Management of Immuno­therap­y-Related Toxicities, Version 1.2022

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ABSTRACT

The aim of the NCCN Guidelines for Management of Immunotherapy-Related Toxicities is to provide guidance on the management of immune-related adverse events resulting from cancer immunotherapy. The NCCN Management of Immunotherapy-Related Toxicities Panel is an interdisciplinary group of representatives from NCCN Member Institutions, consisting of medical and hematologic oncologists with expertise across a wide range of disease sites, and experts from the areas of dermatology, gastroenterology, endocrinology, neurooncology, nephrology, cardio-oncology, ophthalmology, pulmonary medicine, and oncology nursing. The content featured in this issue is an excerpt of the recommendations for managing toxicities related to CAR T-cell therapies and a review of existing evidence. For the full version of the NCCN Guidelines, including recommendations for managing toxicities related to immune checkpoint inhibitors, visit NCCN.org.

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
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Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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The complete NCCN Guidelines for Management of Immunotherapy-Related Toxicities are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Management of Immunotherapy-Related Toxicities members can be found on page 405. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.
Overview

CAR T cells represent a newer class of immunotherapy agents that is increasingly being incorporated into the treatment regimens of certain refractory or relapsed hematologic malignancies, specifically subtypes of B-cell non-Hodgkin lymphoma (NHL), adult and pediatric B-cell acute lymphoblastic leukemia (ALL), and multiple myeloma (MM). CAR T cells are genetically reprogrammed T cells that express CARs, synthetic receptors that can be designed to target tumor surface antigens. This treatment is a type of adoptive cell therapy and can be referred to as a “living drug.” The intent of CAR T-cell therapy is to induce a potent antitumor immune response by merging the specificity of an antibody with the cytotoxic and memory functionality of T cells. Currently approved CAR T-cell anticancer therapies are generated from autologous T lymphocytes that are genetically modified to recognize and kill tumor cells that express specific antigens. Although CAR T-cell therapy has uniquely powerful activity in several B-cell malignancies, it is also accompanied by specific toxicities requiring specialized expertise in management. This text provides an overview of CAR T-cell therapies and NCCN recommendations for the management of CAR T-cell–related toxicities in patients with cancer based on available evidence and clinical experience. For a discussion of the efficacy data for CAR T-cell therapies, see the NCCN Guidelines for treatment of cancer by site at NCCN.org.

Design and Structure of CARs

CARs are engineered proteins that include an antigen recognition domain, a hinge region, a transmembrane domain, and at least 1 intracellular domain (Figure 1). The antigen recognition domain is an extracellular targeting domain derived from a single chain fragment variable that mimics an antibody’s antigen binding region and recognizes specific antigens expressed on the surface of tumor cells in an HLA-independent manner. For currently approved CAR T cells, the single chain fragment variable recognizes either cluster of differentiation 19 (CD19), for B-ALL and B-NHL, or B-cell maturation antigen (BCMA), for MM. Some agents under investigation have antigen recognition domains with a different structure or target novel antigens. For example, the antigen recognition domain of ciltacabtagene autoleucel is comprised of 2 llama-derived single variable domain on a heavy chain domains that can bind 2 distinct BCMA epitopes.

### PRINCIPLES OF PATIENT MONITORING FOR CAR T-CELL–RELATED TOXICITIES

**Before and During CAR T-Cell Infusion**
- Baseline cardiac assessment, such as echocardiogram. Consult with cardiology if previous cardiac history or concern from assessment.
- Perform central venous access, preferably with double or triple lumen catheter, for IV fluid and possible vasoressors use.
- Perform cardiac monitoring at least at the onset of grade 2 cytokine release syndrome (CRS) until resolution to 5 grade 1, clinically significant arrhythmia, and additionally as clinically indicated.
- Tumor lysis prophylaxis and monitoring are recommended for patients with large tumor burden and aggressive histologies, as per standard institutional guidelines.
- Start seizure prophylaxis on the day of infusion for CAR T-cell therapies known to cause CAR T-cell–related neurotoxicity (eg, levetiracetam 500–750 mg orally every 12 hours for 30 days).
- Baseline neurological evaluation, including ICE scores (for adults) or CAPD scores (for children less than 12 years) prior to CAR T-cell therapy. Consider baseline brain MRI.
- Baseline CRP and serum ferritin

**Post-CAR T-Cell Infusion**
- Hospitalization or extremely close outpatient monitoring at centers with CAR T-cell experience. Close monitoring in the hospital is preferable with current products used for adults; however, extremely close outpatient monitoring may be possible at centers with outpatient transplant experience.
- Hospitalization is warranted for patients at the first sign of CRS or neurotoxicity (including fever, hypotension, or change in mental status).
- Monitor CBC, CMP (including magnesium and phosphorus), and coagulation profile daily.
- CRP and serum ferritin should be rechecked at least 3 times per week for 2 weeks post-infusion. Consider daily checks during CRS.
- CRP can normalize prior to the onset of neurotoxicity.
- Vital signs to allow clinical assessment for CRS should be done at least every 8 hours, or when the patient’s status changes, during the peak window of CRS risk (typically the first 1-2 weeks post-infusion).
- Neurotoxicity assessment should be done at least twice daily or when the patient’s status changes (typically occurs 1-2 weeks post-infusion, but late onset up to a month or later may occur).
- If neurologic concern develops, more frequent assessments are recommended.
- Monitor for CRS, neurotoxicity, and other toxicities for the duration recommended by the CAR product package insert (at least 4 weeks post-infusion for most patients). Patients should refrain from driving or hazardous activities for at least 8 weeks following infusion.

See Overview of CAR T-Cell Therapy-Related Toxicities (CART-2)
CAR T-cell therapies typically have an immunoglobulin-like hinge domain that separates the antigen recognition domain from the transmembrane domain. Approved agents have an IgG4, CD28, or CD8α hinge domain. Optimization of this domain may increase access to the antigen and improve the efficiency of CAR expression and activity. It is critical for CAR constructs to have a transmembrane domain, which enables the CARs to be embedded within the T-cell membrane, and may contribute to CAR T-cell signaling. Most available CAR T-cell therapies use a CD8α or CD28 transmembrane domain.

