Toxicity from adoptive cell therapy can produce the cytokine release syndrome, causing patients to present with fever, tachycardia, hypotension, and multi-organ failure.
- The febrile neutropenic patient should be evaluated carefully for an occult bacterial infection and managed with the expectation of empiric broad-spectrum antibiotics initiated in the emergency department.
- Scoring systems to identify low-risk patients with febrile neutropenia have not yet been prospectively validated for patients presenting to the emergency department.
- Early consultation with the patient's oncologist can be helpful in directing the assessment and disposition of patients with cancer therapy-related toxicity.

Although emergency providers are familiar with the adverse effects of older therapies, such as neutropenic fever and tumor lysis syndrome, the rapidly changing landscape of cancer therapy requires providers not only to keep abreast of treatment guidelines for these better-known complications, but also to familiarize themselves with the newer modalities and their associated toxicities and treatment options.

Newer Strategies in Cancer Treatment

Immuno-oncology currently is perhaps the most exciting area in cancer research and has created a paradigm shift in the management of cancer. Immunotherapy works by potentiating the patient's immune response to tumor cells, as opposed to traditional modalities that target the tumor directly.[7,8] Several classes of immunological agents have been developed or are being studied currently. These agents include immune checkpoint inhibitors (ICIs), targeted therapies, adoptive cell immunotherapy, and cancer vaccines.

Immune Checkpoint Inhibitors

By evading the intrinsic immune checkpoints, cancer cells can escape the immune mechanism that is supposed to eliminate the cells expressing tumor antigens.[9] Immune checkpoints are comprised of multiple pathways that regulate crucial steps of T-cell mediated immunity to maintain tolerance to self-antigens and prevent autoimmunity.[10] These pathways are initiated primarily through T-cell inhibiting and stimulating receptors and their ligands, such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death-1 (PD-1) protein, and programmed cell death ligand-1 (PD-L1).[7] The upregulation of CTLA-4 or PD-1 by some tumors can suppress the immune system in fighting disease by putting brakes on T cells. By acting against these receptors, checkpoint inhibitors block the immune evasion by cancer cells and encourage their destruction by the host immune system.[11,12]

Immune checkpoint inhibitors became an area of great interest over the past decade following clinical trials demonstrating improved survival in advanced melanoma patients. Previously there was no approved therapy for advanced melanoma. The first agent to be studied and approved by the FDA was the anti-CTLA-4 monoclonal antibody ipilimumab.[13,14] Next to emerge were antibodies against PD-1 or its ligand PD-L1, which resulted in long-term responses and minimal side effects in patients with several types of cancer, including melanoma; lung, kidney, bladder, and triple-negative breast cancer; and chemotherapy-refractory Hodgkin disease.[11,12] Anti-PD-1 therapy was found to be superior to standard-of-care chemotherapy as well as CTLA-4 inhibition in some cases. In 2014, the FDA approved pembrolizumab and nivolumab, two drugs in this class.[15] Several ICIs, which are approved for use in a variety of cancers, have emerged as a result of the rapid pace of ongoing research. (*See Table 1.*) A combination of CTLA-4 and PD-1 inhibitors has been associated with more favorable outcomes than with either monotherapy, leading to the development of various combination therapies.[15-17]

In addition to cancer, researchers also are studying ICIs for their potential role in the treatment of HIV[19,20] and autoimmune disease type 1 diabetes.[21] Emergency providers will be more likely to encounter patients receiving checkpoint inhibition therapy in the future given the growing expansion of indications for its use.

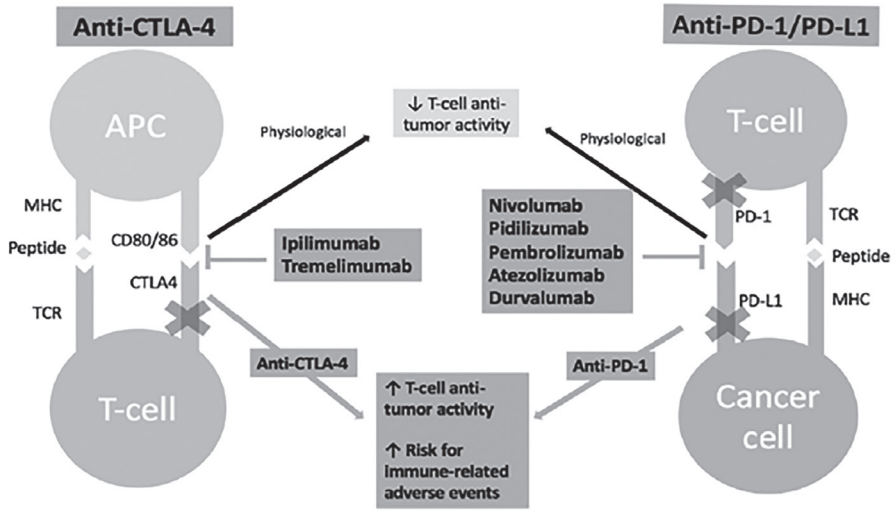
Toxicity Related to Checkpoint Inhibitor Therapy

ICIs have improved the treatment of various cancers significantly by producing effective antitumor responses. However, because of their blockade of down regulators of the immune system, they can be associated with unique immune-related adverse events (IRAEs). IRAEs commonly are seen in up to 90% of patients receiving CTLA-4 inhibitors and up to 70% of patients receiving anti-PD-1/PD-L1 agents.[22] The recently approved combination therapy of ipilimumab (CTLA-4 inhibitor) with nivolumab (PD-1 inhibitor) is associated with a more severe adverse effect profile than with either individual agent.[23] IRAEs comprise a wide range of toxicities that can closely resemble autoimmune disease.

Several features distinguish the toxicity profiles of IRAEs from those of conventional chemotherapy or targeted therapy. IRAEs potentially can involve every organ system in the body. They also can cause long-term effects that may present in a delayed manner months to years following the discontinuation of checkpoint inhibitor therapy. (*See Table 2.*)

These features make it challenging to manage the complications arising from immune checkpoint therapy in the ED because most providers may not be familiar with their presentation or have

Figure 1. Mechanism of Action of Anti-CTLA-4 and Anti-PD-1 Agents



An APC presents a foreign or perceived non-self-peptide fragment via its MHC, which binds and stimulates a TCR. Activation of the TCR leads to expression of CTLA-4, which binds with a greater affinity to CD80/86 and promotes self-tolerance and prevents autoimmunity in normal conditions. The anti-CTLA-4 therapies inhibit this co-inhibitory pathway and lead to enhanced T-cell stimulation and tumor surveillance. On the right side of the figure, a similar mechanism is seen for the anti-PD-1/PD-L1 agents. PD-L1 is expressed on cancer cells (among others) and also inhibits T-cell activation when binding to the PD-1 expressed on the surface of the T cell. Anti-PD-1/PD-L1 treatment leads to the inhibition of this inhibitory pathway and leads to enhanced T-cell activity against tumors. APC = antigen presenting cell; MHC = major histocompatibility complex; TCR = T-cell receptor.

