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REVIEW ARTICLE

Toxicities of Immunotherapy for the Practitioner

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ABSTRACT

The toxicities of immunotherapy for cancer are as diverse as the type of treatments that have been devised. These range from cytokine therapies that induce capillary leakage to vaccines associated with low levels of autoimmunity to cell therapies that can induce damaging cross-reactivity with normal tissue to checkpoint protein inhibitors that induce immune-related adverse events that are autoinflammatory in nature. The thread that ties these toxicities together is their mechanism-based immune nature and the T-cell–mediated adverse events seen. The basis for the majority of these adverse events is a hyperactivated T-cell response with reactivity directed against normal tissue, resulting in the generation of high levels of CD4 T-helper cell cytokines or increased migration of cytolytic CD8 T cells within normal tissues. The T-cell immune response is not tissue specific and may reflect a diffuse expansion of the T-cell repertoire that induces cross-reactivity with normal tissue, effectively breaking tolerance that is active with cytokines, vaccines, and checkpoint protein inhibitors and passive in the case of adoptive cell therapy. Cytokines seem to generate diffuse and nonspecific T-cell reactivity, whereas checkpoint protein inhibition, vaccines, and adoptive cell therapy seem to activate more specific T cells that interact directly with normal tissues, potentially causing specific organ damage. In this review, we summarize the toxicities that are unique to immunotherapies, emphasizing the need to familiarize the oncology practitioner with the spectrum of adverse events seen with newly approved and emerging modalities.

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TOXICITIES OF CANCER VACCINES

Assessing the toxicities from cancer vaccines is complicated by the variety of antigens targeted, the diversity of formulations, the adjuvants used, and their combination with immunomodulators that may induce autoimmune phenomenon. Vaccine therapies may promote type 1 immunity, with induction of cytolytic T cells, or type 2 immune reactivity, which can induce T-helper 2 cells that bolster antibody production or B cells that mature into antibody-producing plasma cells. Most vaccines for melanoma have been directed against melanocyte differentiation antigens. Vitiligo may occur after administration of melanoma vaccines and is associated with a beneficial outcome.[1,2] A confounder is the practice of combining vaccines with other forms of immune therapy.[3] Vaccination may enhance a tissue-destructive immune response that was already present at low levels in patients with melanoma and other cancers.[4]

Cancer vaccines are generally associated with minimal toxicity. A recent review reported adverse events (AEs) in trials of cancer vaccines administered with various adjuvants.[5] This review evaluated 239 phase I and II studies performed between 1990 and 2011, with a total of nearly 5,000 patients. A total of 162 grade 3 and five grade 4 AEs were attributed to vaccination. These low rates occurred despite many vaccines inducing an immune response against self–tumor-associated antigens. Local injection site reactions and constitutional symptoms such as myalgia and flu-like syndromes were the most common toxicities seen. Of the three cancer vaccine trials that reported reaching a dose-limiting toxicity, two used live attenuated bacterial vectors (*Listeria monocytogenes* and *Neisseria meningitides*). In both studies, hypotension, controlled with standard medical support, was dose limiting.[6]

Why are cancer vaccines associated with limited to no toxicity? Many targeted tumor-associated antigen proteins are markedly overexpressed in cancer cells but are found at low or undetectable levels in normal cells. Aberrantly overexpressed self-proteins (eg, human epidermal growth factor receptor 2 [HER2], p53, and survivin) are the most common type of antigen exploited for active immunization,[7] and the one approved cancer vaccine encodes a prostatic acid phosphatase fusion protein.[8] Overexpression of self-proteins allows unique peptide epitopes to be expressed in high enough numbers at the cell surface to trigger a T-cell response. These

peptides are not available when the self-protein is present at normal levels.[9] T-cell responses against overexpressed self-proteins may selectively elicit tumor-specific immunity but not immunity against nonmalignant tissues expressing the targeted protein.[10,11] Vaccines directed against epidermal growth factor receptor and HER2 did not impact normal skin or cardiac function.[12-16] Both epidermal growth factor and HER2 are markedly upregulated in tumor compared with nonmalignant tissues. Effective immune responses against tumor-regression antigens will also likely target neoantigens not on normal cells.

