Clinical Infectious Diseases

INVITED COMMENTARY

Inflammatory and Infectious Syndromes Associated With Cancer Immunotherapies

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Immunotherapy using antibodies to immune checkpoint molecules or targeted chimeric antigen receptor-modified T cells (CAR-T cells) represent dramatic advances in cancer treatment. These therapies mediate immune-related adverse events that may mimic or amplify infectious presentations. Checkpoint inhibitor therapy may be associated with diverse irAEs including mild skin, endocrine, and autoimmune manifestations or severe inflammatory processes including colitis, pneumonitis, myocarditis, and shock. CAR-T-cell therapies may induce toxicities including cytokine-release syndrome with fevers and multiorgan dysfunction, CAR-T-cell–related encephalopathy syndrome with altered mental status and neurologic dysfunction, or hemophagocytic lymphohistiocytosis-macrophage–activation syndrome. Infectious risks may relate to prior cancer therapies or to treatments of inflammatory dysregulation, including corticosteroids and inhibitors of tumor necrosis factor–α and interleukin-6. Immune activation may unmask subclinical infections. Clinical approaches must attempt to identify infections in the face of immunotherapy-associated inflammatory processes. Empirical antimicrobial therapies should not be delayed based on the presumption of noninfectious syndromes.

Keywords. immune checkpoint inhibitors; chimeric antigen receptor-modified T cells; cytokine-release syndrome; CAR-T-cell–related encephalopathy syndrome; tocilizumab.

Immune modulation, or “immunotherapy,” is a cornerstone of organ transplantation, cancer therapy, and infectious diseases (eg, adoptive cell transfer therapies for viral infections). Cancer immunotherapy began with William B. Coley’s injections of Streptococcus species into solid tumors, eliciting inflammatory responses [1]. Cytokine therapies (eg, for melanoma) were dramatically altered by immune checkpoint inhibitors (ICIs) that target cell surface immune checkpoint receptors (ICRs) (Figure 1). ICRs normally prevent nonspecific or excessive activation of T cells including CTLA-4 (cytotoxic T-lymphocyte-associated protein-4) and PD-1 (programmed cell death receptor-1) or PD-1L (PD-1 ligands; Table 1). Immune effector cells such as T-lymphocytes, with genetically engineered receptors for tumor antigens, are used in adoptive cell transfer. These chimeric antigen receptor T cells (CAR-T cells) and bispecific T-cell–engaging antibodies (BiTEs) are infused, engraft, proliferate, and kill tumor cells and provide long-term surveillance. Each therapy is associated with immune-related adverse events (irAEs) that may mimic or amplify infectious syndromes; the risk for infection may be increased by the immunosuppressive management of these toxicities. Differentiation of irAEs from infection is often challenging. This review examines mechanisms and adverse events associated with newer cancer immunotherapies and clinical approaches to management.

IMMUNE CHECKPOINT INHIBITORS

Mechanisms of Action and Therapeutic Uses of Immune Checkpoint Inhibitors

Cancer cells evade immune attack via physical barriers, rapid tumor growth, microenvironments unsuitable for immune cells, and limiting display of tumor or histocompatibility antigens for immune targeting. Over time, immune responses are downregulated to avoid damage to normal tissues and targeting of “self” antigens [2]. Cell surface receptors that limit activation of T cells, including CTLA-4 and PD-1, are called ICRs (Figure 1).

CTLA-4 is induced in T cells with antigen binding to the T-cell receptor (TCR). CTLA-4 normally engages B7/CD-86 on the surface of antigen-presenting cells to dampen the immune response (Figure 1A) [3–6]. CTLA-4 also upregulates regulatory T-cell (Treg) function, decreasing responses to cancer antigens [4, 7, 8]. Antibodies to CTLA-4 create unrestrained activation of naive T cells and decrease immunosuppression by Tregs, augmenting the quantity and activity of effector T cells within tumors [9]. The fully humanized anti-CTLA-4 monoclonal antibodies ipilimumab (immunoglobulin [Ig] G1) and tremelimumab (IgG2) are used in treatment of melanoma and other malignancies [4, 10–12] (Table 1).

PD-1 is a transmembrane protein found on T cells, B cells, natural killer (NK) cells, monocytes, and dendritic cells
Immune checkpoint inhibitors regulate various components in the T-lymphocyte response to tumors. 

**A. CTLA-4 Checkpoint Inhibition**

The cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)–mediated immune checkpoint is induced in T cells at the time of initial antigen binding. The level of CTLA-4 induction depends on the amplitude of T-cell receptor (TCR)–mediated signaling; high-affinity ligands induce higher levels of CTLA-4. CTLA-4 normally dampens the immune response via binding to B7/CD86 on the surface of antigen-presenting cells. When the TCR binds antigen, CTLA-4 is transported to the cell surface. Blockade of CTLA-4 allows unrestrained CD8+ effector or cytotoxic T-cell activation.