Reprinted with permission from: Hryniewicki AT, Wang C, Shatsky RA, Coyne CJ. Management of immune checkpoint inhibitor toxicities: A review and clinical guideline for emergency physicians. *J Emerg Med* 2018;55:489-502.

access to patients' medical history. In a recent study, researchers found that one-fourth of ED visits by cancer patients at a comprehensive cancer center were related to IRAEs.[24] Immune checkpoint therapy usually can be continued with close monitoring in the presence of mild IRAEs, while moderate to severe reactions may be associated with organ dysfunction and death, emphasizing the significance of prompt recognition of these adverse effects by emergency providers.

The gastrointestinal, dermatological, endocrine, and pulmonary systems typically are involved in IRAEs, while involvement of the cardiovascular, renal, musculoskeletal, hematologic, neurological, and ocular systems has been reported less frequently.[18,23,26,27] (*See Table 3.*)

The kinetics of IRAE onset follow a predictable pattern. Dermatologic toxicities appear first, followed by colitis after one to three doses of ICIs. Autoimmune hepatitis and endocrinopathies occur late in the treatment course and at times can be seen as late as 24 weeks after treatment.[28]

Reactions to ICIs are graded by severity, with grades 1 and 2 signifying mild severity, and grades 3 and 4 indicating more significant toxicity. Grade 5 refers to death related to the adverse event.[29] (*See Table 4.*)

Dermatologic Toxicities

Dermatologic toxicities are the earliest and most commonly seen IRAEs from both CTLA-4 and PD-1/ PD-L1 inhibitor therapy.[30] Although symptoms such as a maculopapular rash, vitiligo, lichenoid reactions, eczema, or pruritis often can be mild, they still can be dose-limiting and therefore may limit the efficacy of the treatment regimen. The development of serious skin toxicities, such as severe rash with eosinophilia to Stevens-Johnson syndrome or toxic epidermal necrolysis, has been reported in about 4% of patients.[18] Cutaneous sarcoidosis and Sweet syndrome (acute febrile neutrophilic dermatosis) have been reported. Mucosal involvement, including dry eyes, dry mouth, and mucositis, has been noted with PD-1 agents.[30]

Grade 1 and 2 dermatitis can be managed with topical emollients, topical or oral glucocorticoids, and oral antihistamines. Grade 3 and 4 dermatitis is managed with oral corticosteroids.

Gastrointestinal Toxicities

Gastrointestinal adverse events typically present as diarrhea or in a more severe form as colitis. These effects occur more commonly with ipilimumab (a CTLA-4 inhibitor) than with anti-PD-1 agents.[22] Identifying severe forms of colitis is crucial, given that diarrhea is a very common IRAE associated with ipilimumab, with nearly 30% to 40% of patients receiving the drug developing this complaint.[13] The emergency provider needs to assess the patient carefully and perform necessary investigations, including computed tomography (CT) imaging if needed, to determine the etiology of the diarrhea. Serious forms of colitis, including small bowel obstruction, diverticulitis, enterocolitis, gastrointestinal bleeding, and perforation, can occur. In some instances, colitis with CTLA-4 inhibitors can present like Crohn's disease with ulcerations and granulomas.[22] Testing for *Clostridium difficile* and cytomegalovirus is recommended in cases of severe diarrhea and abdominal pain.[31]

Treatment of grade 1-2 colitis ranges from supportive care to oral corticosteroids, with high-dose intravenous steroids reserved for more severe cases. If the patient appears unstable or critically ill, there should be a low threshold to initiate treatment with the anti-TNF-alpha agent infliximab.[18,22,33] Infliximab also should be started in patients with colitis without a response to high-dose corticosteroids within three days or in those who experience a relapse of symptoms during a steroid taper.[28]

Hepatic Dysfunction

Hepatic dysfunction caused by ICIs usually is asymptomatic and is detected during routine laboratory testing as an elevation in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Severe grade 3 hepatitis is rare among patients being treated with a single ICI, but it can be seen in about 14%

Table 1. Current Checkpoint Inhibitors and Their Indications[18]

Drug Class	Drug Name	Indication
CTLA-4 Inhibitor	Ipilimumab	Advanced melanoma, melanoma after surgery
PD-1 Inhibitor	Nivolumab	Hodgkin lymphoma, HNSCC, advanced lung cancer, metastatic renal cell cancer, advanced melanoma, high microsatellite instability tumors, Merkel cell carcinoma
	Pembrolizumab	Recurrent/metastatic HNSCC, metastatic NSCLC, advanced melanoma, renal cell carcinoma, Merkel cell carcinoma
PD-L1 Inhibitor	Atezolizumab	Melanoma, HNSCC, renal cell carcinoma, classical Hodgkin lymphoma, high microsatellite instability tumors, Merkel cell carcinoma, metastatic NSCLC, urothelial carcinoma
	Durvalumab	Melanoma, HNSCC, renal cell carcinoma, classical Hodgkin lymphoma, high microsatellite instability tumors, Merkel cell carcinoma
	Avelumab	Melanoma, HNSCC, renal cell carcinoma, classical Hodgkin lymphoma, high microsatellite instability tumors

HNSCC = head and neck squamous cell carcinoma, NSCLC = non-small cell lung cancer

of patients using combination therapy. Management involves corticosteroid administration. In severe cases that do not respond to steroids, mycophenolate may be administered, as infliximab has the potential to worsen hepatotoxicity.[18]