The one currently approved cancer vaccine, sipuleucel-T, results in a favorable toxicity profile, with transient chills, fatigue, and fever commonly seen within 24 hours of an injection, although less than 4% of AEs were grade 3 or 4.[8,17] Back pain and chills were the most common overall grade 3 to 4 AEs of sipuleucel-T, observed in 2% of patients. Although the low toxicity seen with cancer vaccines may reflect immunity of low avidity, the use of antigen-specific cancer vaccines in conjunction with checkpoint inhibitors does not seem to result in additive or enhanced toxicity.[18]

TOXICITIES OF CYTOKINES

Recombinant human interferon alfa (IFN) is approved by the US Food and Drug Administration (FDA) for the treatment of hairy cell leukemia and adjuvant treatment of patients with resected high-risk melanoma. High doses of the cytokine interleukin-2 (IL-2) produced durable antitumor responses in patients with advanced renal cell carcinoma or melanoma, leading to its FDA approval in 1992 and 1998, respectively. Nonetheless, the enthusiasm for the use of these agents has been tempered by their frequent and severe AEs.

Constitutional symptoms are the most common with IFN, with more than 80% of patients reporting fever and fatigue[19]; headache and myalgias are also common. These symptoms can be controlled with nonsteroidal anti-inflammatory drugs, whereas severe fatigue often requires a treatment hiatus with dose reduction.

Neuropsychiatric issues are uncommon but potentially severe. As many as 10% of patients complain of confusion, and less than 1% of patients develop psychosis.[20] Up to 45% of patients reported depression,[21,22] with rare suicides observed. Prophylactic antidepressants may reduce the risk of depression,[21] but IFN is relatively contraindicated in those with a history of severe depression. Other patients should be monitored closely, with antidepressant therapy instituted at the earliest sign of depression.

Up to one third of patients on IFN have diarrhea, which is usually well controlled with over-the-counter medications.[22] Two thirds of patients have nausea and anorexia. Antiemetics often alleviate the nausea; however, this can lead to significant weight loss. In the initial study of adjuvant IFN for patients with high-risk melanoma, two deaths were reported as a result of hepatic toxicity.[23] Patients with grade 3 liver toxicity (AST/ALT $>$ 5$\times$ upper limit of normal) should have IFN held until transaminase levels return to grade 1 and then IFN restarted with a 33% to 50% dose reduction.

Thrombocytopenia and leukopenia occur in up to 10% of IFN patients and can be managed with dose interruption and dose reduction. Rarely thrombotic thrombocytopenia purpura and hemolytic anemia have been reported requiring permanent drug discontinuation.[24,25]

Hyperthyroidism or hypothyroidism occurs in 10% to 15% of IFN patients.[26] Hyperthyroidism typically precedes a prolonged period of hypothyroidism. Sarcoid is rare and can be a diagnostic dilemma especially in patients with melanoma or lymphoma, presenting as skin lesions masquerading as subcutaneous metastases or as fluorodeoxyglucose-avid mediastinal lymph nodes on positron emission tomography scans.[27] Patients with new mediastinal adenopathy during IFN should have a diagnostic evaluation rather than assuming disease progression. Vitiligo, lupus, rheumatoid arthritis, polymyalgia rheumatica, and psoriasis have also been observed.[28,29] Patients with preexisting autoimmune conditions will frequently experience exacerbation of their illness on IFN and should receive this therapy with caution. Some investigators have reported that these autoimmune events may be associated with an improved treatment outcome.[30]

High-dose IL-2 should be administered in an inpatient setting including cardiac monitoring and hemodynamic support delivered by an experienced team. IL-2 can cause fever, chills, and fatigue.[31] GI AEs such as nausea, vomiting, anorexia, diarrhea, transaminitis, and cholestasis with hyperbilirubinemia are also common.[31] IL-2 administration leads to increased vascular permeability, inducing fluid retention including pleural effusions and occasionally pulmonary edema, hypotension, and prerenal azotemia. Hypotension is often dose limiting but can be managed even outside the intensive care unit with vasopressor support.[31,32] β-Agonist therapy can precipitate atrial arrhythmias; thus, patients receiving vasopressors should have telemetric cardiac monitoring.

