Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

Schneider et al.
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Background & Methodology
Introduction

• Immunotherapy has revolutionized the treatment of many different types of cancers. The use of immune checkpoint inhibitors (ICPis) is rising exponentially.\(^1\)

• Despite the clinical benefits of the immune checkpoint blockade therapy, its use is associated with a spectrum of side effects that is quite different from other systemic therapies.

• The side effects may involve any organ or system of the body but gastrointestinal, dermatological, hepatic, endocrine, and pulmonary toxicities predominate, and there should be a high level of suspicion that any changes are treatment related.

• The incidence and onset of immune-related adverse effects (irAEs) varies based on the class and dose of ICPi administered, the type of cancer, and factors related to the patients.

• In general, patients receiving anti-PD-1/PD-L1 antibodies have a lower incidence of any grade irAEs than those treated with anti-CTLA-4 agents, with combinations increasing the incidence, severity, and onset of irAEs.\(^2\)

• Variable onsets have been described for the different toxicities, from early occurrence within days to delayed onset up to 26 weeks, with a median onset of approximately 40 days.\(^2\)

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Introduction (cont.)

• ICPi therapy can, in general, continue in the presence of mild irAEs, with close monitoring.

• Moderate to severe irAEs may be associated with life-threatening declines in organ function and quality of life, and fatal outcomes have been reported; these toxicities require early detection and proper management.

• Combination therapy that includes ICPis plus chemotherapy, targeted therapy, radiation therapy, intratumoural therapies, other immunomodulators, or adoptive cell therapy are being investigated and may offer additional long-term survival benefits.

• While management of toxicities related to combination therapy is beyond the scope of this guideline, clinicians should be aware of the potential for novel toxicities with combination therapies and attempt to distinguish the causative agent(s) for appropriate management.

• With the increasing use of immunotherapy 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 Questions

This clinical practice guideline addresses two overarching clinical questions:

1. How should clinicians manage immune-mediated adverse events in adult cancer patients treated with immune checkpoint blockade antibodies?
2. How can adverse events related to steroid use be prevented and managed?
Target Population and Audience

Target Population

• Adult cancer patients receiving treatment with immune checkpoint blockade inhibitors 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 immune checkpoint inhibitors, and their caregivers.
Summary of Recommendations
Summary of Recommendations

The following are general recommendations that should be followed irrespective of affected organs.

For organ-specific and systemic toxicities management, please see Tables 1-11 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:

• Patient and family caregivers should receive timely and up-to-date education about immunotherapies, their mechanism of action, and the clinical profile of possible irAEs before initiating therapy and throughout treatment and survivorship.

• There should be a high level of suspicion that new symptoms are treatment-related.

• In general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, except for some neurologic, hematologic, and cardiac toxicities.

• Consider holding ICPIs for most grade 2 toxicities and resume when symptoms and/or lab values revert ≤ grade 1. Corticosteroids (initial dose of 0.5–1 mg/kg/d of prednisone or equivalent) may be administered.
Summary of Recommendations

Key Recommendations (cont.)

• Hold ICPis for grade 3 toxicities and initiate high dose corticosteroids (prednisone 1-2 mg/kg/d or equivalent). Corticosteroids should be tapered over the course of at least 4-6 weeks. If symptoms do not improve with 48-72 hours of high dose steroid, infliximab may be offered for some toxicities.

• When symptoms and/or lab values revert ≤ grade 1, rechallenging with ICPis may be offered, however, caution is advised especially in those patients with early-onset irAEs. Dose adjustments are not recommended. Rechallenge with PD-1/PD-L1 monotherapy may be offered in patients with toxicity from combined therapy with a CTLA-4 antagonist once recovered to ≤ grade 1.

• In general, grade 4 toxicities warrant permanent discontinuation of ICPis, except for endocrinopathies that have been controlled by hormone replacement.
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 immunotherapies, 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 immunotherapeutic agent and to report any changes in health status to each provider.

- In most cases, irAEs can be managed with treatment interruption and/or supportive care and for some patients will involve a multidisciplinary team to address specific symptoms. Adverse events can often be managed effectively, especially when they are identified early.
Patient and Clinician Communication (cont.)

- Education addressing the safe handling of medications, infection control, and safe sexual practices is important in supporting optimal management of irAEs.\(^4\)

- Using a questionnaire or standard assessment may assist the provider and patient to recognize possible irAEs.

- 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.\(^5\) 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.\(^3\) 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.
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 CAR T-cell 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
- CTLA-4, cytotoxic T-lymphocyte-associated antigen-4
- GI, gastrointestinal
- GU, genitourinary
- ICPi, immune checkpoint inhibitor
- irAE, immune-related adverse effect
- PD-1, programmed cell death-1
- PD-L1, programmed cell death ligand 1
- PGIN, Practice Guidelines Implementation Network
References

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