Endocrine Toxicities

Endocrine toxicities associated with checkpoint inhibitor therapy account for about 10% of IRAEs. They are unique because they can be permanent, as in cases of adrenal insufficiency, or transient. They also can precipitate underlying chronic endocrinopathies and require long-term treatment for months to years after discontinuation of the offending agent.[18,28,30] Thyroid disorders and hypophysitis comprise the majority of endocrine IRAEs. Adrenal insufficiency, type 1 diabetes, and hypercalcemia are observed less commonly. Hypophysitis is a condition in which either the pituitary gland or its stalk is inflamed. It can result in hypopituitarism with hypogonadotropic hypogonadism, hypothyroidism, and central adrenal insufficiency. Hypophysitis usually develops about two to four months after initiation of checkpoint inhibitor treatment and occurs in 10% to 17% of patients taking ipilimumab.[18] Undiagnosed hypophysitis may be fatal. It can present with vague symptoms, such as anorexia, insomnia, headache, nausea, fatigue, and decreased libido. Because of these nonspecific symptoms, a high index of clinical suspicion is needed to prevent this life-threatening complication of treatment. The diagnosis can be made with laboratory markers for hypopituitarism, such as thyroid-stimulating hormone (TSH), or with magnetic resonance imaging (MRI), which will demonstrate pituitary enlargement or thickening of the pituitary stalk. Hypothyroidism is seen in about 4% of patients receiving PD-1/PD-L1 treatment. Hyperthyroidism also may occur but is associated more with CTLA-4 inhibitors.

Cancer patients receiving checkpoint blockade therapy may present to the ED with thyrotoxicosis, diabetic ketoacidosis, or acute adrenal insufficiency.[34] The approach to the management of these conditions depends on the underlying endocrinopathy. Hyperthyroidism is treated with thyroid suppressive medications, such as methimazole, propylthiouracil, steroids, and beta-blockers. Acute adrenal insufficiency requires prompt initiation of intravenous steroids. Diabetic ketoacidosis is managed with insulin and hypothyroidism with hormone replacement.

Respiratory Adverse Effects

Respiratory adverse events present as pneumonitis. Although the incidence of pneumonitis is relatively low, it is associated with a higher mortality than other IRAEs and can be refractory to steroids in some cases. Risk factors include combination immunotherapy and pulmonary comorbidities.[30] Since several ICIs are approved for the treatment of lung cancer, adverse events are observed more frequently in this group given the presence of underlying lung disease.[35-37] Signs and symptoms of pneumonitis include dry persistent cough, dyspnea, fever, fine inspiratory crackles, and chest pain. Patients may deteriorate rapidly even with grade 1 symptoms; therefore, clinicians should have a low threshold to obtain CT imaging and admit the patient.

Pneumonitis may be observed on a chest CT as new pulmonary infiltrates or ground-glass opacities. Providers should consider the possibility of other differential diagnoses, such as acute respiratory distress syndrome (ARDS), acute interstitial pneumonia, pulmonary edema, or tumor progression, that can present with similar symptoms and CT findings.[38] ICI-induced pneumonitis is managed by supportive measures such as oxygen administration followed by high-dose corticosteroids and infliximab based on the grade of presentation. Mycophenolate should be considered for pneumonitis that is severe, life-threatening, or refractory to initial therapy.[18,33]

Other Toxicities

Cardiac IRAEs include myocarditis, pericarditis, arrhythmias, and heart failure.[26] Immediate and permanent discontinuation of ICIs is recommended with any cardiac IRAE, even those that are grade 1.[32] Neurological

Table 2. Characteristics of Immune-Related Adverse Events[25]

Simultaneous	Multiple types of IRAEs can occur at the same time.
Heterochronus	IRAEs emerge one after the other in varying intervals.
Persistent	IRAEs can occur months to years after cessation of treatment.
Association with response	Patients with IRAEs have demonstrated greater clinical benefits and overall survival compared to those without IRAEs.

IRAE = Immune-related adverse event

Table 3. Spectrum of Clinical Manifestations of Immune-Related Adverse Events

Organ	Manifestations
Neurologic	Aseptic meningitis, encephalitis, transverse myelitis
Ocular	Uveitis, iritis, epscleritis, blepharitis
Hematologic	Autoimmune hemolytic anemia, thrombotic thrombocytopenic purpura/immune thrombocytopenia, lymphopenia, acquired hemophilia
Dermatologic	Inflammatory dermatitis, bullous dermtoses, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome
Endocrine	Hypophysitis, primary hypothyroidism, hyperthyroidism, primary adrenal insufficiency
Renal	Nephritis
Cardiovascular	Myocarditis, pericarditis, arrhythmias, heart failure, vasculitis
Gastrointestinal	Diarrhea, colitis, hepatitis
Musculoskeletal	Inflammatory arthritis, polymyalgia, myositis, myasthenia gravis, Guillain-Barre
Respiratory	Pneumonitis

manifestations may range from Bell's palsy to encephalopathy, transverse myelitis, and aseptic meningitis. Renal injury presents as tubulointerstitial nephritis within three months following the initiation of CTLA-4 therapy. Nephritis associated with PD-1 inhibitors often is late in onset, three to 10 months after treatment initiation.[39] Renal IRAEs usually are reversible with corticosteroids and require dialysis only in rare cases. Ocular involvement is rare and includes dry eyes, episcleritis, conjunctivitis, and uveitis. Topical steroid drops usually are sufficient to treat most ocular IRAEs.[40] Hematologic IRAEs present as autoimmune hemolytic anemia, neutropenia, thrombocytopenia, or acquired hemophilia.

Other Emerging Therapies and Their Toxicities

Cellular Immunotherapy: Adoptive Cell Transfer

A major principle of the immunologic treatment of cancer is to attack the cancer cell with activated T-lymphocytes. Cellular immunotherapy involves the administration of tumor-reactive T-cells. These cells can be created in two ways.

The first approach is to harvest and then grow tumor infiltrating lymphocytes, which then are administered back to the patient. This approach is used in melanoma and some other cancers.

The second approach is to create chimeric antigen receptor-engineered T-cells (CAR-T) by introducing tumor-specific receptors into the patient's T-lymphocytes harvested from peripheral blood. These chimeric cells then are grown before administration.

Patients are given chemotherapy to achieve leukoreduction or depletion of their own white blood cells so that the adminstered CAR-T cells have less interference when attacking the tumor cells. These tumor-reactive T-cells then function by eliciting a graft-versus-tumor response.[41]

The use of activated, tumor-reactive T cells has produced favorable outcomes in metastatic cancers such as B-cell lymphoma, melanoma, cervical cancer, and synovial sarcoma.[28]

The use of a preparative chemotherapy regimen results in neutropenia and thrombocytopenia, placing patients at risk for developing bleeding and sepsis. Cytokine-release syndrome (CRS) and tumor lysis syndrome are other common complications of CAR-T therapy. These require expert management and often can be lethal.

