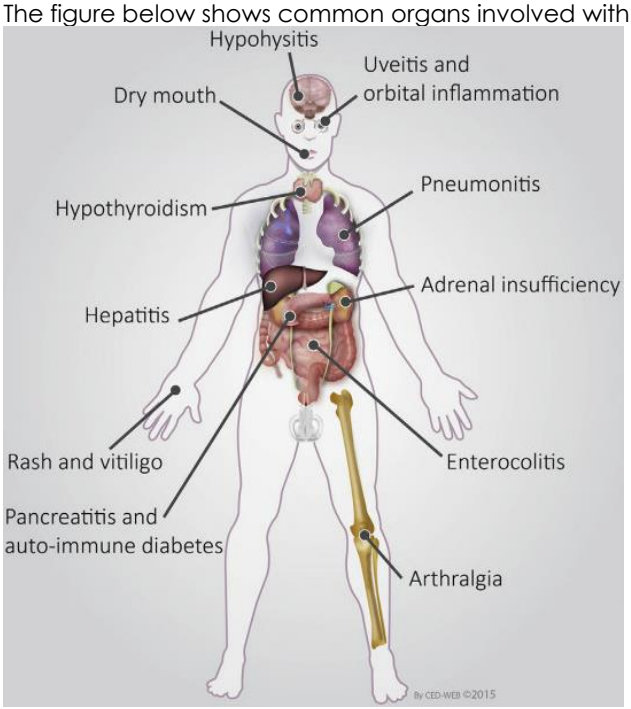
Immune Checkpoint Inhibitor Toxicity in Adults

Introduction

1. Immune checkpoint inhibitors (ICPi) are antibodies used to enhance the immune system's response to malignant cells[3]
    a. Some indications for ICPi include melanoma, non-small cell lung cancer, breast cancer, and gastric cancer[4]
2. Common ICPi include cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors, programmed cell death receptor 1 (PD-1) inhibitors, and programmed cell death ligand 1 (PD-L1) inhibitors

Drug class	Drugs
CTLA-4 inhibitors	Ipilimumab, tremelimumab
PD-1 inhibitors	Nivolumab, pembrolizumab, cemiplimab, dostarlimab
PD-L1 inhibitors	Atezolizumab, durvalumab, avelumab

3. Despite their clinical benefits, ICPi have been associated with several immune-related adverse effects (IrAEs)
    a. The most common sites for IrAEs to occur are dermatologic, gastrointestinal, hepatic, and endocrine[5]
        i. The most common sites for severe IrAEs are gastrointestinal, hepatic, and pulmonary[1]
    b. The figure below shows common organs involved with IrAEs[2]



4. IrAEs are graded based on location and severity of symptoms, which ranges from Grade 1 to Grade 4[1,4,5]
5. The incidence of IrAEs associated with ICPi medications ranges from 39-85%, with combination regimens at higher risk[1]
6. Management of IrAEs is dependent on Common Terminology Criteria for Adverse Events (CTCAE) Grade, but usually involves holding the ICPi and starting immunosuppressive agents

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Common Medications[3]

	Steroids	Infliximab (Remicade)	Vedolizumab (Entyvio)
Dose	Depends on grade and location of ADE	5 mg/kg IV on week 0, can be repeated in 2 weeks and again at 6 weeks if needed	300 mg IV at 0, 2, and 6 weeks and then once every 8 weeks thereafter if needed
Administration	Can be given topically, PO, or IV depending on grade and location of ADE	Administer over at least 2 hours	Given IV over 30 minutes Monitor for infusion reaction
Adverse Effects	Adrenal suppression, hyperglycemia, infection, gastrointestinal upset, mood disturbances, insomnia	Infection, hepatotoxicity, infusion reactions, malignancy	Infusion reactions, hepatotoxicity, progressive multifocal leukoencephalopathy, infection
Comments	Most regimens will require taper over 4-6 weeks	Infusion should begin within 3 hours of reconstitution and dilution Do NOT infuse with other agents If infusion reaction occurs – can give antihistamines, acetaminophen, and/or corticosteroids and restart infusion at lower rate	No renal or hepatic adjustment

