Immune-Related Adverse Events Associated with Immune-Checkpoint Inhibitors

Immune checkpoint inhibitors are monoclonal antibodies which promote the recognition and killing of tumor cells by the immune system. These drugs work by having immune cells identify cancer cells as foreign or prevent cancer cells from evading the immune response. They are being used to treat a variety of malignancies including melanoma, non-small cell lung cancer, diffuse large B-cell lymphoma, hepatocellular carcinoma, and urothelial cancer, among others. However, immune-related adverse events (irAEs) are a potentially life-threatening complication of these novel therapies that must be promptly recognized and treated.

Pathophysiology

Multiple mechanisms play a role in iRAEs:

- T-cell activity against antigens also present in healthy tissue
- Upregulation of inflammatory cytokines
- Modulation of pre-existing antibodies
- Increased complement activity
- Microbe-specific effects

Risk Factors

The incidence of irAEs is **highest in patients receiving combination immune checkpoint blockade** with some clinical trials reporting significant reactions in over 50% of patients.

Timing: May occur within weeks to months of treatment.

Clinical Presentation and Grading

The spectrum of presentations for iRAEs is broad and almost any organ system can be involved. Clinicians must maintain a high index of suspicion for an iRAE in any patient on immune checkpoint inhibitors presenting with new systemic symptoms including the following manifestations:

Cardiovascular	Myocarditis, arrythmias, heart failure, pericarditis
Respiratory	Pneumonitis
Endocrine	Hyper/hypothyroidism, adrenal insufficiency, new onset diabetes, hypophysitis
Gastrointestinal	Colitis, hepatitis, pancreatitis
Neurologic	Aseptic meningitis, encephalitis, neuropathy, myasthenia gravis, Guillain-Barre syndrome
Hematologic	Autoimmune hemolytic anemia, cytopenia, TTP, HUS, ITP, acquired hemophilia
Dermatologic	Rash, Stevens Johnson syndrome, TEN, DRESS

Grade 1 Minimal/No Symptoms → **Grade 2** Mild to Moderate Symptoms → **Grade 3** Moderate to Severe Symptoms → **Grade 4** Life-threatening Symptoms

Work-Up and Treatment

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Initial Management:

- Immune checkpoint inhibitor toxicity is potentially reversible → A trial of ICU-level care in patients with organ failure is warranted
- Hold or permanently discontinue the immune checkpoint inhibitor
- iRAEs may be difficult to differentiate from infection (e.g., pneumonia vs. pneumonitis)
  - Provide empiric antibiotic coverage until infection can be ruled out

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Additional Work-Up (PRN depending on organ systems involved):

- For all patients: ESR, CRP, TSH
- Suspected cardiac involvement: Troponins, ECG, TTE, BNP
- Suspected pulmonary involvement: CXR, CT chest, bronchoscopy with BAL
- Suspected CNS involvement: MRI brain, LP, EEG

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Immunosuppression:

- Immunosuppressive agents should be started for all Grade 3 or 4 iRAEs and should be considered in Grade 2 iRAEs.
- To help determine grading, organ-specific symptom criteria are available here.

Mainstay of treatment for Grade 3 or 4 IRAEs necessitating ICU care is generally **high-dose steroids** with or without additional immunosuppressive agents.

- Typical steroid dosing: Methylprednisolone or prednisone 1-2mg/kg/day
- Pulse dose steroids may be indicated for progressive life-threatening symptoms: Methylprednisolone 1g IV daily x 3 days
- Second-line agents include:
  - Infliximab (avoid in hepatitis)
  - Mycophenolate mofetil
  - Intravenous immunoglobulin
  - Cyclophosphamide

Involve the patient's primary oncologist or the oncology team at your hospital.