

FAST FACTS AND CONCEPTS #375
IMMUNOTHERAPY RELATED ADVERSE EFFECTS WHEN TREATING CANCER
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Background: Check-point immunotherapy is a rapidly evolving treatment paradigm for solid organ cancers (1). These medications are often antibodies that target key regulators of the immune system to unleash an immune-system attack on cancer cells. Examples include cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors (e.g. ipilimumab) or programmed death receptor-1 (PD-1) inhibitors (e.g. pembrolizumab and nivolumab). See *Fast Fact #277* for more information. While heightened immune response against the tumor cells is intended, healthy tissues can also be attacked leading to unintended inflammation of almost any organ system. This has led to a unique set of immune-related adverse events (IRAEs). Given the expanding use of check-point immunotherapy, clinical awareness of IRAEs is important among generalist and palliative care clinicians.

IRAEs: Early recognition of IRAEs is paramount. The National Cancer Institute along with the National Institute of Health published definitions for adverse events. Grade 1-2 IRAEs are considered mild to moderate in severity. Grade 3 is more severe and often requires hospitalization. Grade 4 is a life-threatening IRAE and Grade 5 represents a fatal IRAE (2,3). Some IRAE's are misattributed to disease progression by clinicians unfamiliar with immunotherapy. Therefore, it is important to inform the patient's primary oncologist whenever an IRAE is suspected or identified. *While corticosteroids are common treatments which help manage IRAEs, it is strongly advised that clinicians confer with the patient's oncologist before initiating them as they may temper the oncologic response of immunotherapy.*

- **Cutaneous:** Pruritus, vitiligo, and an erythematous, maculopapular rash involving the trunk and extremities are the most common IRAEs (2,4). They typically manifest 2-3 weeks after treatment initiation which is much earlier than other IRAEs. Cutaneous toxicities are more common with CTLA-4 inhibitors, except for vitiligo which occurs more often with PD-1 inhibitors (5). The development of a rash, particularly vitiligo, may be a favorable prognostic sign corresponding with improved progression-free and overall survival (4). In rare cases, severe cutaneous reactions like Steven's Johnson Syndrome or toxic epidermal necrolysis occur, which usually require urgent ICU admission along with a dermatology and oncology consultation.
Management: Grade 1 toxicities are usually treated with topical emollients, urea-containing creams, oral anti-histamines, and topical steroids (4). For grade 2 toxicities, immunotherapy is often held until the reaction improves to a grade 1. Oral prednisone at 0.5-1 mg/kg/day can be considered with a taper over 4 weeks. Grades ≥ 3 toxicity require IV methylprednisolone (or equivalent) at 1-2 mg/kg/day with a taper over 4 weeks. For grade 4 toxicities, e.g. those with bullous lesions and/or mucous membrane involvement, immunotherapy is typically discontinued permanently.
- **Gastrointestinal:** Diarrhea, colitis, and hepatitis are quite common. In fact, diarrhea occurs in >50% of patients treated with CTLA-4 inhibitors (2). Most GI IRAEs begin 5-10 weeks after immunotherapy exposure, except for hepatitis which often begins 6-16 weeks after treatment exposure (2,4). Colitis often presents as abdominal cramping or bloating, blood or mucous in the stool, and fever. Patients with hepatitis often have an asymptomatic elevation in their liver function tests but then eventually develop nausea, vomiting, jaundice, and abdominal pain. Iatrogenic deaths from CTLA-4 inhibitors are usually related to colonic perforation from unrecognized colitis (5).
Management: Grade 1 toxicities often require observation and supportive care. See *Fast Fact #96* for management of diarrhea. For grade 2, immunotherapy is held until toxicities improve to grade 1 or resolve. Four weeks of oral prednisone could be considered. Grade ≥ 3 toxicities are treated with IV methylprednisolone (at similar dose as cutaneous reactions) and usually require hospitalization and permanent discontinuation of the immunotherapy. Infliximab can be considered for most GI IRAEs refractory to IV corticosteroids, except for hepatitis, as it can worsen hepatotoxicity (6).
- **Pulmonary:** Although the incidence of pneumonitis is only 2-6%, with a slight predominance in those treated with PD-1 inhibitors, it can be fatal (4). IRAE-induced pneumonitis may present initially with

only a dry cough or mild dyspnea, hence high clinical suspicion is needed to make the diagnosis. Onset time varies but is usually between 8-14 weeks (6).

Management: Recommendations mirror those for GI IRAEs except that empiric antibiotics should be considered for grade ≥ 3 toxicities (6).

- **Endocrine:** Clinically significant immune-related endocrinopathies occur in about 10% (4). Hypothyroidism, hyperthyroidism, adrenal insufficiency, and Type 1 diabetes mellitus (DM) are most common and can have significant clinical consequences if not recognized.

Management: An endocrinology consultation is usually recommended since life-long hormone replacement therapy may be required (6,7). Once stabilized, most can resume immunotherapy.

- **Rare IRAEs:** There have been case reports of fatal myocarditis and neurologic toxicities such as myasthenia gravis and acute inflammatory neuropathies (often labeled as Guillain-Barre syndrome). Immunotherapy is permanently discontinued for grade ≥ 3 cardiac or neurologic IRAEs (8). IVIG and/or plasmapheresis may be required for IRAEs refractory to IV corticosteroids (8).
- **Pseudoprogression:** Though not an IRAE, it represents a unique response to immunotherapy and involves immune cell tumor infiltration. This can cause the appearance of tumor growth or new lesions on radiologic imaging. Pseudoprogression usually resolves within 6-12 weeks but it can be difficult to discern from true cancer progression. It is relatively uncommon, occurring in just 2-14% (9). Still, its diagnosis requires considerable clinical judgement and can have important prognostic implications. In general, if patients are doing well clinically, immunotherapy is continued, and lesions are reassessed via a short-interval radiologic study. If the patient is clinically deteriorating, the imaging findings usually represent true disease progression.

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