Early studies also found that CAR constructs require a domain to activate T cells, also known as a T-cell activation domain. All approved agents use a CD3ζ signaling domain for this function. Although the T-cell activation domain was the only intracellular domain included in “first-generation” CAR T-cell constructs, currently available “second-generation” CAR constructs now also include either a CD28 or 4-1BB intracellular costimulatory construct. The binding of a costimulatory receptor such as CD28 or 4-1BB to its cognate ligand on an antigen-presenting cell (APC) provides an additional signal for normal T-cell activation; therefore, inclusion of a CD28 or 4-1BB costimulatory domain within CAR constructs enhances the activation, proliferation, and antitumor activity of CAR T cells (Figure 1). Different costimulatory domains appear to be associated with changes in expansion kinetics, persistence, and possibly toxicity. Unfortunately, efforts to evaluate the superiority of each type of costimulatory domain based on efficacy and safety data have been inconclusive due to various factors, such as differences in other CAR domains, clinical trial design, and toxicity grading systems. Newer-generation CAR constructs with more or different costimulatory domains, as well as with a variety of antigen targets, including solid tumor antigens, are currently under active development.

Figure 1. (Top) For the full activation and proliferation of T cells, 2 signals are required. Signal 1 results from the interaction between the peptide antigen expressed on the antigen presenting cell (APC) and the T-cell receptor. Signal 2 results from the interaction between a costimulatory receptor (such as CD28 or 4-1BB) expressed on T cells and its corresponding ligand expressed on APCs. (Bottom) Chimeric antigen receptors (CARs) are modular structures comprised of an antigen recognition domain, a hinge domain, a transmembrane domain, and at least 1 intracellular domain. Intracellular domains of currently available CAR T cells include a costimulatory domain (derived from CD28 or 4-1BB) and a T-cell activation domain. Incorporation of both types of intracellular domains in a single construct is thought to enable CARs to transduce both signal 1 and signal 2 on binding to the tumor antigen, thereby enhancing the activation and proliferation of CAR T cells.

Targets of Currently Approved CAR T Cells

CD19

CD19 is a transmembrane glycoprotein that is a member of the immunoglobulin superfamily and is an important regulator of B-cell signaling and B-cell activation. Due to its expression at all stages of B-cell differentiation, except for hematopoietic stem cells, CD19 is considered a...
| OVERVIEW OF CAR T-CELL THERAPY-RELATED TOXICITIES | Axicabtagene Ciloleucel, Brexucabtagene Autoleucel, Idecabtagene Vicleucel, Lisocabtagene Maraleucel, and Tisagenlecleucel<sup>a</sup>

**CRS (CART-3)** | • Typical time to onset: 2–3 days; however, CRS may occur as early as hours after infusion and as late as 10-15 days post-infusion
• Typical duration: 7–8 days
• Manifestation may include fever, hypotension, tachycardia, hypoxia, and chills. CRS may be associated with cardiac, hepatic, and/or renal dysfunction.
• Severe events may include hypotension, hypoxia, atrial fibrillation and ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).<sup>b</sup>

**Neurologic Toxicity (CART-4)** | • Typical time to onset: 4–10 days
• Typical duration: 14–17 days
• Transient neurological symptoms can be heterogeneous and include encephalopathy, delirium, aphasia, lethargy, headache, tremor, myoclonus, dizziness, motor dysfunction, ataxia, sleep disorder (eg, insomnia), anxiety, agitation and signs of psychosis.
• Severe events including seizures, depressed level of consciousness, as well as fatal and serious cases of cerebral edema, have occurred.

**Hemophagocytic Lymphohistiocytosis/Macrophage-Activation Syndrome (HLH/MAS) (CART-3)** | • Criteria for considering HLH/MAS:
  - Rapidly rising and high ferritin (>5000 ng/mL) with cytopenias in the context of fever, especially if accompanied by any of the following:
    - Grade 3 increase in serum bilirubin, AST, ALT
    - Grade 3 oliguria or increase in serum creatinine
    - Presence of hemophagocytosis in bone marrow or organs based on histopathologic assessment of cell morphology and/or CD68 IHC.

**Miscellaneous** | • Patients may exhibit cytopenias for weeks to months following lymphodepleting chemotherapy and CAR T-cell therapy infusion.
• Long-term B-cell aplasia and hypogammaglobulinemia can occur in patients with a complete remission after CAR T-cell therapy infusion.
• After anti-CD19 CAR T-cell therapy, consider monthly 400–500 mg/kg IVIG replacement for select patients with hypogammaglobulinemia (those with serum IgG levels <400–600 mg/dL AND serious or recurrent infections [particularly bacterial]). Continue IVIG until serum IgG levels normalize and infections resolve. The optimal IgG threshold to use may depend on patient characteristics and infection frequency/severity.

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**BCMA**

BCMA is a transmembrane protein that is a member of the tumor necrosis factor receptor superfamily.<sup>29–31</sup> Expressed on the surface of mature B cells, but not naïve B cells or other hematopoietic cells, BCMA is thought to promote the survival of plasma cells in the bone marrow.<sup>29,30,32,33</sup> BCMA was identified as a promising biomarker and drug target for MM based on several findings. Serum BCMA levels were observed to be higher in patients with MM compared with those without MM.<sup>34,35</sup> Multiple studies found that BCMA is expressed in malignant cells from patients with MM.<sup>36–38</sup> Furthermore, over-expression of BCMA promoted cell proliferation in both in vitro and in vivo models.<sup>40</sup> Currently the only BCMA-targeting CAR T-cell therapy approved in the United States is idecabtagene vicleucel, which was approved in 2021 for the treatment of MM.<sup>8</sup> Ciltacabtagene autoleucel is another BCMA-targeted CAR T-cell therapy that is being considered by the FDA for approval for the treatment of relapsed or refractory MM.<sup>41</sup>