Thrombocytopenia, anemia, coagulopathy, or impairment of neutrophil chemotaxis leading to an increased incidence of catheter infections may occur.[33,34] Antibiotic prophylaxis has greatly reduced the incidence of catheter infections.[35] Almost all IL-2 AEs resolve rapidly on holding or discontinuing the drug and can be readily managed by those experienced with IL-2 treatment.

Autoimmunity, neurotoxicity, and myocarditis can worsen or persist for a period of time after IL-2 discontinuation.[31,32] Autoimmune disorders such as thyroid dysfunction may take 6 to 10 months to resolve, and vitiligo can be progressive.[36,37] IL-2 neurotoxicity can be subtle, consisting of lethargy and irritability, or it can present as florid psychosis.[32] Neurotoxicity can peak 24 hours after the last dose and requires vigilance by the physician and staff to recognize it early. Rarely, patients develop myocarditis, most commonly at around day 6 of the first cycle of therapy and associated with an increase in cardiac enzymes. Although this usually resolves within a few days without sequelae, it occasionally produces reversible cardiac dysfunction and ventricular ectopy[32]; therefore, patients should be placed on telemetry until cardiac enzymes normalize and should receive subsequent IL-2 with extreme caution.

IL-2 seems to mediate toxicity through release of nitric oxide, IL-1, tumor necrosis factor α, and IFN-γ.[38,39] Multiple trials of toxicity-modifying agents have been conducted[40-42]; however, no inhibitor of IL-2 toxicity has sufficiently dissociated the toxicity from the antitumor activity of IL-2 to merit widespread use.

TOXICITIES OF ADOPTIVE CELL THERAPY

The administration of activated, tumor-reactive, ex vivo expanded T cells can effectively treat patients with certain widely metastatic

cancers.[43] These tumor-reactive T cells are grown from tumor-infiltrating lymphocytes (TILs) within melanoma and human papillomavirus–related cancers, or they can be genetically engineered by introducing tumor-specific receptors into the patient's own peripheral-blood lymphocytes (PBLs), both administered with nonmyeloablative chemotherapy to enhance engraftment and persistence of transferred cells followed by systemic IL-2.[44] High objective response rates with appreciable rates of complete response have been observed in melanoma[45] and in patients with metastatic cervical cancer treated with TILs.[46] Cloned anti-NY-ESO1–reactive T-cell receptor (TCR) –engineered PBLs induced high rates of response and durable complete responses in patients with melanoma and synovial sarcoma.[47] Another class of receptor-engineered PBLs uses a chimeric antigen receptor (CAR) derived from the variable portions of a monoclonal antibody that is fused to the intracellular T-cell–signaling chain CD3-ζ. This approach has been effective in treating B-cell malignancies expressing the target antigen CD19.[48,49] However, adoptive cell therapy can induce treatment-related toxicities that require a high level of expertise to manage.

The use of a preparative chemotherapy regimen for lymphodepletion causes 7 to 10 days of neutropenia and thrombocytopenia, which reverses spontaneously. Before hematopoietic recovery, patients are at risk for sepsis and bleeding, although severe events are uncommon or amenable to supportive management. Sepsis remains the dominant cause of the 1% to 2% rate of treatment-related mortality with cell therapy that includes lymphoid depletion.