**B. PD1 Checkpoint Inhibition**

The programmed cell death protein 1 (PD-1) pathway regulates inflammatory responses by effector T cells within peripheral tissues and tumors. Activated T cells upregulate PD-1; inflammatory signals in tissues induce the expression of PD-1 ligands (PD-1L or B7-H1). The combination of PD-1/PD-1L downregulates the activity of T cells and limits tissue damage. This effect is useful in modulating responses to infection in tissues under normal conditions. In cancer, chronic induction of PD-1 on T cells induces an exhausted or anergic state in T cells. Inhibition of PD-1 or PD-1L allows unrestrained CD8+ effector or cytotoxic T-cell activation. Abbreviations: APC, antigen-presenting cell; IFN-γ, interferon gamma; IFNGR, interferon-gamma receptor; MHC, major histocompatibility complex; TCR, T-cell receptor.
that dampen effector T-cell responses within peripheral tissues when bound by ligands PDL-1 (CD274/B7-H1) or PDL-2 (CD 273/B7-DC) (Figure 1B) [4]. Normally, activated tumor-infiltrating T cells upregulate PD-1 while many malignant cells increase expression of PD-1 ligand (PD-1L), downregulating T cells upregulate PD-1 while many malignant cells increase expression of PD-1 ligand (PD-1L), downregulating T-cell antitumor immune responses [13, 14]. Normally, activated tumor-infiltrating T cells upregulate PD-1 while many malignant cells increase expression of PD-1 ligand (PD-1L), downregulating T-cell antitumor immune responses [13, 14]. Chronic antigen exposure in cancer may also induce T-cell apoptosis or anergy and increased Treg production [15–18]. Antibodies directed at PD-1 or PDL-1 ligand upregulate T-cell antitumor activities and are used for diverse malignancies [4, 19–21](Table 1).

<table>
<thead>
<tr>
<th>Table 1. Immunotherapies for Cancer: Common Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>Immune checkpoint inhibitors</td>
</tr>
<tr>
<td>PD-1 ligands</td>
</tr>
<tr>
<td>PD-1 ligands</td>
</tr>
<tr>
<td>PD-1 ligands</td>
</tr>
<tr>
<td>Chimeric antigen receptor T cells</td>
</tr>
<tr>
<td>CD47-SIRPα antibodies (macrophage checkpoints)</td>
</tr>
<tr>
<td>Anti-CD19</td>
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<td>Anti-CD20</td>
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<tr>
<td>Anti-CD22</td>
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<tr>
<td>Anti-CD20</td>
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<tr>
<td>CD30</td>
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<tr>
<td>Anti B-cell maturation antigen</td>
</tr>
</tbody>
</table>

| Abbreviations: DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; PD-1, programmed cell death receptor-1; RCC, renal cell carcinoma; SIRP, signal-regulatory-protein. |

**Mechanisms of ICI Toxicity**

On-target effects of ICI therapies with increased T-cell cytotoxicity produce tumor lysis, fever, and bystander cell damage. Upregulated immune function may target normal tissues expressing ICR (eg, CTLA-4 on pituitary tissue), release of inflammatory cytokines, antibody binding and complement activation on normal cells, and, possibly, activation of preexisting autoimmune cells and antibodies. Some mechanisms are unclear (Table 2) [22]. "Off target" manifestations may be systemic or organ specific and may be life-threatening. The common irAEs often mimic infection with fever, colitis, skin rashes, myalgias, pneumonitis, and endocrine dysfunction [23, 24]. Most occur without known prior autoimmunity [25].

**Clinical Features of ICI Toxicity**

Clinical responses to antitumor effects of ICI blockade may evolve over months [4, 22]. Toxicities may also manifest weeks to months after initial treatment, but beyond 3–6 months is unusual (see Table 2) [4, 24, 26–28]. irAEs of anti–CTLA-4 therapies (most often colitis and hypophysitis) are more severe than with PD-1/PD-1L antibodies; these occur in up to 90% of patients with CTLA-4 blockade and more than 70% with PD-1/PD-1L antibodies (Table 2) [23, 24]. No biomarkers predict specific toxicities. Toxicity varies by agent, dose, and type of malignancy [29]. Less common toxicities emerge with prolonged therapy or later (eg, pancreatitis, cardiomyopathy, nephritis, uveitis, or neuropathy). Intolerance of one agent does not predict recurrence with another. Combination therapy with CTLA-4 and PD-1 pathway antagonists increases the rate and severity of toxicities [30, 31]. Distinguishing normal or beneficial immune-related responses from toxicities may be difficult; tumor enlargement and fever may result from ICI-related inflammation and necrosis [22, 32]. Similarly, inflammation associated with infection may be augmented and indistinguishable from the side effects of ICI (Figure 2). Influenza vaccination after ICI therapy may increase irAEs, notably central nervous system (CNS) toxicities [33]; prospective studies of vaccination in these hosts are, however, lacking.

**ICI Skin Toxicities**

Skin rash is common in ICI therapy for melanoma and the earliest toxicity overall, generally an erythematosus or maculopapular rash is seen on extremities or the trunk 2 to 3 weeks into therapy (Table 2) [24, 34–36]. ICI rash is graded by severity (eg, rash with skin sloughing) and body surface area. Vitiligo is common, but generalized pruritus and delayed hypersensitivity reactions, with or without erythematous macules and papules, may occur [37]. Inflammatory skin lesions include Sweet syndrome, dermatomyositis, and acute generalized exanthematous...
Table 2. Common Presentations of Immune Checkpoint Inhibitor-related Toxicities