**Overall CAR T-Cell Treatment Schema**

CAR T-cell therapy is a multistep process that can take several weeks to complete.<sup>42</sup> The first step is leukapheresis, the procedure of collecting white blood cells (including T cells) from a patient’s blood.<sup>4,43–44</sup> The cells are subsequently sent to a laboratory, where T cells are isolated, activated, and transduced with a CAR transgene (typically delivered via a lentiviral or retroviral vector). Transduced T cells are then expanded, harvested, and prepared for infusion.<sup>4,43–45</sup> Finally, patients are infused with the CAR T cells. Prior to infusion, patients undergo lymphodepletion chemotherapy (LDC). The goal of LDC is to prevent immunologic rejection of the infused CAR T cells to maximize their expansion and persistence. LDC typically consists of fludarabine and cyclophosphamide.<sup>5,10,46–47</sup> Bendamustine is an alternative option before tisagenlecleucel infusion in patients with relapsed or refractory diffuse large B-cell lymphoma who had a prior
Despite the promising benefits of CAR T-cell therapies in the treatment of certain cancers, clinicians need to be aware of the serious and potentially fatal toxicities that may occur with the use of this newer class of agents. Overall, the most common and unique toxicities associated with CAR T-cell therapies are cytokine release syndrome (CRS) and neurotoxicity, and are entirely distinct from the immune-related adverse events that occur with the use of immune-checkpoint inhibitors. In addition, some toxicities (eg, hypogammaglobulinemia) are a direct result of on-target/off-tumor activity of the CAR T cells, and others (eg, infections) may occur as an indirect consequence of the immunosuppressed state of the patient. Fortunately, CAR T-cell therapy–related toxicities are almost always reversible and can be managed by the judicious use of immunosuppressive medications.

Principles of Patient Monitoring
The NCCN panel has provided recommendations on monitoring patients who receive CAR T-cell therapies based on available evidence and clinical experience, as detailed subsequently and on CART-1 (page 388). For effective toxicity management, clinicians need to closely monitor patients before, during, and after CAR T-cell infusions to ensure the early recognition of and intervention for specific adverse reactions related to treatment. Patients with underlying organ dysfunction may experience additional complications when treated with CAR T-cell therapies; proactive management and multidisciplinary involvement is especially crucial for these patients.

### Before and During CAR T-Cell Infusion

Due to the potential cardiac manifestations of CAR T-cell–related toxicities, especially for those with underlying risk, a baseline cardiac assessment (such as an echocardiogram) is recommended. Consultation with cardiology may be warranted for patients with cardiovascular comorbidities at baseline. Central venous access,
preferably with double or triple lumen catheter, for intra-
venous fluid and possible vasopressor use is recom-
mended. Cardiac monitoring should be performed at the
onset of clinically significant arrhythmia and additionally
as clinically indicated. For patients with large tumor burden
and aggressive histologies, standard tumor lysis prophylaxis
and monitoring are recommended. Seizure prophylaxis
(e.g., levetiracetam 500–750 mg orally every 12 hours for
30 days) are often used on the day of infusion, espe-
cially for CAR T-cell therapies that are known to cause
more severe CAR T-cell–related neurotoxicity (e.g., axi-
cabtagene and brexucabtagene). Because of the poten-
tial for severe neurotoxicity, all patients should receive
baseline neurologic evaluation, including immune effector
cell-associated encephalopathy (ICE) scores (for adults) or
Cornell Assessment of Pediatric Delirium (CAPD) scores
(for children less than 12 years) prior to CAR T-cell therapy.
Some centers require baseline brain MRI. Assessment of
C-reactive protein (CRP) and serum ferritin levels is rec-
ommended at baseline.

Post-CAR T-Cell Infusion
Hospitalization or extremely close outpatient monitoring
at centers with CAR T-cell experience is recommended.

Close monitoring in the hospital is preferred with current
products for adults; however, extremely close outpatient
monitoring may be possible at centers with outpatient
transplant experience. Hospitalization is warranted for
patients at the first sign of CRS or neurotoxicity, including
fever, hypotension, or change in mental status. Complete
blood count, complete metabolic panel (including mag-
nesium and phosphorus), and coagulation profiles
should be monitored daily. CRP and serum ferritin
should be rechecked at least 3 times per week for 2 weeks
postinfusion. Daily levels can be considered if CRS
occurs. Vital signs to allow clinical assessment for CRS
should be done at least every 8 hours, or when the
patient’s status changes, during the peak window of CRS
risk, which is typically the first 1 or 2 weeks postinfusion.
The time to onset of fever, and therefore CRS, may be
earlier in patients treated with CD28 costimulatory
domain-containing products (xicabtagene ciloleucel
and brexucabtagene autoleucel) compared with 4-1BB
costimulatory domain-containing products (lisagenle-
cleucel, lisocabtagene maraleucel, and idecabtagene
vicleucel). Note that CRS may normalize before the onset
of neurotoxicity. Neurotoxicity assessment (as described
subsequently) should be done at least twice daily or
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CAR T-CELL–RELATED NEUROTOXICITY GRADING

**Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool**

- Orientation: orientation to year, month, city, hospital: 4 points
- Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points
- Following commands: ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”): 1 point
- Writing: ability to write a standard sentence (eg, “Our national bird is the bald eagle”): 1 point
- Attention: ability to count backwards from 100 by 10: 1 point

<table>
<thead>
<tr>
<th>Neurotoxicity Domain</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICE score</td>
<td>7-9</td>
<td>3-6</td>
<td>0-2</td>
<td>0 (patient is unarousable and unable to perform ICE)</td>
</tr>
<tr>
<td>Depressed level of consciousness</td>
<td>Awakens spontaneously</td>
<td>Awakens to voice</td>
<td>Awakens only to tactile stimulus</td>
<td>Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, stupor or coma</td>
</tr>
<tr>
<td>Seizure</td>
<td>N/A</td>
<td>N/A</td>
<td>Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention</td>
<td>Life-threatening prolonged seizure (&gt;5 min); or repetitive clinical or electrical seizures without return to baseline in between</td>
</tr>
<tr>
<td>Motor findings</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Diffuse focal motor weakness such as hemiparesis or paraparesis</td>
</tr>
<tr>
<td>Elevated ICP/cerebral edema</td>
<td>N/A</td>
<td>N/A</td>
<td>Focal/local edema on neuroimaging</td>
<td>Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing’s triad</td>
</tr>
</tbody>
</table>


**CAR T-CELL–RELATED NEUROTOXICITY SYNDROME (ICANS) Consensus Grading for Adults**

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

- A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
- Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
- Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Management Strategies for Specific CAR T-Cell Therapy-Related Toxicities

An overview of CAR T-cell therapy–related toxicities is shown in the algorithm (see CART-2, page 390). The presentation and the management of specific toxicities related to CAR T-cell therapies are discussed in the following sections. It is critical to recognize that the exact timing, frequency, severity, and optimal management of CAR T-cell-related toxicities vary between products, and are likely to vary further as newer products gain approval. The NCCN Guidelines attempt to provide guidance that is generally applicable, but clinicians must imperatively consult their institutional guidelines and the prescribing information for individual agents for specific management strategies.