A cytokine-driven syndrome can be observed shortly after administration of T cells. This cytokine release syndrome (CRS) resembles sepsis, with fever, tachycardia, vascular leak, oliguria, and hypotension; severe cases show multiorgan failure. These events are also seen with high-dose IL-2. When systemic IL-2 is given with T cells, the syndrome onset is more rapid and is likely a direct consequence of the IL-2. Without IL-2, it may appear later (day 5 through 7 after T-cell infusion). Even severe renal failure, coma, and respiratory failure usually reverse completely with supportive care. In a recent study of CD19 CAR in leukemia, all patients had some degree of CRS, with a 27% rate of severe CRS requiring pressor support.[50] One group administering CAR-modified T cells targeting CD19 to patients with B-cell malignancies identified IL-6 as a mediator of hemodynamic toxicities and administered tocilizumab, an IL-6 receptor–blocking antibody, to patients showing early signs of CRS with apparent benefit.[51] Treatment typically consists of supportive care with intravenous fluid, nonsteroidal anti-inflammatory drugs, vasopressors (if needed), and other measures while awaiting spontaneous recovery.

Autoimmunity induced by administered T cells may occur. This has observed when a receptor targeting a normal self-protein is retrovirally engineered into autologous PBLs. The level and distribution of normal tissue expression and the importance of those tissues will determine the consequences of such an on-target, off-tumor immune attack. When proteins of melanocytic origin were targeted with TCRs against MART-1 and gp100, cutaneous, ocular, and internal ear toxicities (all sites with melanocytes) occurred.[52] This was managed with local or topical corticosteroids but was an unacceptable toxicity that limited the development of TCRs targeting those tissue differentiation antigens. When carcinoembryonic antigen was targeted on colorectal cancer, all three treated patients experienced severe, potentially life-threatening colitis.[53] Although anti-CD19 CAR targets all B cells, benign and malignant, the toxicities related to the loss of normal B cells seems acceptable given the frequent responses observed in patients with refractory lymphoma or leukemia.[54] Intravenous immunoglobulin G can be given and any infections addressed in a patient with B-cell depletion.

Unrecognized expression of antigen at a critical site was suspected of causing fatal toxicity with rapid pulmonary edema, hypoxia, and lung injury when ERBB2 was targeted with a CAR,[55] and liver injury associated with CAR–T cells against carbonic anhydrase IX occurred in patients with clear cell kidney cancer.[56] When life-threatening toxicities occur from T-cell administration (either from cytokine release or autoimmunity), standard interventions include high-dose corticosteroids and alemtuzumab (anti-CD52 antibody) to suppress or delete lymphocytes (which might obviate any antitumor effects as well). Adding a suicide gene to transferred T cells has been advocated, and many current protocols use this approach, but it remains unclear whether this can be actuated in time to abort permanent damage.

Because administration of melanoma TILs only occasionally causes significant autoimmunity, the question remains as to what antigen(s) they recognize. Recent evidence suggests that TILs target tumor-specific mutations lacking immunologic cross-reactivity with corresponding wild-type epitopes.[57,58]

Another toxicity can arise when receptor-engineered T cells acquire new and unexpected specificities for molecules other than their nominal target. Cross-reactivity against a different epitope has occurred with non-native TCRs and is thought to be the source of isolated cases of major toxicity. A murine TCR against the human germline tumor antigen MAGE-A3 was found to recognize a similar epitope in MAGE-A12, also presented by HLA-A0201. The two epitopes differed at the P2 amino acid, where the methionine in the MAGE-A12 epitope was coincidentally also an excellent HLA-A0201–binding anchor residue. Although MAGE-A3 was not expressed in normal tissues, MAGE-A12 was expressed in the brain, and two patients suffered irreversible CNS injury.[59] Another MAGE-A3 epitope, presented by HLA-A0101, was targeted by a TCR modified to enhance avidity. This TCR recognized an epitope from titin, a protein present in cardiomyocytes. Two patients treated with this CAR had fatal cardiac toxicity.[60]