Overview of Evidence

Author, year	Design/ sample size	Intervention & Comparison	Outcome
Siminaggio[6], 2019	Retrospective cohort study, N = 93 patients	Intervention: Rechallenge of anti-PD-1 or anti-PD-L1 after grade 2 or higher IrAE in any cancer type, could be either monotherapy or combination ICPi Comparison: Non-rechallenged	In the 40 patient who were rechallenged, the same or a different IrAE occurred in 22 patients (55%). When a second IrAE occurred, it was not more severe than the first As long as patients are closely monitored, anti–PD-1 or anti–PD-L1 rechallenge appears to have an acceptable toxic effect profile
Zou[7], 2021	Retrospective observational cohort study, N = 184 patients	Intervention: Receipt of either infliximab or vedolizumab after first-line corticosteroid therapy in patients with immune-related diarrhea and colitis in patients with any cancer type, could be either monotherapy or combination ICPi Comparison: infliximab versus vedolizumab	Vedolizumab versus infliximab • Shorter steroid exposure (35 vs 50 days, p<0.001) • Fewer hospitalizations (16% vs 28%, p=0.005) • Shorter hospital stay (median 10.5 vs 13.5 days, p=0.043) • Longer time to clinical response (17.5 vs 13 days, p=0.012) Higher recurrence of IrAE • Longer durations of immune checkpoint inhibitors treatment (OR 1.01, p=0.004) • Steroid use (OR 1.02, p=0.043) • Infliximab use alone (OR 2.51, p=0.039) Favorable overall survival • ≥3 doses of immunosuppression therapy (p=0.011) • Fewer steroid tapering attempts (p=0.012)
Schneider[5], 2022	Systematic review by a multidisciplinary panel of experts, N = 175 studies	Intervention: steroids, immunosuppressive therapy, dose modification or discontinuation of therapy, organ-specific management, hospitalization, consultation to subspecialties, and best supportive care in patients with any cancer type, could be either monotherapy or combination ICPi Comparison: Either no intervention or best supportive care	Recommendations for management of ICPi are dependent upon CTCAE grade and affected organs General recommendations include giving patients and caregivers education, holding/discontinuing ICPi if necessary, administering corticosteroids, and considering infliximab

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Common Toxicities of ICPi[1]

Drug/combination	Most common adverse effects (Grade 1-4)	Most common Grade 3-4 Toxicity	Management
Ipilimumab	Dermatologic (43.5%) Gastrointestinal (29.0%) Hepatic (3.8%) Endocrine (7.6%)	Gastrointestinal (7.6%): enterocolitis, diarrhea, pancreatitis, esophagitis	See Gastrointestinal Toxicity Management
Nivolumab	Dermatologic (29.1%) Gastrointestinal (11.2%) Endocrine (7.8%)	Hepatitis (2-3%)	See Hepatic Toxicity Management
Pembrolizumab	Dermatologic (10.7%) Gastrointestinal (8.1%) Endocrine (6.9%)	Pneumonitis (1.8%)	See Pulmonary Toxicity Management
Atezolizumab	Diarrhea (18–20%)	Diarrhea (1-2%)	See Gastrointestinal Toxicity Management

Gastrointestinal Toxicity Management[1,5]

Grade	Definition	Timing	Treatment
3	Diarrhea: ≥ 7 stools/day, incontinence; i.v. fluids indicated > 24 h; interfering with ADLs Colitis: severe abdominal pain, medical intervention indicated Ileus Fever	Nivolumab/ipilimumab: ~ 50 days Pembrolizumab: 6 months	• Hold ICPi • Blood and stool infection work-up, inflammatory markers, imaging, endoscopy, and GI consult • Methylprednisolone IV 1–2 mg/kg/day or equivalent ○ Role of steroids in pancreatitis is not well defined • Add prophylactic antibiotics for opportunistic infections • Consider adding other anti-inflammatory agents (infliximab 5 mg/kg)
4	Peritoneal signs consistent with bowel perforation, life-threatening	Nivolumab/ipilimumab: ~ 50 days Pembrolizumab: 6 months	• Discontinue ICPi • Blood and stool infection work-up, inflammatory markers, imaging, endoscopy, and GI consult • Methylprednisolone IV 1–2 mg/kg/day or equivalent • Add prophylactic antibiotics for opportunistic infections • Consider adding other anti-inflammatory agents (infliximab 5 mg/kg)

Hepatic Toxicity Management[1,5]

Grade	Definition	Timing	Treatment
3/4	AST, ALT > 5x ULN or Total bilirubin > 3x ULN	6-14 weeks after initiation	• Hold ICPi • Consult GI • Prednisone 1–2 mg/kg/day or equivalent • Do NOT give infliximab • Consider prophylactic antibiotics for opportunistic infections

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Pulmonary Toxicity Management[1,5]			
Grade	Definition	Timing	Treatment
3/4	Severe new symptoms: dyspnea, cough, fever, chest pain, and fine inspiratory crackles Worsening or severe hypoxia	7-24 months after initiation	• Hold/discontinue ICPi • Pulmonary consult and ID consult • Methylprednisolone IV 2 mg/kg/ day • If symptoms severe, patient may be appropriate for infliximab, cyclophosphamide, IVIG, or mycophenolate • Consider prophylactic antibiotics for opportunistic infections

Conclusions

- Management options for ICPi toxicity include holding/discontinuing the ICPi, administering corticosteroids, and administering other immunosuppressive agents such as infliximab or vedolizumab
    - It is important to consult a specialist before taking these steps
- Choice of management depends on CTCAE grade and organs affected
    - For Grade 3/4 toxicity, start with IV steroids
        - Except for pancreatitis
    - If steroid refractory, consider immunosuppressive agents, such as infliximab
- It is important to recognize ICPi toxicity early so that it can be managed appropriately
- For specific recommendations on ICPi toxicity, view the American Society of Clinical Oncology Guidelines:
    - Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update (ascopubs.org)

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