**CRS**

CRS has been reported with all FDA approved CAR T-cell therapies and is one of the most common adverse events that occur with both CD19- and BCMA-directed CAR T cells. Due to the different grading scales used to assess CRS severity in clinical trials, differences in CAR T-cell design and generation, and clinical trial design (including study population, dose regimen, and treatment protocols), a wide range of CRS rates have been reported with different CAR T-cell therapies. Therefore, toxicity rates from trials of different agents may not always be directly comparable.

**Presentation and Onset**

CRS is defined by the American Society for Transplantation and Cellular Therapy (ASTCT) as a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells (eg, lymphocytes, myeloid cells). Specific CRS manifestations may include fever, hypotension, tachycardia, hypoxia, and...
The overactivation of immune effector cells leads to the release of inflammatory cytokines, which ultimately results in endothelial injury and capillary leak that can present clinically as hemodynamic instability and organ dysfunction. IL-6, IL-1, IFN-γ, and TNF-α are involved in the pathogenesis of CRS. IL-6 is considered a central mediator of CRS and is thought to provide an activating signal to CAR T cells. In normal conditions, IL-6 binds to membrane-bound IL-6 receptor (IL-6R) on certain immune effector cells and has anti-inflammatory properties; this is referred to as the classic signaling pathway. However, when IL-6 levels are increased (such as during CRS), IL-6 may bind to the soluble form of IL-6R (sIL-6R) and induce a proinflammatory response via activation of a trans signaling pathway.

**Risk Factors**

Several risk factors for severe CRS have been identified, although these vary across studies and likely across indications. These generally (but not always) include increased CAR T-cell expansion and higher tumor burden (including high disease burden in bone marrow).

**Grading**

The NCCN Guidelines follow the ASTCT Consensus Grading scale for CRS, which used a consensus approach to harmonize the various CRS definitions and grading systems that were previously used in pivotal clinical trials. The grades are defined by presence of fever (≥38°C), the severity of hemodynamic compromise, and that of hypoxia. Fever defines the onset of CRS, with a temperature of ≥38°C not attributable to any other cause being the only symptom required for the classification as...
grade 1 CRS. Other types of organ dysfunction were not included in the ASTCT grading criteria. Laboratory parameters (eg, CRP or specific cytokines) were also not included in the definition or the grading scale for CRS, as it was deemed that there was insufficient evidence to support their use in this context.60 However, these parameters may become more important in the future with additional studies. Refer to CART-3 in the algorithm (page 391) for the adapted definitions of each CRS grade.

Overall Management Strategy for CRS
Management of CRS in patients who received CAR T-cell therapy consists of both direct targeting and nonspecific immunosuppressive strategies to counter the overactive immune cells and increased cytokine levels. Generally, patients are administered a combination of tocilizumab and corticosteroids, in addition to receiving supportive care.

Anti-IL-6 Therapy
Tocilizumab is a humanized, IgG1κ anti-IL-6R antibody that was approved by the FDA in 2017 for the treatment of severe or life-threatening CAR T-cell–induced CRS in adults and pediatric patients aged 2 years and older.72,73 Tocilizumab binds to both soluble and membrane-bound IL-6R and is hypothesized to block the downstream signal transduction pathways implicated in CRS.74 Tocilizumab is currently the only anti-IL-6 therapy approved by the FDA for the treatment of CRS.

This approval was based on a retrospective study of patients with hematologic malignancies who developed severe or life-threatening CRS and received tocilizumab after treatment with tisagenlecleucel (n=45) or axicabtagene ciloleucel (n=15) in prospective trials.72,73 CRS was resolved within 14 days of the first tocilizumab dose in 69% and 53% of patients in the tisagenlecleucel and axicabtagene ciloleucel cohorts, respectively. No adverse reactions were reported in this study, although infections, cytopenias, elevated liver enzymes, and lipid dysregulation have been reported with tocilizumab use in clinical trials for other conditions.72,73

Although it is approved for severe or life-threatening cases, many centers and the prescribing information for individual agents advise using tocilizumab at lower grades of CRS.6–8,75 For example, the prescribing information for axicabtagene ciloleucel states that tocilizumab can be considered for grade 1 CRS if CRS symptoms persist for more than 24 hours.6 This is supported by data from an exploratory safety management cohort of the ZUMA-1 trial, which demonstrated that patients who received earlier intervention with tocilizumab and/or corticosteroids for CRS (as early as grade 1) had numerically lower rates of grade 3 or greater CRS (2%) compared with patients who received intervention at later CRS grades (12%).76