Adoptive cell therapy is a powerful and promising approach to cancer therapy that has uncovered novel toxicities that occur when tumor-associated antigens are targeted. Multiple registration trials are under way with CD19 CARs, increasing the likelihood that this treatment will soon enter practice and highlighting the need to be aware of its AEs. Ultimately, the less toxic approaches to adoptive cell therapy will include the use of normal T-cell repertoires against tumor-specific mutated epitopes, but the logistics of implementing this remain formidable and await the development of new technology.[61]

TOXICITIES OF CHECKPOINT PROTEIN INHIBITORS

Three checkpoint protein inhibitory antibodies have been approved since 2011, including ipilimumab, which blocks CTLA-4, and pembrolizumab and nivolumab, which block PD-1. These antibodies have entered routine practice for the treatment of patients with melanoma and will likely be approved in the future for multiple other tumor types. Checkpoint protein inhibition is associated with on- and off-target, cell and metabolic toxic effects that need to be carefully

monitored and managed during and after treatment.[62,63] Autoimmune-like syndromes have been reported in a significant proportion of patients receiving checkpoint protein inhibitors like ipilimumab and PD-1 and PD-L1 antibodies. It is recommended that all patients receiving these agents routinely have thyroid function studies, complete blood counts, and liver function and metabolic panels at each treatment and at intervals of 6 to 12 weeks for the first 6 months after finishing treatment. Adrenocorticotropic hormone, cortisol, and in men, testosterone should also be checked in patients who develop fatigue and nonspecific symptoms. Follow-up testing may need to increase in frequency based on individual response and AEs that occur. Corticosteroids can reverse nearly all of the toxic manifestations of these drugs, but they should be used only for grade 3 to 4 or prolonged grade 2 immune-related AEs.

For the CTLA-4–blocking antibody ipilimumab, toxicities are dose related, because the rate of grade 3 to 4 drug-related serious AEs increased from 5% to 18% when the dose was increased from 3 to 10 mg/kg and was 0% at a dose of 0.3 mg/kg, with no deaths related to treatment.[64] In a large phase II study of ipilimumab 10 mg/kg, the rate of grade 3 to 4 immune-related AEs (irAEs) was 22%.[65] In contrast, the toxicities of PD-1 blockade with nivolumab are similar at doses ranging from 0.3 to 10 mg/kg.[66-69] In one study of 34 patients who received nivolumab at 1, 3, or 10 mg/kg, two of 34 patients had grade 3 to 4 irAEs (colitis and optic neuritis).[68] In 281 patients with melanoma, renal cell carcinoma, lung cancer, and other tumors who received nivolumab at doses from 0.3 to 10 mg/kg, 5% of patients had grade 3 to 4 irAEs.[69] In a phase III trial of previously untreated patients with stage IV melanoma receiving nivolumab 3 mg/kg (the FDA-approved dose), grade 3 or 4 drug-related AEs occurred in 11.7%, with 6.8% discontinuing therapy as a result of AEs, including 1% each with elevated liver functions and diarrhea.[70] The reported grade 3 to 4 AEs of the PD-1 antibody pembrolizumab seem to be somewhat higher at a dose of 10 mg/kg every 2 weeks than 2 mg/kg (the FDA-approved dose) or 10 mg/kg every 3 weeks.[71] In a recent phase II study of pembrolizumab, drug-related grade 3 or 4 AEs occurred in 12% of patients, with 5% of patients having drug-related serious AEs; 3% of patients discontinued treatment because of drug-related AEs, and no drug-related deaths were reported.[72] The most common drug-related AEs of any grade were fatigue, pruritus, and rash, which are the most common AEs of all checkpoint protein antibodies.[73-76] The AE profiles of the two anti–PD-1 antibodies pembrolizumab and nivolumab seem remarkably similar.