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Common Medical/Oncologic Diagnoses</th>
<th>Immune-related Diagnoses of Checkpoint Inhibitors</th>
<th>Time, Weeks</th>
<th>Infectious Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wasting/Asthenia</td>
<td>Metabolic disorder, tumor progression, paraneoplastic syndromes, malnutrition, chronic pain, drugs (eg, opiates, steroids), depression, encephalopathy (eg, drug), organ dysfunction</td>
<td>Hypo/hyperthyroidism, diabetes, hypophysitis, adrenal insufficiency, anemia, nephritis, colitis, induced autoimmune disorders, neutromuscular pains, inflammatory syndrome, immune reconstitution</td>
<td>6-12</td>
<td>Endocarditis, PML, sepsis, colitis, chronic infections (syphilis, viral), thrush</td>
</tr>
<tr>
<td>Skin</td>
<td>Drug reaction, hepatic dysfunction (pruritus)</td>
<td>Maculopapular rash, pruritus, vitiigo, autumome (pemphigus, eczema, psoriasis), vasculitis, inflammatory Sweet syndrome, dermomyositis, drug-related eosinophils with systemic symptoms, pyoderma gangrenosum</td>
<td>2-3</td>
<td>Sepsis (candidemia, bacteremia), septic emboli (Staphylococcus, Streptococcus, Pseudomonas, Candida, Fusarium), shingles, herpes simplex, cellulitis</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Aspiration, metastatic tumor, PE, bleeding, pneumothorax, anemia, respiratory suppression (pain medication, CNS tumor), heart failure</td>
<td>Pneumonitis (and organizing pneumonitis), sarcoidosis, interstitial fibrosis, myasthenia, polyradiculoneuropathy (pain, weakness), pericarditis, myocarditis</td>
<td>1-2 and/or 12-16</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Gastrointestinal including hepatic</td>
<td>Metastatic tumor, drug, neoptropic colitis, pancreatitis, cholangitis, diabetes, bowel obstruction or perforation, hypercalcemia, thrombosis, malnutrition, hepatitis</td>
<td>Oral mucositis, dry mouth (Sjögren syndrome), enterocolitis, pancreatitis, perforation, hepatitis, cholangitis (primary biliary cholangitis), hyper/hypothyroidism, adenalin insufficiency, autoimmune hepatitis</td>
<td>4-6 oral, 6-12 colon</td>
<td>Thrush, Clostridium difficile colitis, enteric pathogens and parasites, viral (norovirus, CMV), perforation, peritonitis, hepatitis viruses (hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus), adenovirus, hepatosplenic candidiasis, leptospirosis, mycobacteria</td>
</tr>
<tr>
<td>Nervous system, seizures</td>
<td>Metastatic tumor (carcinomatous meningitis), drug neurotoxicity, paraneoplastic, hypercalcemia, diabetes (stroke, hyperosmolar), encephalopathy (metabolic)</td>
<td>Hyphophysitis with aseptic meningitis, vasculitis (stroke), PRES, myelitis, mononeuritis, fever, polyradiculopathy, Guillain-Barre, autoimmune vasculitis, myasthenia, encephalitis</td>
<td>6-13</td>
<td>Encephalitis, meningitis, epidural abscess, vasculitis (syphilis and endocarditis), fungal (Cryptococcus and mold), viral (human immunodeficiency virus, HSV, CMV, VZV, measles), PML, immune reconstitution (tuberculosis, Cryptococcus)</td>
</tr>
<tr>
<td>Headache</td>
<td>CNS metastasis (carcinomatous meningitis), intracranial hypertension, CNS bleed, stroke, embolus, drug toxicity, PRES</td>
<td>Hyphophysitis (pituitary enlargement), immune reconstitution, vasculitis (stroke), PRES</td>
<td>6-12</td>
<td>Meningitis (bacterial, viral, Cryptococcus), encephalitis (HSV/VZV), endocarditis with septic embolus, abscess (Aspergillus)</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>As above and metabolic (hyperpyrexia, hypercalcemia, renal/hepatic dysfunction), drug (infusion), MI, PRES, PE, anemia, secondary tumor, malnutrition, brain radiation</td>
<td>As above and hyperosmolar diabetes, adrenal insufficiency, hypophysitis, PRES, multiple sclerosis, steroid withdrawal</td>
<td>6-12</td>
<td>As above and sepsis (colonic perforation), viremia (CMV, adenovirus, diarrhea, immune reconstitution, syphilis, toxoplasmosis, PML ULC virus)</td>
</tr>
<tr>
<td>Renal</td>
<td>Drug (diuretics), radiologic contrast media, hypotension, heart failure, thrombosis, tumor (invasion, obstruction), dehydration (colitis), hepatorenal syndrome, SIADH (CNS tumor)</td>
<td>Nephropathy, TTP, HUS</td>
<td>12</td>
<td>BK virus, adenovirus, Clostridium difficile colitis, sepsis, septic emboli, obstruction (fungus ball)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Metastasis, pathologic fractures, thrombosis</td>
<td>Arthritis, myositis, polyneuropathy, rheumatoid arthritis, polymyalgia rheumatic, psoriatic arthritis, seronegative polyarthritis, sarcoidosis</td>
<td>V</td>
<td>Infectious arthritus and myositis</td>
</tr>
<tr>
<td>Eye</td>
<td>Radiation, tumor, optic neuritis, drug</td>
<td>Uveitis, encephalitis, retinitis, optic neuritis, vasculitis, myasthenia</td>
<td>V</td>
<td>Retinitis, uveitis (CMV, toxoplasma, syphilis), brainstem infection/abscess</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Metastatic tumor to thorax, PE, MI, pneumothorax, heart failure</td>
<td>Myocarditis, pericarditis, pleuritis, vasculitis, hyperthyroidism, immune reconstitution</td>
<td>V</td>
<td>Myocarditis, pericarditis, pleuritis, immune reconstitution, shingles, sepsis</td>
</tr>
<tr>
<td>Hypotension</td>
<td>As above and adenalin metastasis, hypothyroidism, steroid withdrawal</td>
<td>As above and myocarditis, pericarditis, pleuritis, vasculitis, hypothyroidism, adrenal insufficiency (granulomatosis, thrombosis)</td>
<td>V</td>
<td>As above and adenalin (CMV), sepsis</td>
</tr>
<tr>
<td>Systemic</td>
<td>Anemia (drug, bleeding, nutritional deficiency), hemolytic-uremic syndrome, marrow metastasis (fibrosis), splenomegaly, myelodysplasia, hemarin-induced thrombocytopenia, SIADH</td>
<td>Anemia, pancytopenia, thrombocytopenia (TTP), thrombotic microangiopathy, hypothyroidism, myelodysplasia, Evans syndrome, APLS, nephropathy</td>
<td>V</td>
<td>Parvovirus, CMV, disseminated intravascular coagulation; sepsis, APLS</td>
</tr>
</tbody>
</table>

Most toxicities occur within the first few weeks to months of therapy and are more common and severe in combination therapy. Times to adverse events vary with roughly 1/3 occurring after the second, third, and subsequent doses. Most diagnoses, including underlying tumor, may be associated with fever, chills, or systemic syndromes suggestive of “viral syndromes.” Prior chemotherapy, cytopenia, and colititation influence infectious risk.