A proposed alternative to tocilizumab is siltuximab, an anti-IL6 antibody that is approved for the treatment of Castleman’s disease.77 By targeting the same pathway as tocilizumab, siltuximab would theoretically also be a viable treatment option for CRS. An additional potential advantage of siltuximab over tocilizumab is that the latter targets the receptor for IL-6 without sufficient central nervous system (CNS) penetration. This causes a transient rise in serum IL-6 levels, which some have postulated may worsen neurotoxicity by increasing cerebrospinal fluid IL-6 levels.65,78 This potential increase in the neurotoxicity is an important concern in general with the use of tocilizumab for CRS and may support the more frequent use of corticosteroids in conjunction with tocilizumab in more recent management guidelines. For persistent refractory CRS after 1 or 2 doses of tocilizumab, the guideline recommends considering the addition of corticosteroids. Despite the theoretical advantage of the IL-6-targeting siltuximab, there is limited data in the formal clinical trial setting supporting the use of this agent for CRS.72,73 Anakinra, an IL-1Ra antagonist currently approved for the treatment of several inflammatory conditions,80 is considered another potential alternative to tocilizumab for the treatment of CRS following CAR T-cell therapy. The rationale for targeting IL-1 is primarily based on evidence from two preclinical studies, which demonstrated that IL-1 blockade protected against CRS in mouse models without impacting the antitumor activity of the CAR T-cells.65,66 While there are some reports in patients that suggest anakinra may be effective for managing CAR T-cell therapy–associated CRS,81,82 there is also limited data supporting use of anakinra in this setting. Data from ongoing clinical trials will shed light on whether siltuximab and anakinra are viable alternatives to tocilizumab for the treatment of CRS.

Corticosteroids
Corticosteroids play an important role in CRS management in addition to anti-IL-6 therapy. Although the use of corticosteroids may alleviate the symptoms of CRS, there is theoretical concern that the use of higher doses of steroids could suppress CAR T-cell expansion and persistence, and therefore reduce the antitumor benefit of CAR T-cells.83 However, this concern has not been supported in most studies, and corticosteroids are a cornerstone of CRS management. Furthermore, in the context of axicabtagene, the use of corticosteroids, either with milder CRS (or even prophylactically) appear to be associated with preserved efficacy, lower risk of severe CRS, and lower cumulative use of steroids.76,84,85 The most commonly used corticosteroids are dexamethasone and methylprednisolone. For patients with neurologic symptoms, dexamethasone may be preferred due to better penetration of the blood–brain barrier.86 If steroids are used for
the management of CRS, a rapid taper should be used when symptoms begin to improve.

Options for Steroid-Refractory CRS
If CRS does not improve after tocilizumab and steroids, workup for infections need to be considered and managed as appropriate. In addition to siltuximab and anakinra, other agents can be considered for patients who are refractory to both tocilizumab and corticosteroids, including the Janus associated kinase (JAK) 1/2 inhibitor ruxolitinib, cyclophosphamide, extracorporeal cytokine adsorption with continuous renal replacement therapy, intravenous IgG (IVIG), and antithymocyte globulin; however, data supporting the use of these agents are mostly anecdotal or from small case series.®+ This will likely change in the future as results from ongoing clinical trials mature.

NCCN Recommendations for CRS
Urgent intervention is required to prevent the progression of CRS; however, other potential causes of inflammatory response, including infections and malignancy progression, should be ruled out. Empirical treatment for infections is warranted in patients who are febrile and neutropenic. Organ toxicities associated with CRS may be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, but clinicians should be aware that these do not influence CRS grading under the ASTCT system. Organ toxicities should receive a thorough workup and appropriate management. Fever is defined as a temperature that is above 38°C that is not attributable to any other cause. For patients with CRS who receive antipyretics or anti-cytokine therapy, such as tocilizumab or steroids, fever is not required to grade subsequent CRS severity. For these cases, hypotension or hypoxia will determine CRS grading. See subsequent sections (and CART-3 and CART-3A [pages 391 and 392]) for detailed treatment recommendations for CRS by grade.

In general, after each dose of anti-IL-6 therapy or corticosteroids, the need for subsequent dosing should be assessed. As per the prescribing information for axicabtagene ciloleucel, consider the use of prophylactic corticosteroids in patients after weighing the potential benefits and risks. Steroid prophylaxis for axicabtagene ciloleucel is dexamethasone 10 mg orally once daily for 3 days, with the first dose starting before CAR T-cell infusion; however, use of dexamethasone in this setting may increase the risk of grade 4 and prolonged neurologic toxicities. Additionally, antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity.

Grade 1 (fever ≥38°C): For prolonged CRS (longer than 3 days) in patients or those with significant symptoms, comorbidities, and/or are elderly, 1 dose of tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg) can be considered. For patients treated with axicabtagene ciloleucel or brexucabtagene autoleucel, tocilizumab can be considered if CRS symptoms persist for ≥24 hours. For patients treated with lisocabtagene maraleucel, tocilizumab for grade 1 CRS that develops <72 hours after infusion, and consider adding 1 dose of dexamethasone 10 mg; for CRS that develops ≥72 hours after infusion, treat symptomatically. For patients who received idecabtagene or lisocabtagene, consider administering dexamethasone 10 mg intravenously every 24 hours for early-onset CRS (<72 hours after infusion). Additional supportive care for grade 1 CRS includes sepsis screen and empirical broad spectrum antibiotics (especially in neutropenic patients), judicious use of intravenous fluids, electrolyte repletion, and management of specific organ toxicities.

For grade 2 (fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula or blow-by), tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg/dose) is recommended and can be repeated in 8 hours if no improvement is observed. No more than 3 doses should be administered in 24 hours, with a maximum of 4 doses total. Dexamethasone 10 mg intravenous every 12 to 24 hours (or equivalent) can be considered (depending on the product) for persistent refractory hypotension after 1 or 2 doses of an anti-IL-6 therapy. Note that some centers and manufacturer recommendations suggest the use of corticosteroids routinely for grade 2 CRS. Cardiac monitoring should be performed at least at the onset of grade 2 CRS until resolution to grade 1 or less. Additional supportive care for grade 2 CRS includes intravenous fluid bolus as needed, management as per grade 3 if no improvement is seen within 24 hours of starting anti-IL-6 therapy, and symptomatic management of organ toxicities. For those with persistent refractory hypotension after 2 fluid boluses and anti-IL-6 therapy, clinicians should start vasopressors, transfer the patient to an ICU, consider an echocardiogram, and initiate more thorough methods of hemodynamic monitoring. Telemetry and electrocardiogram, along with assessment of troponin and brain natriuretic peptide should be performed if tachycardia persists.