CRS, also known as cytokine storm, is the massive release of cytokines resulting in severe systemic inflammation. CRS has many features similar to sepsis, including fever, tachycardia, hypotension, and multi-organ failure. Supportive care with intravenous fluids, nonsteroidal anti-inflammatory drugs, empiric antibiotics, and vasopressors, if needed, is recommended.

Autoimmunity may occur due to anti-CD 19 CAR-T cells in the treatment

Table 4. Grading and Management of Immune-Related Adverse Events[18,28,30,32]

Severity Grade (CTCAE)	Grade 1	Grade 2	Grade 3	Grade 4
Grade definition	Asymptomatic or mild symptoms	Moderate; limiting ADL	Severe but not immediately life-threatening	Life-threatening consequences
Type of care	Ambulatory	Ambulatory	Hospitalization	Hospitalization; consider ICU
Checkpoint inhibitor	Continue with close monitoring	Continue if dermatologic or endocrine, suspend if other	Suspend, resume based on risk vs. benefit	Discontinue permanently
Common IRAEs and Their Management				
Dermatitis	Diffuse rash < 10% BSA, mild pruritis	Maculopapular rash 10% to 30% BSA, intense pruritis	Maculopapular rash > 30% BSA with bullae, ulceration, or hemorrhage, SJS/TEN	
Management	Oral antihistamine, topical steroid	Topical steroid and oral antihistamine, consider systemic steroid	Systemic steroids – Prednisone 0.5 to 1 mg/kg/day Oral antihistamine, GABA-agonist Monitor for progression to SCAR	
Diarrhea; colitis	Asymptomatic or < 4 to 6 stools/day	Abdominal pain, blood in stool	Severe abdominal pain, ileus, fever Peritoneal signs, bowel perforation > 7 stools/day, incontinence, IV hydration	
Management	Observation	Prednisone oral 1 to 2 mg/kg/day	Prednisone IV 1 to 2 mg/kg/day, prophylaxis antibiotic, GI/surgery consult	
Endocrinopathy	Asymptomatic or mild, lab finding	Signs of endocrine dysfunction, IRAE requiring urgent medical intervention	Suspicion of adrenal crisis, severe headache, visual field cut	
Management	No intervention	Endocrinology consult Hypophysitis: MRI pituitary – prednisone 1 to 2 mg/kg/day if abnormal, hormone replacement Central adrenal insufficiency: hydrocortisone 100 mg IV Central hypothyroidism: levothyroxine 1 mg/kg Hyperthyroidism: Graves' disease guidelines Type 1 diabetes: Start insulin, assess for DKA	Rule out sepsis, prednisone 1 mg/kg/day, ICU management of adrenal crisis	
Pneumonitis	Asymptomatic to mild symptoms	Symptomatic, limiting ADLs, mild hypoxia	Severe symptoms, worsening hypoxia	
Management	Monitor, O_2 sat, low threshold for imaging	Pulmonary and infectious disease consults Prednisone 1 mg/kg/day Prophylactic antibiotics, admit	Pulmonary consult and infectious disease consults Methylprednisolone IV 2 mg/kg/day infliximab, cyclophosphamide, IVIG, or mycophenolate for severe symptoms, ICU admission Prophylactic antibiotics	
Hepatitis	AST, ALT > ULN to 3 x ULN (or) T. Bili > ULN to 1.5 x ULN	AST, ALT > 3 x to 5 x ULN (or) T. Bili 1.5 x to 3 x ULN	AST, ALT > 5 x ULN (or) T. Bili > 3 x ULN	
Management	Rule out other drug-induced liver injury, infectious, malignant, thrombotic Close follow-up	Rule out other etiologies Start prednisone 0.5 to 1 mg/kg/day	Prednisone 1 to 2 mg/kg/day Consider prophylactic antibiotics Consult GI	

CTCAE = common terminology criteria for adverse events; ICU = Intensive care unit; BSA = body surface area; GI = gastroenterology; ADL = activities of daily living; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; SCAR = severe cutaneous adverse reaction; IV = intravenous; IVIG = intravenous immunoglobulin; ULN = upper limit of normal; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LFT = liver function test; T. Bili = total bilirubin

Table 5. Summary Recommendations for the Management of Immune-Related Adverse Events[24,30,32]

- High level of suspicion that new symptoms are treatment-related
- Close communication with oncologist regarding patient's ED visits
- Grade 1 – continue drug, topical therapy/symptomatic relief if needed, no systemic steroids
- Grade 2 – hold ICIs; oral steroids may be administered
- Grade 3 or 4 – initiate intravenous systemic steroids in the ED, consult oncologist
- Rare cases not responding to steroids may need infliximab or mycophenolate

of B-cell lymphoma. This results in loss of noncancerous B-cells as well. Intravenous immunoglobulin may be required in B-cell-depleted patients presenting with infections.

Another peculiar complication noted from CAR-T therapy is cross-reactivity with non-tumor antigens resulting in off-target toxicities against healthy tissues and organs. Irreversible central nervous system injury and fatal cardiac toxicity are among the reported cross-reactions.[28]

At present, more than 100 clinical trials utilizing CAR-Ts for a variety of hematological malignancies and solid tumors are registered.[41] Undoubtedly, more protocols employing adoptive cell transfer for more indications will come into use in the near future, making it necessary for providers to familiarize themselves with these agents and the unique complications as a result of this therapy.

Cellular Immunotherapy: Cancer Vaccines

Dendritic cell or vaccine therapy provokes antitumor responses by causing dendritic cells to present tumor antigens to lymphocytes, which primes them to kill other cells that present the same tumor antigen. Sipuleucel-T is the only vaccine available currently. It has been approved for use in metastatic prostate cancer.

Vaccines generally are associated with minimal toxicity, even when used in combination with checkpoint inhibitors.[42] Vaccines can produce transient chills, fever, and fatigue the first day following an injection. Back pain and chills also can be observed but generally are self-limited and resolve within 24 to 48 hours following vaccine administration.