Abbreviations: APLS, antiphospholipid antibody syndrome; CMV, cytomegalovirus; CNS, central nervous system; HSV, herpes simplex virus; HUS, hemolytic uricemic syndrome; JCV, JC virus, John Cunningham virus; MI, myocardial infarction; PE, pulmonary embolus; PML, progressive multifocal leukoencephalopathy; PRES, posterior reversible encephalopathy syndrome; SIADH, syndrome of inappropriate antidiuretic hormone; TTP, thrombotic thrombocytopenia purpura; V, variable, often late, generally autoimmune; VZV, varicella zoster virus.
pustulosis (Table 2). Rarely, skin vasculitis has contributed to Stevens-Johnson syndrome/toxic epidermal necrolysis. Patients may present with immunobul-lous manifestations, suggesting dermatitis herpetiformis, bullous pemphigoid, or bullous erythema multiforme, suggesting staphylococcal or streptococcal infection, herpes simplex virus, or herpes zoster infections. Autoantibodies (such as antinuclear antibody, SS-A/Anti-Ro) may emerge. Photosensitivity may occur. Blood cultures and skin biopsy may define atypical skin lesions.

**ICI Endocrine Toxicities**

Endocrine disorders are common with most ICIs, occurring 6–12 weeks into therapy (Table 2) [38, 39]. Patients develop constitutional symptoms (ie, fatigue, myalgias, dizziness, nausea) with thyroid dysfunction; hypothyroidism, often with antithyroid antibodies, is more common than hyperthyroidism [40]. Thyroid dysfunction occurs more commonly with PD-1 inhibitors. Pituitary involvement occurs in 17% of patients with CTLA-4 blockade, with fatigue, gonadal dysfunction, behavioral changes, or temperature intolerance generally in males [38]. Hypophysitis may cause elevated intracranial pressure or neurologic symptoms localizing to the sella with headache or diplopia (Table 2). Brain magnetic resonance imaging (MRI) with sella views is useful to establish the diagnosis. Primary adrenal insufficiency and type 1 diabetes are less common. Patients treated with ICIs should undergo hormonal testing including thyroid function tests (TSH, T4), adrenocorticotropic hormone, and cortisol levels.

**ICI Gastrointestinal Toxicities**

Oral mucositis and dry mouth occur early in therapy (2–6 weeks) and are more common with PD-1 inhibitors (Table 2). Colitis is the most common severe complication of ICI therapy; more than 50% experience diarrhea and 20%–30% have colitis. Colitis presents with voluminous diarrhea, hematochezia, abdominal pain, polyarthritis, nausea, and/or fever and may include ulcers, fistulae, abscesses, and rarely perforation or toxic megacolon [26]. Perforation may reflect tumor lysis or immune colitis. Colitis is more common with CTLA-4 antagonists than with PD-1/PD-L1 antibodies and appears later in therapy (4–6 weeks) [24, 27]. Small bowel enteritis is uncommon. Histopathology typically exhibits neutrophilic infiltrates and apoptosis of epithelial cells within crypts; lymphocytic infiltrates may be seen [41]. Computed tomography (CT) may demonstrate bowel wall edema, abscess, or perforation. Up to 10% experience hepatitis, usually asymptomatic elevations of aspartate transaminase and alanine transaminase levels; hepatitis occurs in up to 30% of patients receiving combination ICI therapy (Table 2) [29, 42]. Pancreatitis is uncommon. Positive antinuclear, smooth muscle, and other autoantibodies and histopathology consistent with autoimmune hepatitis may be found [42]. Immunocompromised patients with colitis after ICI therapy require microbiological studies (Table 2) for *Clostridium difficile* and common viruses including cytomegalovirus (CMV; quantitative blood nucleic acid testing) and norovirus [43]. Colonic ulceration may predict failure to respond to steroid therapy. Nonsteroidal antiinflammatory medications may increase the risk of colitis [44].

**ICI Pulmonary Toxicities**

Pulmonary irAEs during ICI therapy mimic pneumonia and may be life-threatening [45–48]. Pneumonitis has a median onset approaching 3 months, with some earlier cases (ie, 7–9 days) [34, 49]. Dyspnea and cough may be prominent; some radiologic processes are asymptomatic. PD-1/PD-L1 antagonists carry greater pulmonary toxicity than CTLA-4 antibodies. Up to 6% of patients who receive PD-1/PD-1L antagonists develop pneumonitis (Figure 2), which may progress to acute respiratory distress syndrome (ARDS); combinations of PD-1/PD-1L and CTLA-4 blockade risks toxicity in up...
to 12% [31, 46–48]. Chest pain may accompany immune pericarditis-myocarditis, pleural tumor, or shingles.

Chest radiographs in pulmonary irAE typically demonstrate more prominent lower lobe processes; 75% have all lobes involved [46, 48]. Ground-glass opacities are universal, with reticular opacities appearing frequently; 60% have consolidation. Centrilobular nodules and traction bronchiectasis occurs in less than 15% of the patients; 65% develop cryptogenic organizing pneumonia. Radiologic patterns that suggest nonspecific interstitial pneumonitis, hypersensitivity pneumonitis, or interstitial pneumonitis/ARDS occur in 10%–15% of patients each. Some radiographs suggest sarcoidosis. Radiologic images are affected by interstitial fibrosis from prior radiation or chemotherapy or concomitant infections.