Toxicities with PD-1 antibodies may vary with the histology treated. In Hodgkin lymphoma, five (22%) of 23 patients receiving nivolumab had grade 3 drug-related toxicities, with rash, thrombocytopenia, fatigue, and pyrexia prominent among them.[77] Two patients had infusion reactions, which are commonly observed when nivolumab is combined with a vaccine.[78] In a phase II randomized dosing trial of nivolumab in renal cell cancer, there was no clear dose relationship of toxicity at doses from 0.2 to 10 mg/kg.[79] In patients with non–small-cell lung cancer receiving nivolumab, grade 2 to 3 pneumonitis was observed in 7%, compared with only 2% of patients receiving pembrolizumab.[80] The PD-L1 antibody MPDL3280A has also been tested in melanoma, with a 13% rate of grade 3 to 4 drug-related AEs, most commonly consisting of liver function abnormalities and fatigue. No colitis or pneumonitis was seen, suggesting that the spectrum of AEs may be different with PD-L1 compared with PD-1 blockade.[81,82]

Symptomatic pneumonitis is rare with ipilimumab, at a rate of 1%, with asymptomatic findings on computed tomography scans or x-rays that rapidly resolve if the drug is held.[83,84] However, patients receiving PD-1 antibodies can have symptomatic, diffuse infiltrates radiographically, often associated with shortness of breath, increased sputum, fevers, chest pain, and hemoptysis.[66-69] Bronchoscopy findings include a diffuse lymphocytic infiltrate on biopsy and brushings. High-dose corticosteroids induce resolution of symptoms in most patients, but the course of recovery may be prolonged, and computed tomography findings lag behind clinical recovery. The rate of grade 2 to 3 pneumonitis is lower in melanoma than in non–small-cell lung cancer (1% to 2% *v* 7%, respectively),[80] suggesting that pre-existing lung damage might contribute to this toxicity. Drug-related hepatitis is seen in 1% to 2% of patients with checkpoint protein inhibitors, and grade 3 to 4 liver function abnormalities may, like PD-1 antibody–induced pneumonitis, be slow to resolve and require high-dose corticosteroids and even mycophenolic acid. In contrast, grades 3 to 4 colitis occurs in 6% to 14% of patients receiving ipilimumab, but in only $\leq$ 1% of those receiving PD-1/PD-L1 antibodies. In a recent trial of 90 patients treated with nivolumab with or without a peptide vaccine, no grade 3 to 4 colitis was observed.[68] Colitis, with onset commonly at 4 to 6 weeks and resolution to baseline within 6 weeks, is observed with PD-1/PD-L1 blockade, but recovery can be prolonged, and colonic perforation and obstructive symptoms are potential dangers, similar to ipilimumab. High doses of corticosteroids are required for severe colitis caused by ipilimumab or PD-1 antibodies.[85,86] Infliximab should be administered to patients whose colitis fails to resolve within 3 days of high-dose corticosteroids or to those who experience a relapse of colitis symptoms with corticosteroid taper. Enteritis sparing the colon with small bowel obstruction can also be seen with ipilimumab or PD-1 blockade.[87] Immune-related hematologic and neurologic toxicities can rarely be seen with ipilimumab or with PD-1/PD-L1 antibodies. Encephalitis, Guillain-Barré syndrome, and a myasthenia gravis–like syndrome have been observed with ipilimumab[86,88] or PD-1 blockade, as have rare cases of autoimmune thrombocytopenia and leukopenia.[89,90] Bone marrow suppression is rare and likely on an autoimmune basis for ipilimumab. Dose-limiting arthralgias are rarely observed with ipilimumab but have been documented with nivolumab and pembrolizumab, sometimes requiring the use of injected or even oral corticosteroids for relief. The irAEs of PD-L1 antibodies do not seem to be as frequent as with PD-1 antibodies, with a 9% overall rate of drug-related grade 3 to 4 toxicity in one study that accrued 207 patients.[91] A specific concern in patients with endocrinopathies is the difficulty in delivering subsequent IL-2 therapy, including as a component of adoptive cell therapy, to patients with inadequate adrenal function on replacement corticosteroids.