Cytokines: IFN and IL-2

Recombinant human interferon alfa (IFN) is used in the treatment of hairy cell leukemia and resected high-risk melanoma. High doses of the cytokine interleukin-2 (IL-2) produced durable antitumor responses in patients with advanced renal cell carcinoma and melanoma. Both agents are associated with frequent and severe adverse effects. Constitutional symptoms such as fatigue and myalgias are seen most commonly. Severe fatigue may require a treatment hiatus and dose reduction.

Neuropsychiatric adverse effects can be debilitating. Up to 10% of patients experience confusion and up to 45% report depression. Such patients presenting to the ED with florid psychosis or suicidality often provide a limited history, thus emphasizing the need for collateral history including a list of medications from family members or other sources, particularly in the presence of serious comorbid illnesses.

Gastrointestinal adverse effects, such as diarrhea, nausea, and anorexia, are seen in one-third of patients. Collectively, these can lead to significant weight loss. Hepatic toxicity also is observed. Cytokine therapy should be withheld in patients with AST or ALT levels greater than five times the upper limit of normal. Thrombocytopenia, hemolytic anemia, and leukopenia also can occur. As with ICIs, cytokine-related hypothyroidism typically is preceded by hyperthyroidism.[28] Patients with new mediastinal lymphadenopathy during IFN therapy should be evaluated for sarcoidosis.

Interleukin-2 induces fluid retention due to increased vascular permeability. This can present as pulmonary edema, hypotension, or prerenal azotemia. Thrombocytopenia, anemia, coagulopathy, or inhibition of neutrophil chemotaxis can lead to an increased susceptibility to infection. In the first week of therapy, rare cases of myocarditis have been observed; these cases usually resolve in a few days without sequelae. It may mimic acute coronary syndrome with acute chest pain or shortness of breath and elevated troponins. Telemetry and cardiac enzymes need to be monitored in these cases.

Neutropenic Fever: Updates

Most patients with cancer still receive more traditional chemotherapeutic agents as frontline care. Emergency medicine physicians must remain current on how to manage the complications from treatment with these agents.

Most chemotherapeutic agents impair neutrophil production, often producing neutopenia and increasing the risk for infection. Infection in the neutropenic patient may not produce the symptoms and signs commonly seen in otherwise healthy patients; fever may be the only finding of infection in the neutropenic patient.[43]

Febrile neutropenia is defined as a single oral temperature of greater than 38.3° C (101° F) or a sustained temperature of greater than 38° C (100.4° F) for one hour in a patient who has an absolute neutrophil count of less than 500 cells/mL.[44]

Although only 40% to 50% of patients with febrile neutropenia subsequently are found to have an infectious etiology for the fever, it is imperative to consider antibiotic administration in a timely and judicious fashion for these vulnerable patients.[43] In 2013, the American Society of Clinical Oncology (ASCO) issued guidelines for antibiotic treatment of patients with febrile neutropenia, as well as guidelines to assist in the identification of patients who might be candidates for either in-hospital or outpatient antibiotic therapy.[44]

Updated guidelines published in 2018 recommend initial monotherapy with anti-pseudomonal coverage for all patients, with vancomycin added only for skin or soft tissue infections, pneumonia, suspected catheter-related infections, or hemodynamic instability.

Table 6. Multinational Association for Supportive Care in Cancer (MASCC) Score

Feature	Score
Symptom severity	None or mild = 5 Moderate = 3 Moribund = 0
Systolic blood pressure < 90 mmHg	No = 5 Yes = 0
Active chronic obstructive pulmonary disease (needs oxygen, steroids, and/or bronchodilators)	No = 4 Yes = 0
Type of tumor	Solid = 4 Hematologic, no prior fungal infection = 4 Hematologic, prior fungal infection = 0
Status on the onset of fever	Outpatient = 3 Inpatient = 0
Age < 60 years	Yes = 2 No = 0
Range 0-26. Score > 21 = low risk; score ≤ 21 = high risk	

Table 7. Clinical Index of Stable Febrile Neutropenia (CISNE) Score

Feature	Score
Eastern Cooperative Oncology Group (ECOG) Performance Score: At least capable of all self-care, may not do work activities, but out of bed > 50% of day	Yes = 0 No = 2
Stress-induced hyperglycemia: Initial blood glucose ≥ 121 mg/dL or ≥ 250 mg/dL in patients with diabetes or taking steroids	Yes = 0 No = 2
Chronic obstructive pulmonary disease: Therapy with one or more of the following: steroids, supplemental oxygen, or bronchodilators	Yes = 1 No = 0
Cardiovascular disease history: Cor pulmonale, heart failure, cardiomyopathy, hypertensive heart disease, arrhythmias, valvular disease, other structural malformations	Yes = 1 No = 0
Mucositis: With grade ≥ 2 (painful erythema, edema, or ulcers, but eating/swallowing possible)	Yes = 1 No = 0
Monocytes < 200/mm^3	Yes = 1 No = 0
Range 0-8. Score of 0 = low risk; score 1-2 = intermediate risk; score ≥ 3 = high risk	

Modifications of this treatment regimen should be considered for patients with a prior history of methicillin-resistant *Staphylococcus aureus*, extended-spectrum beta-lactamase (ESBL)–producing gram-negative bacteria, and carbapenemase-producing organisms or vancomycin-resistant enterococci (VRE).[45]

Scoring systems, such as the Multinational Association for Supportive Care in Cancer score (MASCC) and the Clinical Index of Stable Febrile Neutropenia (CISNE) score, have been validated in the outpatient hematology/oncology clinic setting and the inpatient setting to help estimate the risk for developing serious complications in patients with febrile neutropenia. (*See Tables 6 and 7.*) These scoring systems, together with clinical judgment and the patient's ability to access care in a timely fashion, have been suggested as helpful in determining which patients might be considered for safe discharge with outpatient antibiotic treatment and early follow-up.[45]

In 2017, Coyne et al compared the CISNE and MASCC scores for patients presenting to the ED.[46] They looked at the ability of each tool to identify patients who might do poorly clinically, with the development of organ failure, altered mental status, hypotension, bacteremia, or a requirement for an upgrade in level of care. The MASCC score is calculated by assessing the severity of the patient's presenting subjective complaints, patient age, history of chronic obstructive pulmonary disease (COPD), type of malignancy, and whether the patient is hypotensive on exam or exhibits signs of dehydration. The higher the score, the lower the risk the patient is believed to have for a serious medical complication, with scores greater than 21 considered to be low risk. CISNE is a less subjective measure, with a score of 0 considered low risk for complications. It includes patient history of COPD, chronic cardiovascular disease, presence and severity of chemotherapy-induced mucositis, hyperglycemia, and a functional performance assessment (Eastern Cooperative Oncology Group) of patient activities of daily living and overall well-being.

