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Management of Immune-Related Adverse Events in Patients Treated with Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline

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1 Background & Methodology

Introduction

- Chimeric antigen receptor T-cell (CAR T) therapy is an expanding immunotherapeutic approach and is currently used for several hematological neoplasms.
- CAR T therapy modifies T-cells to redirect them to eradicate malignant cells and offers durable and sustained remissions in many patients.
- The most notable advantage of CAR T-cell therapy is the short treatment time needed, administered with a single infusion and close monitoring.[1]
- CAR T-cell therapy is regarded as a living drug, as cells are expected to persist in the long term with efficacy that may last for decades.[1,2]
- However, they can also be associated with severe toxicities, such as cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS).
- Although these toxicities are most often manageable and reversible with proper supportive care, they can be fatal, and they require close vigilance and prompt treatment. Timely recognition of these toxicities and early intervention reduces morbidity and mortality.

Introduction (cont.)

- The guideline offers expert guidance on the diagnosis, evaluation, and management of CRS, ICANS, and other potential but less common toxicities related to CAR T-cell therapy, including hemophagocytic lymphohistiocytosis (HLH), B-cell aplasia, cytopenias, disseminated intravascular coagulation (DIC), and infections.
- With the increasing use of CAR T-cell therapy in cancer treatment regimens, it is imperative that clinicians be knowledgeable about the symptoms associated with these agents, how best to monitor them, and their recommended management.

ASCO Guideline Development Methodology

- The ASCO Clinical Practice Guideline Committee (CPGC) guideline process includes:
  - a systematic literature review by ASCO guidelines staff
  - an expert panel provides critical review and evidence interpretation to inform guideline recommendations
  - final guideline approval by ASCO CPGC

- The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

Clinical Question

This clinical practice guideline addresses one overarching clinical question:

1. How should clinicians manage immune-mediated adverse events in adult cancer patients treated with chimeric antigen receptor (CAR) T-cell therapy?

Target Population and Audience

Target Population

- Adult cancer patients receiving treatment with CAR T-cell therapy alone.

Target Audience

- Health care practitioners, including oncologists, other medical sub-specialists, emergency medicine, internal and family medicine practitioners, nurses, and pharmacists, who provide care to cancer patients, as well as patients receiving CAR T-cell therapy, and their caregivers.

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2 Summary of Recommendations

Summary of Recommendations

The following are general recommendations that should be followed.

For specific CAR T-related toxicities management, please see Tables 1-7 in the full guideline or the summary of recommendations table available at www.asco.org/supportive-care-guidelines

All recommendations in this guideline are consensus based with benefits outweighing harms.

Summary of Recommendations

Key Recommendations

It is recommended that clinicians manage toxicities as follows:

- Management of short-term toxicities associated with CAR T-cells begins with supportive care for most patients, but may require pharmacological interventions for those without adequate response.
- Management of patients with prolonged or severe CAR T-cell-associated CRS includes treatment with tocilizumab with or without a corticosteroid.
- On the basis of the potential for rapid decline, patients with moderate to severe ICANS should be managed with corticosteroids and best supportive care.
- Steroids should be rapidly tapered once symptoms improve to grade 1.

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3 Discussion

Patient and Clinician Communication

- As immunotherapeutic treatment for cancer continues to evolve with single agents and in new combinations, it is imperative that patients and family caregivers receive timely and up-to-date education about CAR T-cell therapies, their mechanism of action, and the clinical profile of possible irAEs.
- Patient and caregiver education should occur prior to initiating therapy and continue throughout treatment and survivorship.
- An important education point is that immunotherapeutic agents have the ability to influence immune response even after discontinuation. Therefore, patients should be encouraged to alert all health care providers that they are receiving or have received an CAR T-cell therapy and to report any changes in health status to each provider.
- Using a questionnaire or standard assessment may assist the provider and patient to recognize possible irAEs.

Patient and Clinician Communication (cont.)

- Health care professionals should ask patients about any new symptoms or changes in their health—no matter how small they may seem.
- Minor changes in how a patient is feeling may indicate early signs of an adverse event and patients may not attribute the change to their cancer treatment.[3]
- Consistent assessment and documentation at each encounter will also enable the clinical team to note changes that may occur over time.
- Wallet cards detailing symptoms to watch for and how to notify their healthcare provider may be an effective tool to recognize and manage irAEs and may be useful to other healthcare providers caring for patients with a history of immunotherapy.[4]
- The Oncology Nursing Society has an immunotherapy wallet card available for patients and providers. Copies of the card or additional information can be obtained by email at clinical@ons.org.

Health Disparities

- ASCO clinical practice guidelines represent expert recommendations on the best practices to provide the highest level of care, but many patients have limited access to medical care.
- Access to CAR T-cell therapy is dependent on a complex interplay of several factors and stakeholders, including referring physicians, manufacturers, payers, and treatment facilities.[5]
- Evidence of disparate access to CAR T-cell therapy comes from recent systematic reviews[6,7] and, while more studies are necessary to thoroughly understand how the factors intersect to create and maintain disparities in cancer treatment, factors include treatment facility characteristics, geographic location and distance to treatment facility, insurance type, age, race, and income.[5,6]
- Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

Additional Resources

- More information, including a supplement and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines
- Patient information is available at www.cancer.net
- A companion guideline provides recommendations for the management of irAEs in patients treated with immune checkpoint inhibitor (ICPi) therapy, also available at www.asco.org/supportive-care-guidelines

Guideline Panel Members

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Abbreviations

- ASCO, American Society of Clinical Oncology
- CAR T-cell, chimeric antigen receptor T-cell
- CPGC, Clinical Practice Guidelines Committee
- CRS, cytokine release syndrome
- DIC, disseminated intravascular coagulation
- GI, gastrointestinal
- GU, genitourinary
- HLH, hemophagocytic lymphohistiocytosis
- ICANS, immune effector cell-associated neurotoxicity syndrome
- ICPi, immune checkpoint inhibitor
- irAE, immune-related adverse effect
- PGIN, Practice Guidelines Implementation Network

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