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Management of Immunotherapy-Related Toxicities in Patients Treated With Immune Checkpoint Inhibitor Therapy

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GUIDELINE TITLE Management of Immunotherapy-Related Toxicities: National Comprehensive Cancer Network

DEVELOPER National Comprehensive Cancer Network (NCCN)

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FUNDING SOURCE NCCN

TARGET POPULATION Adult patients with cancer receiving treatment with cancer immunotherapy, including immune checkpoint inhibitors (ICIs)

MAJOR RECOMMENDATIONS

- Consultation with the appropriate subspecialty clinicians is encouraged when managing immune-related adverse events (IRAEs). (All recommendations were graded as 2A, defined as "uniform NCCN consensus that the intervention is appropriate based upon lower-level evidence.")
- IRAEs are graded as follows: grade 1, no or mild signs or symptoms; grade 2, moderate; grade 3, severe; grade 4, life-threatening; and grade 5, death.[1]
- Grade 1 IRAEs are generally managed supportively and ICI medications are continued.
- Early intervention with corticosteroids is used for most grade 2 or higher IRAEs. Neurologic, cardiac, and grade 3 or 4 IRAEs should be treated with high-dose methylprednisolone or prednisone (1-2 mg/kg per day). Select IRAEs including hypothyroidism and other endocrine IRAEs may be treated with hormone supplementation without corticosteroids.
- Tumor necrosis factor inhibition is particularly effective for management of ICI colitis and inflammatory arthritis and can be used in other steroid-refractory IRAEs (other than hepatitis and with caution in patients with heart failure). Permanent discontinuation of a given class of ICI (eg, anti–cytotoxic T-lymphocyte-associated protein 4 [CTLA-4], anti–programmed cell death protein 1 [PD-1], or anti–PD ligand 1 [PD-L1]) is generally recommended after a grade 3 or 4 IRAE; however, rechallenge with an alternative may be considered.

Summary of the Clinical Problem

ICIs are monoclonal antibodies that block inhibitory regulatory proteins. Their use leads to T-cell activation, engaging the immune system to treat the malignancy.[2] ICI toxicities, known as IRAEs, range from mild skin rash to fatal myocarditis.[3] There are no clinical trials to guide IRAE management, and treatment is based on management of autoimmune diseases outside the ICI setting.

Characteristics of the Guideline Source

These guidelines were developed and funded by the NCCN and written by the NCCN Management of Immunotherapy-Related Toxicities Panel (**Table**). Panelists were required to disclose conflict of interest (there were none reported). Clinical experts from NCCN member institutions and external parties (patient advocates, clinicians outside the member institutions, industry, and/or payors) submitted requests for areas in need of guidelines and guideline updates. The NCCN guideline staff investigated these queries through a systematic literature review process. Panelists reviewed each comment submitted from member institutions and external parties and all literature review.

Evidence Base

IRAEs are graded according to the *Common Terminology Criteria for Adverse Events* (*CTCAE*) rubric.[1] Grade 1 IRAEs have mild signs or symptoms and generally do not require intervention or discontinuation of ICIs. For grade 2 IRAEs, suspension of ICIs should be considered. Treatment with corticosteroids is indicated. Grade 3 IRAEs require ICI cessation, subspecialty consultation, high-dose corticosteroids, and consideration of a steroid-sparing immunosuppressive agent. Grade 4 IRAEs are life-threatening and necessitate urgent intervention. The guidelines reference a 15% to 90% incidence of any grade of IRAEs with a single ICI. Grade 3 to 5 IRAEs occur in more than half of patients receiving combination ICIs, a quarter of those receiving anti–CTLA-4 alone, and 10% to 20% receiving anti–PD-L1 monotherapy. Specific treatments for IRAEs are based on the involved organ system.

Multimedia

For cardiac IRAEs, which have a prevalence of approximately 1% and a case-fatality rate of approximately 40%, the guidelines recommend early subspecialty consultation and aggressive immunosuppression for grade 2 or higher. This recommendation is based on the potentially fulminant or fatal course of these IRAEs and higher rates of major adverse cardiac events in cases treated with low-dose vs high-dose corticosteroids.[4] Steroid-sparing agents, such as antithymocyte globulin, infliximab, mycophenolate, and/or intravenous immunoglobulin, are recommended for patients who do not respond to corticosteroids within 24 hours, but no large studies were referenced for this recommendation.