For grade 3 (fever with hypotension requiring a vasopressor with or without vasopressin or hypoxia requiring high-flow cannula, face mask, nonrebreather mask, or Venturi mask), anti-IL-6 therapy as per grade 2 is recommended, if the maximum dose is not reached within a 24-hour period. Dexamethasone 10 mg intravenous (or equivalent) should be administered every 6 hours. Patient can be managed as grade 4 if refractory to this treatment. Additional supportive care
for grade 3 CRS includes the transfer of the patient to the ICU, an echocardiogram, hemodynamic monitoring, supplemental oxygen, intravenous fluid bolus and vasopressors as needed, and symptomatic management of organ toxicities.

For grade 4 (fever with hypotension requiring multiple vasopressors, excluding vasopressin, and/or hypoxia requiring positive pressure [eg, continuous positive airway pressure, bilevel positive airway pressure, intubation, mechanical ventilation]), anti-IL-6 therapy as per grade 2 is recommended, if the maximum dose is not reached within a 24-hour period. Dexamethasone 10 mg intravenous (or equivalent) should be administered every 6 hours. If refractory, 3 doses of methylprednisolone 1000 mg/day intravenous can be considered; dosing every 12 hours can also be considered. For example, methylprednisolone intravenous 1,000 mg/day can be administered for 3 days, followed by a rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days. Other agents such as anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG, antithymocyte globulin, or extracorporeal cytokine adsorption with continuous renal replacement therapy might also be considered.

Tocilizumab availability may be limited due to the FDA Emergency Use Authorization for hospitalized patients with severe COVID-19. Under these conditions, the NCCN panel recommends that the use of tocilizumab be limited to a maximum of 2 doses during a CRS episode. Clinicians should also consider using steroids more aggressively (eg, with the first or second dose of tocilizumab). If necessary, replacement of the second dose of tocilizumab with siltuximab or anakinra can be considered, although again there is limited evidence to support this approach and neither of these agents have received FDA approval for the treatment of CRS.

**Neurotoxicity**

Neurotoxicity is another adverse event that commonly occurs with CAR T-cell therapies. As with CRS rates, neurotoxicity incidence rates after CAR T-cell therapy reported in clinical trials vary widely. This is due to many factors, including differences in grading scales, CAR design and development, and clinical trial design. The rates of CAR T-cell-related neurotoxicity can vary across products, and clinicians should familiarize themselves with their frequency for the product(s) they are using.

**Presentation and Onset**

The neurotoxicity that occurs with CAR T-cell therapies has been termed **immune effector cell-associated neurotoxicity syndrome** (ICANS) by the ASTCT, and it is defined as a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells.60

Occasionally, neurologic adverse events may occur in the context of CRS, especially headaches. Neurologic symptoms due to CRS typically happen earlier than ICANS and lack the more generalized encephalopathy and frequent language disturbances of the latter. It is very important to remember that ICANS, unlike CRS, is generally unresponsive to tocilizumab, which is unable to cross the blood–brain barrier when administered intravenously.64,94,95 Data from a preclinical study showed that prophylactic treatment with tocilizumab did not prevent CAR T-cell–induced neurotoxicity in a mouse model.65 Similarly, data from a small study in 43 patients who received CD19-directed CAR T-cell therapy suggested that early intervention therapy with tocilizumab did not have an impact on overall neurotoxicity rates or in preventing severe neurotoxicity events.96 Other studies have also found that tocilizumab did not alleviate neurologic toxicities in patients treated with CD19-directed CAR T-cell therapies.47,94

Transient neurologic symptoms reported to occur with CAR T-cell therapies can be heterogeneous and include encephalopathy, delirium, aphasia, lethargy, headache, tremor, myoclonus, dizziness, motor dysfunction, ataxia, sleep disorder (eg, insomnia), anxiety, agitation, and signs of psychosis. Serious events, such as seizures, depressed level of consciousness, and fatal and serious cases of cerebral edema, have also occurred. Despite similarities with other encephalopathies, the neurotoxicity associated with CAR T-cell therapy has distinct common features, including language disturbances, encephalopathy, and motor dysfunction, which are captured in the ASTCT consensus grading criteria for ICANS.63,64,94,97 Headache alone is not considered a useful diagnostic symptom for ICANS, as it is very common and frequently co-occurs with fever. The ASTCT consensus guidelines include intracranial pressure and edema as domains for ICANS grading, but cerebral edema is very rare and it is unclear if it arises from a distinct pathophysiology.60

The typical time to onset of neurotoxicity is 4 to 10 days after receiving CAR T-cell therapy, with a duration of 14 to 17 days.52,54–57,64,94,98 The duration may be slightly shorter with BCMA-directed CAR T-cell therapies.59,99

**Pathophysiology**

Although the pathophysiology is not yet fully understood, CAR T-cell-related neurotoxicity is thought to occur as a result of endothelium cell activation and leak in the central nervous system, leading to elevated inflammatory
cytokines in the cerebrospinal fluid (CSF). Several cytokines are implicated in the pathophysiology of CAR T-cell related neurotoxicity, including IL-6, IFNγ, and TNFα.

**Risk factors**

CRS is considered a strong risk factor for ICANS, with the severity of CRS correlating with that of ICANS. Other possible ICANS risk factors may include higher disease burden, high baseline inflammatory state, pre-existing neurologic comorbidities, and higher CAR T-cell dose. High-grade ICANS is more common with CD19-directed CAR than BCMA-directed CAR. As with CRS, reported risk factors and incidence vary across studies.

**Grading**

The NCCN panel recommends following the ASTCT ICANS Consensus grading scale, which consists of an ICE score as a standardized assessment for encephalopathy, as well as the following 4 neurologic domains: level of consciousness, seizure, motor findings, and elevated intracranial pressure/cerebral edema. The pediatric version incorporated the CAPD score in place of ICE assessment in children younger than 12 years or those with developmental delay. The overall ICANS grade is the most severe symptom in any of the 5 domains.

By including only the most common and specific neurotoxicity symptoms that would trigger specific interventions, the ASTCT ICANS consensus grading scale improves the ease of grading compared with the method used by earlier trials, which was to grade by CTCAE multiple individual and often overlapping terms (such as encephalopathy and delirium). For seizures, the ASTCT ICANS grading scale considers any single clinical or subclinical electrographic seizure of any type to be a grade 3 event, with prolonged or repetitive clinical or subclinical seizures without a return to baseline in between to be grade 4.