Appropriate sputum studies for bacteria and fungi are helpful (eg, community-acquired viruses, CMV, Pneumocystis jiroveci, mycobacteria, and atypical pathogens) [45–48]. Bronchoalveolar lavage may identify infection or malignancy; most often, lymphocytic predominance is found in ICI pneumonitis [50]. Interpretation of inflammatory markers (eg, erythrocyte sedimentation rate, C-reactive protein, or procalcitonin) is unrewarding. Histopathologic patterns include acute cellular interstitial pneumonitis, organizing pneumonia, or diffuse alveolar damage [45]. Some patients exhibit necrotizing or nonnecrotizing granuloma formation and interstitial fibrosis. Combinations of immune and infectious etiologies may occur, for example, allergic bronchopulmonary aspergillosis [51].

A grading system exists for lung toxicities based on symptoms and radiologic data to guide management [52]. In the absence of infection or other reversible cause of symptoms, clinical and radiographic improvement is rapid (2–3 days) with corticosteroid therapy.

**ICI Nervous System Toxicities**
Up to 6% of patients who receive ICR blockade experience neurologic toxicity, 12%–14% with combination therapy [34, 53, 54]. Most cases occur in the first 6–13 weeks. Toxicities affect both the central and peripheral nervous systems, with symmetric or asymmetric sensory and/or motor or autonomic deficits. Aseptic meningitis may occur. Seizures are uncommon. Encephalitis with seizures is more common in infection than in immune reconstitution, paraneoplastic syndromes, or multiple sclerosis. Acute confusion may reflect hypophysitis, sepsis, vasculitis, or brain metastasis. Neurologic syndromes including myasthenia gravis, transverse myelitis, and Guillain Barré syndrome may occur; others challenge standard classifications [54]. MRI is useful and may suggest autoimmunity (Figure 3). Evaluation is often

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**Figure 3.** Chimeric antigen receptors (CARs) are synthetic receptors expressed on genetically engineered autologous or allogeneic T cells for cytotoxicity against tumor cells. CARs contain an extracellular receptor with transmembrane and intracellular domains to transmit activation signals to T cells when the receptor binds cognate antigen. The extracellular domain is comprised of a single-chain variable fragment of antibody antigen-recognition segments; ligands for other cell-surface receptors may be used. Unrestrained T-cell activation is achieved by the presence of both an MHC-independent signal 1 (TCR) and domains from costimulatory receptors to provide signal 2. Abbreviations: CAR, chimeric antigen receptor; Fv, antibody fragment specific for human lymphocyte antigen CD19; MHC, major histocompatibility complex; TCR, T-cell receptor.
complicated by neutropenia and prior therapies (Table 2). Cerebrospinal fluid (CSF) studies may help exclude infectious etiologies.

ICI Autoimmune, Systemic, and Musculoskeletal System Toxicities

Inflammatory arthritis, myositis, and polymyalgia-like syndromes are the most common immune responses to ICI therapy but may reflect prior processes (eg, gout, ankylosing spondylitis) or infections (eg, hepatitis, mycobacterial or endemic fungal infection) [55]. Autoimmune, rheumatologic, and inflammatory events include immune thrombocytopenia (0.2%), Sjögren syndrome (0.3%), rheumatoid arthritis (0.2%), polymyalgia rheumatica (0.2%), psoriatic arthritis (0.2%), seronegative polyarthritis (0.7%), and sarcoidosis (0.2%) [26, 27, 56].

Infectious Risk and Management of ICI Toxicities

The challenge of ICI therapy is in distinguishing between infection and irAEs (Table 2). ICI therapy has not been associated with major infectious risks beyond the impacts of underlying malignancy and chemotherapy. ICI will, however, enhance inflammation due to infection; antiinflammatory treatments for irAEs will also mask clinical manifestations of infection. Most nonendocrine toxicities are reversible with systemic corticosteroids as 1–2 mg/kg/day prednisone to methylprednisolone 125 mg intravenously daily. Steroids should be avoided if possible given the potential reduction in antitumor responses and infectious risks [27, 28, 34, 52]. Budesonide may be effective for colitis. With systemic steroid therapy, prophylaxis for Pneumocystis and herpesviruses should be considered based on the expected duration of treatment. The use of corticosteroids may mask signs and increase the risk for infection [52]. If irAE symptoms persist despite steroid therapy (1 week), steroid-sparing agents (eg, tumor necrosis factor [TNF] inhibitors) are often required. TNF-α antagonists are indicated after infection is excluded and systemic steroids fail to control symptoms. Screening for tuberculosis, endemic fungi, and viral hepatitis B and C is required prior to these treatments.

Table 3. Common Toxicities Associated With Chimeric Antigen Receptor-T-Cell Therapies