ICI-mediated endocrine toxicities, with an estimated incidence of up to 13% with dual ICIs, generally require only hormone

Table. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Good
Guideline development group composition	Good
Clinical practice guideline–systematic review intersection	Poor
Establishing evidence foundations and rating strength for each of the guideline recommendations	Poor
Articulation of recommendations	Fair
External review	Poor
Updating	Good
Implementation issues	Poor

therapy and not immunosuppression. The exception is high-grade primary adrenal insufficiency or hypophysitis, for which corticosteroids with rapid taper can be considered. High-dose corticosteroids are associated with reduced cancer survival in patients with ICI-associated hypophysitis.[5]

Dermatologic toxicities of any grade can be as frequent as 70% with anti–CTLA-4 and vary considerably in severity. The guidelines recommend continuation of immunotherapy with oral antihistamines and topical corticosteroids for grade 1 and 2 dermatologic toxicities. When bullous dermatitis or Stevens-Johnson syndrome/toxic epidermal necrolysis occurs, urgent dermatology consultation and cessation of immunotherapy are recommended. The guideline stresses the importance of using corticosteroids for severe cutaneous adverse reactions despite the practice of not using systemic corticosteroids for this indication in other settings.

ICI-induced colitis is common, with an incidence of approximately 10% to 14%. The guidelines recommend high-dose intravenous corticosteroids for grade 2 or higher colitis; when grade 3 or higher colitis occurs, addition of infliximab or vedolizumab is recommended if there is no improvement in 2 days.[6,7] A retrospective study supports early institution of steroid-sparing agents, given findings of higher infection rates in cases treated with long-duration systemic corticosteroids (>30 days) compared with short-duration corticosteroids combined with infliximab.[8]

Rheumatologic toxicities, with an overall incidence of up to 7%, are more common with anti–PD-L1 than with anti–CTLA-4 antibodies. ICI arthritis can occur late and persist after ICI cessation. ICI myositis can be fulminant and life-threatening, especially when associated with myocarditis or bulbar myasthenia gravis. Clinicians should consider intra-articular corticosteroid injections for low-grade arthritis and steroid-sparing immunosuppression for high-grade or steroid-refractory rheumatologic toxicities.[9] The authors note that preexisting rheumatologic autoimmune disease is not an absolute contraindication to cancer immunotherapy.

Benefits and Harms

These guidelines provide a compendium of IRAEs and discuss both clinical presentation and management. While the authors discuss the toxicity of IRAE treatments such as corticosteroids, their recommendations for toxicity prevention primarily derive from studies of primary autoimmune diseases and may not be directly applicable to IRAEs. There is also a paucity of literature supporting the recommendations for steroid-sparing agents used for ICI myocarditis or pneumonitis. Given the lack of high-quality published data on IRAE management, it is not surprising that these guidelines lack a strong foundation. It is therefore possible, if not likely, that some recommendations will be found to be ineffective or even harmful in the future.

Discussion

These NCCN recommendations are similar to those proposed by the American Society of Clinical Oncology and the Society for Immunotherapy of Cancer. All follow the *CTCAE* rubric for severity grading and generally recommend ICI continuation for grade 1 and aggressive action for grade 3 or higher IRAEs. They all highlight cardiac toxicity, given its potential severity and rapid progression. The NCCN guidelines, unlike others, discuss the effect of systemic corticosteroids and immunosuppression on ICI efficacy and tumor response. Because the pathophysiology of organ-specific IRAEs can differ (eg, antibody-mediated ICI-induced bullous pemphigoid vs cytotoxic T-cell–mediated ICI myocarditis), creating simple treatment guidelines that apply to all IRAEs is not possible.

Areas in Need of Future Study or Ongoing Research

Prospective observational studies of organ-specific IRAE cohorts managed with standardized protocols will provide needed data to support clinical trials in this area. Because the literature on IRAE management is rapidly increasing, treatment guidelines need to be updated regularly. Further work is also needed to improve the *CTCAE* IRAE severity grading. Information is needed about the safety of treating IRAEs with corticosteroids as well as synthetic and biologic immunosuppressive agents, including their effect on tumor response. Because many patients present with multiorgan toxicities, a guide to multidisciplinary team building and management would be of value.

Related guidelines

American Society of Clinical Oncology clinical practice guideline

Society for Immunotherapy of Cancer consensus recommendations

ARTICLE INFORMATION

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