The ICE component of the ASTCT ICANS grading scale is derived from a 10-point screening tool that enables the objective grading of overlapping encephalopathy terms. ICE is a modified version of the CARTOX-10 screening tool, and evaluates the following abilities: (1) orientation, (2) naming, (3) command following, (4) writing, and (5) attention (see CART-4, page 393). In addition to contributing to the grade of ICANS, the ICE assessment can be used daily or every shift as a screen for the onset of ICANS during the at-risk period.

Please refer to CART-4 (page 393) for additional details on use of the ICE screening tool and the ASTCT ICANS grading scale.
Dexamethasone 10 mg intravenous every 6 hours or methylprednisolone (1 mg/kg intravenous every 12 hours) is recommended for grade 3 neurotoxicity; for patients who received axicabtagene ciloleucel or brexucabtagene autoleucel, methylprednisolone 1 gram daily for 3 to 5 days may be preferable. High-dose corticosteroids are the recommended treatment option for grade 4 neurotoxicity. For example, methylprednisolone IV 1,000 mg/day (may consider twice a day) for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days. Convulsive status epilepticus should be treated as per institutional guidelines.

Patients with grade 3 neurotoxicity or higher should receive ICU care. Clinicians should consider repeating neuroimaging (CT or MRI) every 2 or 3 days if the patient has persistent neurotoxicity that is grade 3 or higher. Patients should also undergo assessment for papilledema or other signs of elevated intracranial pressure. If elevated intracranial pressure is excluded, a diagnostic lumbar puncture may be considered for patients with grade 3 or 4 neurotoxicity. Antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS or neurotoxicity. If steroids are given for the management of ICANS, a fast taper should be used when there is improvement.

Tocilizumab can be used for the treatment of CRS in patients with neurotoxicity and CRS occurring concurrently. It may be preferable to use corticosteroids alone in the patient with grade 1 CRS (fever alone) and concurrent higher grade neurotoxicity due to the possibility that tocilizumab may exacerbate neurotoxicity. Consider transferring the patient to the ICU if the neurotoxicity is associated with CRS that is grade 2 or higher.

**Hemophagocytic Lymphohistiocytosis/Macrophage-Activation Syndrome**

Hemophagocytic lymphohistiocytosis/macrophage-activation syndrome (HLH/MAS) can be described as severe immunologic syndromes caused by uncontrolled immune activation. This is thought to be the result of hyperactivation of macrophages and lymphocytes, increased production of proinflammatory cytokines, infiltration of lymphocytes and histiocytes in tissues and organs, and immune-mediated multiorgan failure.75,103–105 Unlike HLH/MAS that occurs due to underlying genetic mutations (referred to as primary HLH/MAS), CAR T-cell therapy–induced HLH/MAS is considered a secondary HLH/MAS, as it is caused by an immune trigger.104,106 One recent study estimated that HLH/MAS occurs in 3.5% of patients treated with CAR T-cell therapy.107 However, the true incidence of HLH/MAS has been debated, in part due to the close overlap in CRS and HLH/MAS symptoms.75,106,108

A clear diagnosis of HLH/MAS after CAR T-cell therapy can be difficult, because the clinical features and laboratory abnormalities can have substantial overlap with CRS (eg, high fevers, increased ferritin levels).60,63,75,109,110 Most patients with moderate to severe CRS have laboratory abnormalities that meet the classic criteria for HLH, such as elevated CRP, hyperferritinemia, cytopenias, hypofibrinogenemia, coagulopathy, and elevated levels of several serum cytokines, including IL-6, INFγ, sIL-2Rα, and granulocyte macrophage colony-stimulating factor.60,104 Clinical features associated with CAR T cell–induced HLH include fever, multiorgan dysfunction, and CNS issues (eg, headaches, vision disturbances, and issues related to walking), but patients may not have hepatosplenomegaly or evidence of hemophagocytosis.60,75,103

Because HLH/MAS symptoms resolve with the clinical management and resolution of CRS in most cases (and therefore there is no need to directly treat HLH/MAS), an expert panel convened by the ASTCT decided to exclude HLH/MAS from the definition of CRS.60 Furthermore, a separate grading scale for HLH/MAS was not established, due to the degree of similarity with CRS and the lack of available CTCAE terms. Clinical management of HLH/MAS mirrors the strategies used for managing CRS, which consists of anti–IL-6 therapy and aggressive use of corticosteroids; the overall goal of this strategy is to suppress the overactive immune cells responsible for the symptoms.75 A high mortality rate has been linked with refractory HLH/MAS,111,112 and therefore prompt treatment is required. Some cases of late-onset HLH/MAS-like pathology may occur, which may be tocilizumab refractory. For these cases, corticosteroids and anakinra should be considered. There have been anecdotal reports of the resolution of HLH with anakinra administration.107,113,114 As a last resort, etoposide may be an option for HLH/MAS that shows no improvement with these measures; this is primarily based on clinical experience with non–CAR T cell–associated HLH.75,104-106,111-115 In general, this approach is not recommended due to etoposide’s toxicity to T lymphocytes and lack of data in the CAR T-cell setting. Intrathecal cytarabine is another potential option for patients with HLH-associated neurotoxicity,75 however, data supporting use of this agent in this setting is lacking.

**NCCN Recommendations**

The NCCN Panel recommends the following criteria for when there is clinical concern for HLH/MAS: (1) Rapidly rising and high ferritin (>5000 ng/mL) with cytopenias in the context of fever, especially if accompanied by any of the following: grade ≥3 increase in serum bilirubin, aspartate aminotransferase, alanine transaminase; grade ≥3 oliguria or increase in serum creatinine; or grade ≥3 pulmonary edema; (2) presence of hemophagocytosis in...
bone marrow or organs based on histopathologic assessment of cell morphology and/or CD68 immunohistochemistry.

For HLH/MAS, treat as per CRS with tocilizumab and steroids, although the suspicion of HLH/MAS should prompt consideration of higher doses of steroids at a given CRS grade. If no improvement is observed within 48 hours, consider addition of anakinra to corticosteroids. Etoposide or intrathecal cytarabine can be considered as a last resort for HLH with CNS involvement.

