NCCN Guidelines® Updates: Management of Immunotherapy-Related Toxicities

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Management of Immunotherapy-Related Toxicities, published in this issue (page XXXX), include the latest updates. To assist readers interested in noting how the guidelines were updated, highlights of major changes pertaining to the portion of the guidelines published in this issue are provided below. To view the most recent version of the guidelines, visit NCCN.org.

Updates in Version 1.2022 from Version 4.2021 include:

Management of CAR T-Cell–Related Toxicities

CART-1

- Before and During CAR T-Cell Infusion:
  - 1st bullet was added: “Baseline cardiac assessment, such as echocardiogram. Consult with cardiology if previous cardiac history or concern from assessment.”
  - 2nd bullet revised: “...preferably with double or triple lumen catheter, for IV fluid and other infusions in case of toxicities and possible vasopressors use.”
  - 4th bullet was revised: “Tumor lysis precautions prophylaxis and monitoring are recommended for patients with large tumor burden....”
  - 6th bullet revised: “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.”
  - 7th bullet was added: “Baseline CRP and serum ferritin.”

- Post-CAR T-Cell Infusion:
  - 1st bullet was revised: “Hospitalization or extremely close outpatient monitoring at centers with transplant or prior outpatient CAR T-cell transplant experience. Close monitoring in the hospital...”
  - 2nd bullet was revised: “Hospitalization is warranted for patients with at the first sign of CRS or neurotoxicity (including fever, hypotension, or change in mental status) is warranted.”
  - 3rd bullet was revised: “Monitor CBC, CMP (including magnesium and phosphorus), and coagulation profile daily.”
  - 4th bullet was revised: “Baseline CRP and serum ferritin should be rechecked at least 3 times per week for 2 weeks post-infusion. Consider daily checks.”
  - 5th bullet was revised: “Assessment for CRS should be done at least twice daily. 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).”
  - 6th bullet was revised: “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) during the peak window of neurotoxicity risk. If neurologic concern develops, more frequent assessments are recommended at a minimum of every 8 hours to include cognitive assessment and motor weakness.”
  - 7th bullet was added: “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.”

Note: The addition of new language is indicated in italics. Wording that has been removed from the previous version is indicated in strikeout.
CART-2
- CRS:
  - 1st bullet was revised: “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.”
- Neurologic Toxicity:
  - 3rd bullet was revised: “The most common neurologic toxicities include encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia, anxiety, and autonomic neuropathy. Agitation, hyperactivity, or signs of psychosis can also occur. Transient neurological symptoms can be heterogeneous and include encephalopathy, delirium, aphasia, lethargy, headache, tremor, myoclonus, dizziness, motor dysfunction, ataxia, sleep disorder (eg, insomnia), and anxiety, agitation and signs of psychosis.”
  - 4th bullet was revised: “Serious events including seizures, depressed level of consciousness, as well as fatal and serious cases....”
- Hemophagocytic Lymphohistiocytosis/Macrophage-Activation Syndrome (HLH/MAS) During CRS:
  - 1st bullet, 1st sub-bullet was revised: “Rapidly rising and high ferritin (>5000 ng/mL) with cytopenias in the context of CRS fever, especially if accompanied....”
  - Footnote “b” was added.

CART-3
- Cytokine Release Syndrome (CRS), 2nd bullet was revised: “Fever is defined as temperature >38°C... fever is no longer not required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.”
- CRS Grade, Grade 1:
  - Anti-IL-6 Therapy was revised: “For prolonged CRS (>3 days) in patients or those with significant symptoms, and/or comorbidities and/or are elderly....”
  - Additional Supportive Care, 1st bullet was revised: “Sepsis screen and empiric broad-spectrum antibiotics, consider granulocyte colony-stimulating factor....”
- CRS Grade, Grade 2:
  - Additional Supportive Care, 2nd bullet was revised: “...other methods of hemodynamic monitoring. Telemetry, EKG, troponin, and BNP if persistent tachycardia.”

CART-3A
- Footnote “c” was revised: “For HLH/MAS during CRS, treat as per CRS with addition of steroids. If symptoms do not improve within 48 hours, consider etoposide and intrathecal cytarabine for neurotoxicity 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.”
- Footnote “l” was added.
- Footnote “p” was revised: “Other agents such as anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG, ATG, or extracorporeal cytokine adsorption with....”
• Footnote "w" was revised: “Diagnostic lumbar puncture for grade 3-4 neurotoxicity, consider for grade 2. Patients should 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 3-4 neurotoxicity.”
• Footnote "x" was added.