<table>
<thead>
<tr>
<th>Cytokine Release Syndromea</th>
<th>Chimeric Antigen Receptor-modified T-Cell-related Encephalopathy Syndromeb</th>
<th>Hermaphrogytic Lymphohistiocytosis, Macrophage-activation Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever, myalgia, anorexia</td>
<td>Altered mental status (confusion, somnolence, agitation, delirium, disorientation, encephalopathy, insomnia, or aphasia)</td>
<td>Fever, rash, conjunctivitis</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Tremors, seizures</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Dyspnea, hypoxia, fluid retention, diffuse infiltrates</td>
<td>Obtundation</td>
<td>Pulmonary infiltrates, hypoxia, acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Acute coronary syndrome, arrhythmias, heart block, decreased ejection fraction</td>
<td>Cerebral edema, increased intracranial pressure (papilledema), elevated cerebrospinal fluid protein</td>
<td>Confusion, ataxia, brain edema, seizures, posterior reversible encephalopathy syndrome</td>
</tr>
<tr>
<td>Hepatitis (transaminasis), pancreatitis</td>
<td>Pituitary dysfunction</td>
<td>Elevated liver function tests, hepatomegaly, splenomegaly</td>
</tr>
<tr>
<td>Renal (proteinuria, elevated serum creatinine, decreased urine output)</td>
<td>Motor deficits (focal)</td>
<td>Elevated serum creatinine, hyponatremia, syndrome of inappropriate antidiuretic hormone</td>
</tr>
<tr>
<td>Coagulopathy, disseminated intravascular coagulation</td>
<td>...</td>
<td>Hermaphrogyticosis, anemia, coagulopathy, cytopenias, lymphohistiocytic tissue infiltration</td>
</tr>
</tbody>
</table>

Additional, common side effects include B-cell aplasia and hypogammaglobulinemia, dermatitis, and immune defects related to treatment of cytokine release syndrome (CRS). Chimeric antigen receptor-modified T-cell-related encephalopathy syndrome (CRES), and hermaphrogytic lymphohistiocytosis, macrophage-activation syndrome. The incidence of each effect varies with specific immune checkpoint inhibitors studied.

aFor CRS, onset is generally 2–7 days (depending on preparation) but may be delayed. Meticulous fluid balance may prevent fluid overload in capillary leak syndromes. Grade 1 toxicity reflects fever, nausea, fatigue, headache, myalgia, and malaise and requires only supportive care. Grade 2 toxicity requires intervention with intravenous fluid support for hypotension (or low-dose vasopressors), low-flow oxygen (<40% FiO2) supplementation. Grade 3 toxicity requires significant pressor support with supplemental oxygen (>40% FiO2) and may have transaminis or other organ toxicities. Grade 4 toxicity requires ventilator support, intensive care unit stay, and significant organ toxicity.

bFor CRES, onset is generally within 8 weeks (often earlier; may occur during or after CRS). Physical and neurological evaluations (mini-mental status exam) are repeated to identify emerging deficits. Grade 1 toxicity includes mild encephalopathy. Grade 2 toxicity includes moderate encephalopathy with somnolence confusion, dysphasia progressing to seizures. Grade 3 toxicity includes significant encephalopathy, severe aphasia, confusion, disorientation, and somnolence with normal opening pressure, but early papilledema or partial seizures responsive to benzodiazepines.
CAR-T cells that target the CD19 B-cell antigen have been approved for commercial use in patients with relapsed or refractory leukemia and lymphoma. Most recipients have undergone multiple prior cancer therapies, which do not predict cytokine or neurologic toxicities but contribute to subsequent infectious risk [60].

Adverse Events Associated With CAR-T Cells
Toxicities from CAR-T cells occur in recipients in addition to infections related to prior therapies (Table 3). Cytopenias (thrombocytopenia, lymphopenia, neutropenia) reflect both prior therapies and CAR-T–induced B-cell aplasia and hypogammaglobulinemia. Tumor lysis in certain locations (gut, biliary tree, lungs, genitourinary tract) may provoke perforation and release of commensal organisms (eg, peritonitis). Hemorrhagic colitis and cholangitis have been observed. Anaphylaxis has occurred with multiple infusions [62]. Two common and challenging toxicities of CAR-T-cell therapies are cytokine-release syndrome (CRS) and CAR-T–cell–related encephalopathy syndrome (CRES) (Table 3). CRS is most often characterized by high fever, hypoxia, hypotension, acute kidney injury, transaminitis, and multiorgan dysfunction. CRES often presents with confusion and may include seizures and brain edema but most often presents as aphasia and encephalitis without abnormal imaging findings [63–66]. Fulminant hemophagocytic lymphohistiocytosis (HLH) (or macrophage-activation syndrome [MAS]) may be part of the continuum of dysregulated inflammatory responses including cytokine release, lymphohistiocytic tissue infiltration, and multiorgan dysfunction [65–69]. Fatalities have occurred with each of these syndromes, making rapid recognition, staging, and therapy essential [63]. Similar toxicities have been observed in patients treated with other T-cell therapies, such as TCR-gene therapies and bispecific T-cell–engaging antibodies (BiTEs), and with CAR NK cells [70].

Mechanisms and Clinical Features of Toxicities of CAR-T-Cell Therapies
Cytokine-release Syndrome
CRS generally occurs within the first week of therapy and peaks within 2 weeks; timing and frequency vary by disease and CAR-T-cell product. Up to 85% of patients experience some degree of CRS; 26% are severe [60]. CRS is an “on-target effect” of T-cell activation, with TCR binding of cognate antigens with cytokine and chemokine release amplified by target cell death and cytokine elaboration by monocytes, macrophages, NK cells, and dendritic cells (Figure 3). CRS manifests with fever, myalgias, anorexia, and fluid retention and may be confused with viral infection, sepsis, or engraftment syndrome (Table 3). Timing of CRS typically coincides with the neutropenia nadir from conditioning chemotherapy. Evolution may be acute. Multiple organ systems are affected, often including the lungs (tachypnea, diffuse infiltrates, hypoxemia), kidneys (proteinuria and rising creatinine), cardiovascular (hypotension and arrhythmias), hepatitis, pancreatitis, and nervous system (confusion, seizures) [67, 71]. Coagulopathy and disseminated intravascular coagulation are common. Rashes are uncommon. The greatest risk for severe CRS is in patients with bulky disease, in CRS within 3 days of therapy, and with preexisting renal or CNS dysfunction or drug toxicities [66, 72]. Early elevated cytokine levels may anticipate severe CRS. Serum CRP levels are an indirect measure of interleukin (IL)-6 activity in CRS. Ferritin is a delayed marker that peaks 24–48 hours after the peak clinical syndrome. Most manufacturers have independent grading systems to guide diagnosis and therapy; consensus guidelines are emerging.