**Hypogammaglobulinemia**

Hypogammaglobulinemia is another potential risk associated with CAR T-cell therapy, and has been reported in up to 53% of patients who received CAR T-cell therapy in registrational clinical trials.5–10

Characterized by low antibody levels in the blood and an increased risk of infection,116 hypogammaglobulinemia is a consequence of extremely low B-cell or plasma cell counts, referred to as B-cell or plasma cell aplasia, respectively. These types of aplasia are an expected result of the on-target/off-tumor activity associated with the successful use of CAR T-cell therapy, due to the presence of the targeted antigens on nonmalignant B cells or plasma cells.1,106

Long-term hypogammaglobulinemia can occur, even in patients with a complete remission after CAR T-cell therapy infusion. Hypogammaglobulinemia may be treated with the infusion of IVIG, a fractionated blood product derived from the plasma of thousands of individuals and contains antibodies against a wide range of pathogens.117,118 However, at present there is no compelling data for the use of IVIG after CAR T-cell infusion in patients who do not experience frequent or severe infections with hypogammaglobulinemia, and institutional practices vary.

**NCCN Recommendations**

After anti-CD19 CAR T-cell therapy, consider monthly 400–500 mg/kg IVIG replacement for select patients with hypogammaglobulinemia (those with serum IgG levels <400–600 mg/dL and serious or recurrent infections [particularly bacterial]). IVIG should be continued until serum IgG levels normalize and infections are resolved. The optimal IgG threshold to use may depend on patient characteristics and infection frequency or severity.

**Hematologic Toxicities**

Patients who receive CAR T-cell therapy are also at risk for hematologic toxicities, including prolonged cytopenia, such as neutropenia, thrombocytopenia, anemia, and/or leukopenia.

Acute cytopenia is common in patients treated with CAR T-cell therapy; however, grade 3 or higher prolonged cytopenia that remained unresolved weeks or months after infusion are reported frequently in patients treated with CAR T-cell therapies.5–10 Clinicians should be aware that cytopenia may occur in the weeks to months after lymphodepleting chemotherapy and CAR T-cell therapy infusion.

Factors that may contribute to prolonged cytopenias include CRS and ICANS severity, disease burden, the number of prior therapies, baseline blood cell counts, peak CRP and ferritin levels, and CAR construct.62,119,120 Although lymphodepletion may be a contributing factor, the pathophysiology of prolonged cytopenia after CAR T-cell infusion remains unclear.121

Cytopenias are generally managed with transfusion or growth factor support, if the possibility of myelodysplastic syndrome has been ruled out.103,122,123 Growth factors may be considered for persistent cytopenias. The guidelines do not provide specific recommendations on the management of CAR T-cell therapy–associated cytopenia in the current version of the guidelines.

**Infections**

Infections after CAR T-cell therapy are common and have been reported in up to 70% of patients who received CAR T-cell therapy in registrational clinical trials for approved agents.6–10 Bacterial, viral, and fungal infections have all been reported with use of CAR T-cell therapy.124,125 Most infections occur soon after infusion and may occur for a number of reasons, including lymphodepleting or antecedent chemotherapy, CAR T cell–mediated B-cell or plasma cell depletion, prolonged cytopenias, corticosteroid treatment, or as a consequence of the malignancy itself.103,126 The severity of CRS may also be associated with an increased risk of acute infections.124–126 Other potential risk factors for severe infections within the first 30 days include ICANS, tocilizumab, and corticosteroid use.121 Patients remain at increased risk of complications for weeks to months after infusion.58,124–127,128 Infections are generally managed using agents that target the source of infection. Additionally, prophylaxis against vesicular stomatitis virus/herpes simplex virus reactivation and *Pneumocystis jirovecii* pneumonia infections is generally used for patients undergoing CAR T-cell therapy and for several months after. The decision to administer antibacterial or antifungal prophylaxis should be risk-adjusted based on patient characteristics, such as prior lines of suppressive therapy, infection history, etc.129 IVIG replacement therapy may be used for select patients. The guidelines recommend IVIG replacement for certain patients treated with anti-CD19 CAR T-cell therapy who experience serious or recurrent infections (particularly bacterial) concurrently with hypogammaglobulinemia. For additional guidance on infections and vaccinations, see NCCN Guidelines for...
Management of Immunotherapy-Related Toxicities, Version 1.2022

the Prevention and Treatment of Cancer-Related Infections (available at NCCN.org).

**Summary**

CAR T-cell therapies are a novel and revolutionary class of cancer therapies that have shown efficacy against several types of cancers. However, data from clinical trials have shown that all approved CAR T-cell therapies are associated with unique adverse reactions, including CRS and neurologic toxicities. Patient monitoring before, during, and after CAR T-cell therapy is critical for early recognition of potential toxicities and timely intervention. CAR T-cell-related toxicities can generally be reversed through the use of appropriate management strategies, such as immunosuppressive agents. Due to the changing therapeutic landscape, recommendations for management of CAR T-cell toxicities will continue to evolve as data emerge from clinical trials evaluating novel treatment options.

**References**

Management of Immunotherapy-Related Toxicities, Version 1.2022


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<td>Sandip Patel, MD</td>
<td>AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Cultivar; ES Lily and Company; Fate; Genentech, Inc.; Incyte Pharmaceuticals; Merck &amp; Co., Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.</td>
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<td>Pradnya Patil, MD</td>
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<td>Sunil Reddy, MD</td>
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<td>Mabel Ryder, MD</td>
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<td>Bianca Santomasso, PhD, MD</td>
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<td>Jeffrey Sosman, MD</td>
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<td>John Thompson, MD</td>
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<td>Yinghong Wang, PhD, MD</td>
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<td>Vlad G. Zaha, PhD, MD</td>
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Lisa Hang, PhD, has disclosed a spouse receiving employment/governing board, patent, equity, or royalty from Abbott Laboratories, Abbvie, and BD Medical. The remaining NCCN Guidelines Staff have no conflicts to disclose.