Coyne et al enrolled 230 patients, with 226 admitted to the hospital. Most patients did well, but with 25.7% having at least one negative outcome. The CISNE score appeared to have a better specificity for identifying patients hospitalized from the ED who were at lowest risk of developing complications while being treated in the hospital with IV antibiotics compared to the MASCC tool (98.3% vs. 54.2%).[46] Whether these findings can be extrapolated to patients who can be discharged safely from the ED remains to be studied further. Communication between the ED provider and the patient's oncologist is essential before deciding on a treatment plan in well-appearing

patients presenting to the ED with neutropenic fever.[47]

Summary

Cancer patients undergoing treatment are immunocompromised and at high risk for developing early complications leading to critical illness. Compared to complications encountered with conventional chemotherapy, new-generation immunotherapies pose unique diagnostic challenges because their presentation can be vague and nonspecific or can mimic autoimmune diseases. The prevalence of IRAEs is high and is seen in nearly one-fourth of patients undergoing therapy with ICIs.[24] Emergency providers must educate themselves on the spectrum of presentation of IRAEs so they can recognize and accurately diagnose these conditions. For example, a patient undergoing ICI therapy with chest pain may need to be evaluated for pneumonitis and myocarditis in addition to the more common acute coronary syndrome and pulmonary embolism.

Although most toxicities of immunotherapeutic agents can be managed with corticosteroids, this can suppress the desired antitumor effects of the drug. Therefore, emergency providers should consult with the patient's oncologists when intiating steroids or other immunosuppressive agents. Early communication with the patient's oncologists serves a two-way purpose. First, it allows the ED provider to gather information regarding the patient's therapeutic regimen and to anticipate potential complications. Second, it provides the oncologists with information about the patient's ED visit, which will allow them to make modifications to the treatment regimen if necessary. Emergency providers should establish relationships with the oncologists to streamline communication between the specialties regarding treatment of cancer patients. At some cancer centers, oncologists provide patients with wallet cards that contain a list of medications and the adverse effects associated with each, which can be useful during the patient's ED visit.

Emergency providers play a vital role in identifying subtle presentations of the complications of cancer therapy and can prevent devastating outcomes through timely management.

References

1. DeVita VT Jr, Rosenberg SA. Two hundred years of cancer research. *N Engl J Med* 2012;366:2207-2214.
2. Goodman LS, Wintrobe MM, Dameshek W, et al. Nitrogen mustard therapy; use of methyl-bis (beta-chloroethyl) amine hydrochloride and tris (beta-chloroethyl) amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. *JAMA* 1946;132:126-132.
3. Devita VT Jr, Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann Intern Med* 1970;73:881-895.
4. Frei E 3rd, Karon M, Levin RH, et al. The effectiveness of combinations of antileukemic agents in inducing and maintaining remission in children with acute leukemia. *Blood* 1965;26:642-656.
5. Pal SK, Miller MJ, Agarwal N, et al. Clinical Cancer Advances 2019: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology. *J Clin Oncol* 2019, Jan. 31: JCO1802037.
6. Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "silver tsunami": Prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomarkers Prev* 2016;25:1029-1036.
7. Dempke WCM, Fenchel K, Uciechowski P, Dale SP. Second- and third-generation drugs for immuno-oncology treatment — The more the better? *Eur J Cancer* 2017;74:55-72.
8. Chen DS, Mellman I. Oncology meets immunology: The cancer-immunity cycle. *Immunity* 2013;39:1-10.
9. Kyi C, Postow MA. Immune checkpoint inhibitor combinations in solid tumors: Opportunities and challenges. *Immunotherapy* 2016;8:821-837.
10. Pico de Coana Y, Choudhury A, Kiessling R. Checkpoint blockade for cancer therapy: Revitalizing a suppressed immune system. *Trends Mol Med* 2015;21:482-491.
11. Gentzler R, Hall R, Kunk PR, et al. Beyond melanoma: Inhibiting the PD-1/PD-L1 pathway in solid tumors. *Immunotherapy* 2016;8:583-600.
12. Mahoney KM, Freeman GJ, McDermott DF. The next immune-checkpoint inhibitors: PD-1/PD-L1 blockade in melanoma. *Clin Ther* 2015;37:764-782.
13. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711-723.
14. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011;364:2517-2526.
15. Homet Moreno B, Ribas A. Anti-programmed cell death protein-1/ligand-1 therapy in different cancers. *Br J Cancer* 2015;112:1421-1427.
16. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov* 2018;8:1069-1086.
17. Hassel JC, Heinzerling L, Aberle J, et al. Combined immune checkpoint blockade (anti-PD-1/anti-CTLA-4): Evaluation and management of adverse drug reactions. *Cancer Treat Rev* 2017;57:36-49.
18. Hryniewicki AT, Wang C, Shatsky RA, Coyne CJ. Management of immune checkpoint inhibitor toxicities: A review and clinical guideline for emergency physicians. *J Emerg Med* 2018;55: 489-502.
19. Boyer Z, Palmer S. Targeting immune checkpoint molecules to eliminate latent HIV. *Front Immunol* 2018;9:2339.
20. Gay CL, Bosch RJ, Ritz J, et al. Clinical trial of the anti-PD-L1 antibody BMS-936559 in HIV-1 infected participants on suppressive antiretroviral therapy. *J Infect Dis* 2017;215:1725-1733.
21. Orabona C, Mondanelli G, Puccetti P, Grohmann U. Immune checkpoint molecules, personalized immunotherapy, and autoimmune diabetes. *Trends Mol Med* 2018;24:931-941.
22. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: A comprehensive review. *Eur J Cancer* 2016;54:139-148.
23. Collins LK, Chapman MS, Carter JB, Samie FH. Cutaneous adverse effects of the immune checkpoint inhibitors. *Curr Probl Cancer* 2017;41:125-128.
24. El Majzoub I, Qdaisat A, Thein KZ, et al. Adverse effects of immune checkpoint therapy in cancer patients visiting the emergency department of a comprehensive cancer center. *Ann Emerg Med* 2019;73:79-87.