CAR-T-cell–related Encephalopathy Syndrome
CRES often presents within 8 weeks of treatment with altered cognition and may progress to seizures, focal neurologic deficits, and obtundation (Table 3). More severe signs may reflect cerebral edema and increased intracranial pressure. Waxing and waning neurologic symptoms may occur; acute neurologic signs are typically transient. More severe CRES is observed in those with higher grades of CRS [58, 60]. CRES may coexist with CRS within 3–5 days of therapy, notably with fever and fluid retention. However, neurologic symptoms may progress to seizures or altered mental state 2–3 weeks after cytokine-mediated events subside [61, 65, 72, 73]. The mechanisms that underlie CRES are uncertain but not completely independent of CRS given that higher cytokine levels (eg, IL-6 and IL-15) are often found in patients who progress to CRES [61, 72, 74]. However, in later phases of CRES, anticytokine therapy (other than steroids) is ineffective, suggesting that either the course has already been set or that other mechanisms have supervened. Cardiac, renal, and hepatic dysfunction of CRS may contribute to toxic encephalopathy. A role for CAR-T cells in CRES is suggested by the presence of these cells in the CSF without (known) CNS tumor involvement [64, 66, 74]. The inflammatory nature of CRES is often suggested by elevated CSF protein levels and electroencephalogram findings of diffuse generalized slowing or epileptiform discharges without frank seizure activity. MRI and CT scans of the brain generally lack changes with CAR-T-cell neurotoxicity; however, asymmetrical cerebral edema and T2-fluid attenuation inversion recovery (FLAIR) MRI hyperintensity lesions of the brainstem (thalamus, dorsal pons, and medulla) has been seen (Figure 4). Brain herniation has been reported. The duration of CRES varies but often lasts for 3–7 days; recovery is typically complete. Later CRES (after resolution of CRS) is often more severe (seizures, obtundation) and persistent [61]. Grading systems for CRES (Table 3) guide management [52]. Early imaging and lumbar puncture for cytology and microbiological studies merit consideration.
HLH/MAS is a group of immune responses driven by hyperactivation of macrophages and lymphocytes, lymphohistiocytic tissue infiltration, and proinflammatory cytokine production resulting in multiorgan dysfunction. CRS may be an immune trigger, leading to HLH/MAS in the presence or absence of HLH-predisposing genes. Many features of CRS overlap with those of HLH/MAS, including high fever, elevated cytokine levels (including interferon-γ and IL-6), multiorgan dysfunction, CNS effects, elevated lactate dehydrogenase (which may be tumor derived), ferritin, and low serum fibrinogen [75]. Thus, CRS and HLH/MAS might be considered part of a spectrum of systemic hyperinflammatory disorders. Fulminant HLH/MAS is often responsive to anti–IL-6 therapies but resistant to corticosteroid treatment. Some cases of CAR-T-cell–associated HLH/MAS have been lethal, particularly in the setting of concomitant infection. Progression from CRS to HLH/MAS is defined by fever, cytopenia in 2 hematopoietic lineages (red blood cells, white blood cells, platelets), splenomegaly, hemophagocytosis in bone marrow, hypofibrinogenemia with elevated D-dimers, hyperferritinemia (often >10 000 ng/mL), high levels of soluble CD25, low NK-cell activity, or hypertriglyceridemia. These signs may also be seen in patients with progressive hematological malignancies with or without CRS.

Managing the CAR-T Recipient

CRS, CRES, and HLH/MAS are likely related, but distinct, clinical syndromes that may be indistinguishable from infection acutely. Therapies are based on severity (Table 3). In the absence of response to supportive care, anti–IL-6 therapy (tocilizumab) is used, though some added infectious risk is possible (Table 4) [63, 65–67, 76]. Noninfectious hypoxia may respond to anti–IL-6 therapy. Progressive multiorgan dysfunction may require steroid therapy, which may impede CAR-T efficacy [63, 65, 66]. Overly rapid tapering of steroids may provoke relapse of CRES or CRS. Additional studies of the impact of anti–IL-6 therapies and corticosteroids on the efficacy of CAR-T-cell therapies are needed. Some CAR-T-cell constructs incorporate inducible safety or “suicide” genes that can be activated when confronted by intractable side effects, which are under study.

Infection in CAR-T Therapy

Most infections following CAR-T therapy occur during neutropenia and/or following severe CRS, reflecting greater degrees of immune impairment [77, 78]. Most CAR-T recipients have had at least 4 prior treatment regimens (range, 1–11); 38% have had prior autologous or
allogeneic hematopoietic cell transplants [77]. Typical conditioning regimens include cyclophosphamide and fludarabine, which may be associated with prolonged cellular immunodeficiency. Preexisting cytopenia and hypogammaglobulinemia are exacerbated [66, 73, 79]. While neutrophil recovery often occurs within a week, 37% have cytopenias unresolved by day 28, including 53% with marked neutropenia, 35% with febrile neutropenia, and 43% with documented infections [58, 60]. Mucositis may complicate prior chemotherapy [63, 65, 73].