The kinetics of onset of irAEs, particularly with ipilimumab, follow a predictable pattern.[92] Skin-related toxicities occur first; colitis appears next, after one to three doses; and hepatitis and endocrinopathies occur last, often after the third or fourth dose of ipilimumab. Endocrinopathies occur late and have been seen between weeks 12 and 24. The same phenomenon has been observed with nivolumab and pembrolizumab, with rashes and GI toxicity seen early and liver toxicity or endocrinopathies seen later. Long-term follow-up of endocrinopathies with checkpoint protein inhibition suggest that some thyroid function may be restored over time but that dysfunction of the corticosteroid and gonadal axes is likely permanent.[93-95] Rarely, other irAEs may occur after week 24 with any checkpoint-blocking antibodies. In trials including maintenance ipilimumab, colitis has been seen

47 months from initiation of treatment.[96] Nonetheless, PD-1 antibodies have been administered every 2 weeks for 3 or more years in some patients and have been well tolerated, with most irAEs occurring by week 24.[68,69] Toxicities with PD-1/PD-L1 agents may be slower to resolve than with ipilimumab, so long-term surveillance is advised.

Prolonged grade 2 irAEs of the skin and GI tact can be seen with checkpoint protein inhibitors, meriting an oral prednisone taper. Grade 2 skin eruptions that occur with each dose of PD-1 antibody or ipilimumab may resolve with skipping a dose but frequently present with dose-limiting grade 3 toxicity as dosing continues.

The type and pattern of irAEs with ipilimumab vary with the drugs with which it is combined. Ipilimumab with dacarbazine resulted in frequent hepatotoxicity[97,98]; when carboplatin and paclitaxel were added, dermatologic AEs were common.[98] Ipilimumab with vemurafenib also produced severe liver and kidney toxicities that limited the development of this combination.[99] With concurrent nivolumab and ipilimumab, the rate of grade 3 to 4 toxicities was 62%, albeit with response rates of 43% to 53% with long duration.[100] Asymptomatic liver and pancreatic function abnormalities were commonly observed. PD-1 blockade could safely continue after resolution of grade 3 amylase and lipase elevations induced by combination therapy. Delayed second irAEs were also seen, such as abnormal liver function tests observed weeks after colitis or pneumonitis seen after pancreatic function elevation.[100] In contrast, when high doses of IL-2 or bevacizumab were added to ipilimumab, the AEs observed were simply those expected from either drug alone.[75,101] When granulocyte-macrophage colony-stimulating hormone was added to ipilimumab, survival was prolonged, there was a decrease in the grade 3 to 5 AEs (45% *v* 58% or ipilimumab alone; $P = .04$), and less GI toxicity was noted, consistent with prior murine studies.[102] PD-1/PD-L1 antibodies and ipilimumab rarely cause infusion reactions, but when a peptide vaccine with adjuvant was added to nivolumab, the rate of infusion reactions increased to 12%.[68]

Patients with prior autoimmune diseases or a history of viral hepatitis have been excluded from receiving ipilimumab on trials, but recent data suggest that the drug can be given safely to those