25. Nagai H, Muto M. Optimal management of immune-related adverse events resulting from treatment with immune checkpoint inhibitors: A review and update. *Int J Clin Oncol* 2018;23: 410-420.
26. Spallarossa P, Meliota G, Brunelli C, et al. Potential cardiac risk of immune-checkpoint blockade as anticancer treatment: What we know, what we do not know, and what we can do to prevent adverse effects. *Med Res Rev* 2018;38:1447-1468.
27. Ruggeri RM, Campenni A, Giuffrida G, et al. Endocrine and metabolic adverse effects of immune checkpoint inhibitors: An overview (what endocrinologists should know). *J Endocrinol Invest* 2018; Nov. 23. doi: 10.1007/s40618-018-0984-z. [Epub ahead of print].
28. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy for the practitioner. *J Clin Oncol* 2015;33:2092-2099.
29. National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE).* Version 4.03. June 14, 2010. U.S. Department of Health and Human Services, National Institutes of Health.
30. Abdel-Wahab N, Alshawa A, Suarez-Almazor ME. Adverse events in cancer immunotherapy. In: *Advances in Experimental Medicine and Biology*. New York; Springer: 2017.
31. Pernot S, Ramtohul T, Taieb J. Checkpoint inhibitors and gastrointestinal immune-related adverse events. *Curr Opin Oncol* 2016;28:264-268.
32. Brahmer JR, Lacchetti C, Schneider BJ, et al. 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.
33. Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev* 2016;44: 51-60.
34. Torino F, Corsello SM, Salvatori R. Endocrinological side-effects of immune checkpoint inhibitors. *Curr Opin Oncol* 2016;28:278-287.
35. Wu J, Hong D, Zhang X, et al. PD-1 inhibitors increase the incidence and risk of pneumonitis in cancer patients in a dose-independent manner: A meta-analysis. *Sci Rep* 2017;7:44173.
36. Yamaguchi T, Shimizu J, Hasegawa T, et al. Pre-existing pulmonary fibrosis is a risk factor for anti-PD-1-related pneumonitis in patients with non-small cell lung cancer: A retrospective analysis. *Lung Cancer* 2018;125:212-217.
37. 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.
38. Nishino M, Ramaiya NH, Awad MM, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: Radiographic patterns and clinical course. *Clin Cancer Res* 2016;22: 6051-6060.
39. Wanchoo R, Karam S, Uppal NN, et al. Adverse renal effects of immune checkpoint inhibitors: A narrative review. *Am J Nephrol* 2017;45:160-169.
40. Abdel-Rahman O, Oweira H, Petrausch U, et al. Immune-related ocular toxicities in solid tumor patients treated with immune checkpoint inhibitors: A systematic review. *Expert Rev Anticancer Ther* 2017;17:387-394.
41. Resetca D, Neschadim A, Medin JA. Engineering hematopoietic cells for cancer immunotherapy: Strategies to address safety and toxicity concerns. *J Immunother* 2016;39:249-259.
42. Nahas MR, Rosenblatt J, Lazarus HM, Avigan D. Anti-cancer vaccine therapy for hematologic malignancies: An evolving era. *Blood Rev* 2018;32:312-325.
43. Zimmer AJ, Freifeld AG. Optimal management of neutropenic fever in patients with cancer. *J Oncol Pract* 2019;15: 19-24.
44. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpa-

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45. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. *J Clin Oncol* 2018;36:1443-1453.
46. Coyne CJ, Le V, Brennan JJ, et al. Application of the MASCC and CISNE risk-stratification scores to identify low-risk febrile neutropenic patients in the emergency department. *Ann Emerg Med* 2017;69:755-764.
47. Paddock M, Grock A, DeLoughery T, Mason J. Can neutropenic fever ever be low risk? *Ann Emerg Med* 2017;69: 765-767.

CME/CE Questions

1. Which of the following is true regarding immune checkpoint inhibitors?
   a. They regulate humeral immunity.
   b. They have minimal side effects.
   c. They regulate T-cell mediated immunity.
   d. They have shown no benefit in the treatment of hepatitis.
2. Which of the following is true regarding immune-related adverse events?
   a. They are seen in fewer than 10% of patients treated with checkpoint inhibitors.
   b. They are limited to the gastrointestinal tract.
   c. They mimic severe sepsis.
   d. They can present months to years after discontinuation of treatment with checkpoint inhibitors.
3. Which of the following is correct regarding immune-related adverse events?
   a. They mandate immediate discontinuation of the drug.
   b. They have been associated with greater clinical benefits compared to patients without immune-related adverse events.
   c. They require IV steroids for improvement of symptoms.
   d. They typically require admission to the hospital.
4. Which statement is correct about treatment with cytokines?
   a. Cytokine treatment commonly is associated with autoimmune-like symptoms.
   b. Cytokine treatment may cause symptoms of depression in up to 25% of patients.
   c. Cytokine treatment is associated with flu-like symptoms.
   d. Cytokine treatment rarely causes gastrointestinal side effects.
5. Which of the following is true of patients with neutropenic fever?
   a. Neutropenic fever is defined as having a single temperature of 100.4 ˚F.
   b. They are considered low risk if the MASCC (Multinational Association for Supportive Care in Cancer) score is < 21.
   c. They are considered low risk if the CISNE (Clinical Index of Stable Febrile Neutropenia) score is > 0.
   d. Some patients may be discharged after consultation with their oncologist.

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Upon completion of this educational activity, participants should be able to:

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EMERGENCY MEDICINE REPORTS

Managing Complications of New-Age Cancer Therapy

Characteristics of Immune-Related Adverse Events[25]	
Simultaneous	Multiple types of IRAEs can occur at the same time.
Heterochronus	IRAEs emerge one after the other in varying intervals.
Persistent	IRAEs can occur months to years after cessation of treatment.
Association with response	Patients with IRAEs have demonstrated greater clinical benefits and overall survival compared to those without IRAEs.
IRAE = Immune-related adverse event	

Spectrum of Clinical Manifestations of Immune-Related Adverse Events	
Organ	**Manifestations**
Neurologic	Aseptic meningitis, encephalitis, transverse myelitis
Ocular	Uveitis, iritis, epscleritis, blepharitis
Hematologic	Autoimmune hemolytic anemia, thrombotic thrombocytopenic purpura/immune thrombocytopenia, lymphopenia, acquired hemophilia
Dermatologic	Inflammatory dermatitis, bullous dermtoses, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome
Endocrine	Hypophysitis, primary hypothyroidism, hyperthyroidism, primary adrenal insufficiency
Renal	Nephritis
Cardiovascular	Myocarditis, pericarditis, arrhythmias, heart failure, vasculitis
Gastrointestinal	Diarrhea, colitis, hepatitis
Musculoskeletal	Inflammatory arthritis, polymyalgia, myositis, myasthenia gravis, Guillain-Barre
Respiratory	Pneumonitis