Infection occurring with CRS may be unusually severe and poorly responsive to antimicrobial therapy (Figure 2), reflecting amplification of infection-associated cytokines and the effects of anti-cytokine therapies on immunity [80]. Growth factors may accentuate cytokine release. Infections occur in patients who receive higher CAR-T-cell numbers, with more severe CRS/CRES, with treatment for CRS/CRES with tocilizumab and/or corticosteroids, or with intensive care unit (ICU) admission following CAR-T infusion [77, 78]. It is unclear which clinical component among high cytokine levels, immunosuppressive therapies, central line manipulations, or ICU care contribute most to increased infectious risk [63, 65]. The production of CAR-T cells requires central manufacturing and, as for any cell culture system, carries potential microbial contamination.

In one series, 80% of first infections were within the first 10 days after CAR-T infusion, including gram-negative bacterial infections often with antimicrobial resistance [77]. In 53 patients following CAR-T infusion, 42% developed bacterial, fungal, or viral infections in the first 30 days after infusion [78]. Beyond 30 days, viral infections predominate, including respiratory viral infections, CMV viremia and pneumonia, and BK polyoma virus cystitis. Later infections may reflect prolonged immunoglobulin deficiency (up to 46% at day 90) as well as lymphocytopenia [77]. Severe coinfections with CRS include respiratory virus infections (some nosocomial), CMV, human herpes virus-6 or Epstein Barr Virus viremia, Clostridium difficile colitis, cholangitis, and viral encephalitis [58, 63, 65, 73].

Active infections should be controlled prior to conditioning and infusion of CAR-T products, especially given exacerbation of inflammatory processes by cytokine release. The presence of fever should prompt blood and urine cultures, chest radiography, and, based on symptoms, respiratory viral screening, CMV nucleic acid testing, CT scans, lumbar puncture, or brain MRI. Empiric antimicrobial therapy based on symptoms and institutional protocols should not be delayed based on the presumption of CRS or CRES and includes consideration of the pretreatment duration of neutropenia. Tumor lysis may be associated with fevers and, in certain locations, bowel perforation and peritonitis with CAR-T therapy. Persistent B-cell deficiencies are associated with sinopulmonary infections, notably with encapsulated bacteria. Patients should be vaccinated and immunoglobulin levels monitored.

Some infections might be expected with tocilizumab treatment (Table 4) based on experience in rheumatoid arthritis, including upper respiratory tract infections, poor wound healing, colitis with colonic perforation, demyelination or Guillain-Barré syndrome, and reactivation of latent infections due to tuberculosis, endemic fungi, hepatitis B virus, or herpes zoster [81–83]. These typically present after prolonged treatment with tocilizumab, as opposed to 1 or 2 doses that are used for CAR-T-cell-related CRS [76]. With tocilizumab therapy, atypical infections should be considered despite presumed CRS (Table 4) [76]. Invasive sinopulmonary mold infections have occurred with tocilizumab and corticosteroids, notably with neutropenia. Patient screening before tocilizumab therapy is described in Table 4.

CONCLUSIONS

Immunotherapies are promising for many malignancies. Targeting of tumor antigens is becoming more precise. Proinflammatory mechanisms predict most side effects that may mimic or amplify presentations of infectious diseases. Toxicities mandate routine monitoring for common side effects. Given the immunocompromised status of these hosts, aggressive approaches to infectious disease evaluation and, while awaiting microbiological data, empiric antimicrobial therapies are deployed. These can be adjusted based on the presence of neutropenia and specific presentations. Patients who receive systemic corticosteroids and lymphodepletion require prophylaxis for Pneumocystis and herpesviruses. Newer approaches to infectious disease diagnosis (eg, high-throughput sequencing) may identify patients with infection in addition to inflammatory syndromes. Development of more highly specific immune-based therapies may limit both on- and off-target side effects. Recognition of infection remains a key component in the safe deployment of immune-based therapies.

Note

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References

6. Qureshi OS, Zheng Y, Nakamura K, et al. Transl-


CTLA-4 antibodies of IgG2a isotype enhance anti-


12. Motzer RJ, Tannir NM, McDermott DF, et al; CheckMate 214 Investigators. Nivolumab plus ipili-
mumab versus sorafenib in advanced renal-cell can-

13. Ahmadzadeh M, Johnson LA, Hermskirk B, et al. Tumor antigen-specific CDP8 T cells infiltrating the tumor express high levels of PD-1 and are function-


15. Amarnath S, Mangus CW, Wang JC, et al. The PD1-L1 axis converts human TH1 cells into regu-


17. Dong H, Strone SM, Salamoo DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a po-

18. Francisco LM, Salinas VH, Brown KE, et al. PD-L1 regulates the development, maintenance, and func-


20. Horvat TZ, Adel NG, Dang TO, et al. Immune-
related advanced events associated with im-

21. Chuzi S, Tavora F, Cruz M, et al. Combined nivolumab and ipilimumab or mono-


23. Liabbi H, Balmelli C, Kaufmann L, et al. Influenza vaccination of cancer patients during PD-
1 blockade induces serological protection but may raise the risk for immune-related adverse events. J Immunother Cancer 2018; 6:40.


28. Martin SI, Sephr A, Fishman JA. Primary infec-

29. Del Castillo JD, Romero JA, Arguello E, Kry C, Postow MA, Reckamp KL, et al. The spectrum of se-
rious infections among patients receiving immune checkpoint blockade for the treatment of mela-


31. Pradere P, Michot JM, Chambat S, et al. Allergic broncho-pulmonary aspergillosis following treat-


33. Chan MM, Kefford RF, Carlino M, Clements A, Manolios N. Arthritis and tenosynovitis associ-

34. Okuzaki H, Barouk C, Aghamalian N, et al. Clinical features, diagnostic challenges, and management strate-

35. Del Castillo JD, Romero JA, Arguello E, Kry C, Postow MA, Reckamp KL, et al. The spectrum of se-
rious infections among patients receiving immune checkpoint blockade for the treatment of mela-


40. Mufti HV, June CH. Making better chimeric an-