Table 1. Immunotherapy Toxicity

Type of Immunotherapy	General Symptoms	Skin Toxicity	GI Toxicity	Hepatotoxicity	Endocrinopathy	Other Toxicities
Vaccines	Fevers, chills, lethargy	Maculopapular, vitiligo[1]	Rare diarrhea[5]	Rare[5]	None	Local reactions, back pain,[8] rare hypotension[5]
Cytokines: IFN	Fevers, chills, and flu-like symptoms[19]	Maculopapular[19]	Nausea, diarrhea, and rare vomiting[22]	Elevated LFTs common[23]	Thyroiditis; often associated with benefit[24]	Congestive heart failure,[19] anemia,[26] thrombocytopenia,[26] leukopenia,[26] depression[21]
Cytokines: IL-2	Fevers, chills, and lethargy[31]	Petechial and macular[31]	Transient nausea, vomiting, and diarrhea[31]	Elevated LFTs and bilirubin common[31]	Thyroiditis; often associated with benefit[36]	Pulmonary edema,[32] hypotension,[32] azotemia,[32] myocarditis,[32] altered mental status[31]
Cell therapy: TILs	Fevers, chills, and fatigue[43-45]	Maculopapular[43]	Rare diarrhea[43-45]	Elevated LFTs rare[43-45]	Thyroiditis; often associated with benefit[43-45]	Prolonged lymphopenia, CMV infections[43-45]
Cell therapy: CAR	Fevers, chills, and lethargy	Maculopapular	Rare diarrhea	Elevated LFTs with CA-IX CAR[56]	None	Cytokine release with tachycardia, hypotension, oliguria; B-cell aplasia[54]; pulmonary edema[55]
Cell therapy: TCR	Fevers, chills, and lethargy[47]	Maculopapular,[47] vitiligo [52]	Colitis with CEA TCR[53]	Elevated LFTs rare[47]	None	Encephalopathy[59] and carditis[60] with MAGE-3 TCR
Checkpoint protein inhibition: CTLA-4	Fevers, chills, and lethargy[62]	Maculopapular[62]	Diarrhea and colitis with ulceration[62]	Elevated LFTs[62]	Hypophysitis, thyroiditis, and adrenal insufficiency[62]	Neuropathy, nephritis, Guillain-Barré, myasthenia gravis, sarcoid, and thrombocytopenia all rare[62,63]
Checkpoint protein inhibition: PD-1	Fevers, chills, and lethargy[68-72]	Maculopapular[68-72]	Diarrhea and colitis with ulceration: uncommon[68-72]	Elevated LFTs uncommon[68-72]	Hypophysitis, thyroiditis more common, adrenal insufficiency[68-72]	Pneumonitis not common; neuropathy, Guillain-Barré, myasthenia gravis, nephritis, all rare[68-72]
Checkpoint protein inhibition: PD-L1	Fevers, chills, and lethargy[81,82]	Maculopapular[81,82]	Diarrhea and colitis with ulceration: rare[81,82]	Elevated LFTs rare[81,82]	Hypophysitis, thyroiditis more common, adrenal insufficiency[81,82]	Pneumonitis rare; anemia rare[81,82]
Combination checkpoint protein inhibition	Fevers, chills, and lethargy[100]	Maculopapular[100]	Diarrhea and colitis with ulceration; pancreatic lab elevation common[100]	Elevated LFTs common[100]	Hypophysitis, thyroiditis more common, adrenal insufficiency[100]	Pneumonitis not common[100]; neuropathy, Guillain-Barré, myasthenia gravis, nephritis, all rare[100]

Abbreviations: CA-IX, carbonic anhydrase IX; CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; CMV, cytomegalovirus; IFN, interferon; IL-2, interleukin-2; LFTs, liver function tests; TCR, T-cell receptor; TILs, tumor-infiltrating lymphocytes.

patients.[103-105] Nonetheless, extreme caution should be taken in treating patients with recent or ongoing autoimmune conditions, particularly any type of inflammatory bowel disease. The key to successful management of checkpoint protein antibody toxicities is early diagnosis, high suspicion, excellent patient-provider communication, and rapid and aggressive use of corticosteroids and other immune suppressants for irAEs. As of yet, there are no validated biomarkers for the prediction of immunotherapy toxicity, which is a field of active investigation.

Table 1 provides an overview of the toxicities discussed in this article. New immunotherapies for diverse types of cancer will likely be approved in the near future, and proper handling of their unique toxicities will require adoption of new treatment algorithms and a steep learning curve for the practitioner.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Toxicities of Immunotherapy for the Practitioner

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