Summary Recommendations for the Management of Immune-Related Adverse Events[24,30,32]

- High level of suspicion that new symptoms are treatment-related
- Close communication with oncologist regarding patient's ED visits
- Grade 1 – continue drug, topical therapy/symptomatic relief if needed, no systemic steroids
- Grade 2 – hold ICIs; oral steroids may be administered
- Grade 3 or 4 – initiate intravenous systemic steroids in the ED, consult oncologist
- Rare cases not responding to steroids may need infliximab or mycophenolate

Multinational Association for Supportive Care in Cancer (MASCC) Score	
Feature	**Score**
Symptom severity	None or mild = 5 Moderate = 3 Moribund = 0
Systolic blood pressure < 90 mmHg	No = 5 Yes = 0
Active chronic obstructive pulmonary disease (needs oxygen, steroids, and/or bronchodilators)	No = 4 Yes = 0
Type of tumor	Solid = 4 Hematologic, no prior fungal infection = 4 Hematologic, prior fungal infection = 0
Status on the onset of fever	Outpatient = 3 Inpatient = 0
Age < 60 years	Yes = 2 No = 0
Range 0-26. Score > 21 = low risk; score ≤ 21 = high risk	

Grading and Management of Immune-Related Adverse Events[18,28,30,32]				
Severity Grade (CTCAE)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Grade definition	Asymptomatic or mild symptoms	Moderate; limiting ADL	Severe but not immediately life threatening	Life-threatening consequences
Type of care	Ambulatory	Ambulatory	Hospitalization	Hospitalization; consider ICU
Checkpoint inhibitor	Continue with close monitoring	Continue if dermatologic or endocrine, suspend if other	Suspend, resume based on risk vs. benefit	Discontinue permanently
Common IRAEs and Their Management				
Dermatitis	Diffuse rash < 10% BSA, mild pruritis	Maculopapular rash 10% to 30% BSA, intense pruritis	Maculopapular rash > 30% BSA with bullae, ulceration or hemorrhage, SJS/TEN	
Management	Oral antihistamine, topical steroid	Topical steroid and oral antihistamine, consider systemic steroid	Systemic steroids – Prednisone 0.5 to 1 mg/kg/day Oral antihistamine, GABA-agonist Monitor for progression to SCAR	
Diarrhea; colitis	Asymptomatic or < 4 to 6 stools/day	Abdominal pain, blood in stool	Severe abdominal pain, ileus, fever Peritoneal signs, bowel perforation > 7 stools/day, incontinence, IV hydration	
Management	Observation	Prednisone oral 1 to 2 mg/kg/day	Prednisone IV 1 to 2 mg/kg/day, prophylaxis antibiotic, GI/surgery consult	
Endocrinopathy	Asymptomatic or mild, lab finding	Signs of endocrine dysfunction, IRAE requiring urgent medical intervention	Suspicion of adrenal crisis, severe headache, visual field cut	
Management	No intervention	Endocrinology consult Hypophysitis: MRI pituitary – prednisone 1 to 2 mg/kg/day if abnormal, hormone replacement Central adrenal insufficiency: hydrocortisone 100 mg IV Central hypothyroidism: levothyroxine 1 mg/kg Hyperthyroidism: Graves' disease guidelines Type 1 diabetes: Start insulin, assess for DKA	Rule out sepsis, prednisone 1 mg/kg/day, ICU management of adrenal crisis	
Pneumonitis	Asymptomatic to mild symptoms	Symptomatic, limiting ADLs, mild hypoxia	Severe symptoms, worsening hypoxia	
Management	Monitor, O_2 sat, low threshold for imaging	Pulmonary and infectious disease consults Prednisone 1 mg/kg/day Prophylactic antibiotics, admit	Pulmonary consult and infectious disease consults Methylprednisolone IV 2 mg/kg/day infliximab, cyclophosphamide, IVIG, or mycophenolate for severe symptoms, ICU admission Prophylactic antibiotics	
Hepatitis	AST, ALT > ULN to 3 x ULN (or) T. Bili > ULN to 1.5 x ULN	AST, ALT > 3 x to 5 x ULN (or) T. Bili 1.5 x to 3 x ULN	AST, ALT > 5 x ULN (or) T. Bili > 3 x ULN	
Management	Rule out other drug-induced liver injury, infectious, malignant, thrombotic Close follow-up	Rule out other etiologies Start prednisone 0.5 to 1 mg/kg/day	Prednisone 1 to 2 mg/kg/day Consider prophylactic antibiotics Consult GI	

CTCAE = common terminology criteria for adverse events; ICU = Intensive care unit; BSA = body surface area; GI = gastroenterology; ADL = activities of daily living; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; SCAR = severe cutaneous adverse reaction; IV = intravenous; IVIG = intravenous immunoglobulin; ULN = upper limit of normal; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LFT = liver function test; T. Bili = total bilirubin

Clinical Index of Stable Febrile Neutropenia (CISNE) Score	
Feature	**Score**
Eastern Cooperative Oncology Group (ECOG) Performance Score: At least capable of all self-care, may not do work activities, but out of bed > 50% of day	Yes = 0 No = 2
Stress-induced hyperglycemia: Initial blood glucose ≥ 121 mg/dL or ≥ 250 mg/dL in patients with diabetes or taking steroids	Yes = 0 No = 2
Chronic obstructive pulmonary disease: Therapy with one or more of the following: steroids, supplemental oxygen, or bronchodilators	Yes = 1 No = 0
Cardiovascular disease history: Cor pulmonale, heart failure, cardiomyopathy, hypertensive heart disease, arrhythmias, valvular disease, other structural malformations	Yes = 1 No = 0
Mucositis: With grade ≥ 2 (painful erythema, edema, or ulcers, but eating/swallowing possible)	Yes = 1 No = 0
Monocytes < 200/mm^3	Yes = 1 No = 0
Range 0-8. Score of 0 = low risk; score 1-2 = intermediate risk; score ≥ 3 = high risk	

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