Practical Management Pearls for Immune Checkpoint Inhibitor-related Adverse Events

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Learning objectives

• Identify and manage difficult and severe immune-related adverse events from checkpoint inhibitor treatment
• Outline management approaches for steroid-refractory irAEs
• Properly identify the causative agent of adverse events in settings of immunotherapy combinations or sequencing
• Describe areas of controversy in irAE management
Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

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Guideline development

• Developed according to the Institute of Medicine’s Standards for Developing Trustworthy Clinical Practice Guidelines
• Panel consisted of 23 experts in the field
• Recommendations are based upon published literature evidence, or clinical evidence where appropriate
• Consensus was defined at 75% approval among voting members
Clinical questions in ICI toxicities:

• ICIs in high-risk populations (autoimmunity)
• Dose, duration and supportive care with steroids
• Steroid-resistant toxicities
• Difficult-to-diagnose irAEs
• Determining how each agent contributes to toxicity in combination therapy
• ICI re-challenge
Patients with pre-existing autoimmune disorders

- AID flare rate
- De novo irAE rate
- Permanent discontinuation

CTLA-4 pathway
PD-1 pathway
PD-1 or CTLA-4 pathway

- Johnson 2016
- Lee 2016
- Menzies 2017
- Gutzmer 2017
- Richter 2018
- Danlos 2018
- Kahler 2018
- Leonard 2018
- Cortellini 2019
- Tison 2019
- Abu-Sbeih 2020
- Efuni 2020

Boland, J Immunother Cancer 2020
ICI use in patients with solid organ or stem cell transplants

- Patients who relapse after allogeneic SCT:
  - Ipilimumab: 32% response (10 mg/kg); 14% GVHD; 21% irAEs
  - Anti-PD-1: 77% response; 26% died due to new-onset GVHD

- Solid organ data is limited; most is in renal SOT patients
  - One retrospective study (n=39) reported graft loss in 81% and death in 46%
  - Also reported rapid time to rejection with median onset of 21 days

- PD-1 pathway appears to be more critical in allograft immune tolerance compared to CTLA-4 pathway
Practical pearls for high-risk patients

• Patient with underlying autoimmune disease can receive immune checkpoint therapy especially if their autoimmunity requires $\leq 10$mg prednisone/day and is clinically under good control.

• Patients frequently have an increase in organ specific toxicities, but these are largely manageable

• Risk of organ-rejection and GvHD is great in those with prior organ transplant and allogeneic BMT, but this is not uniform
Dosing of steroids

• In general:
  • Grade 2 irAEs: 0.5-1 mg/kg/day oral prednisone or IV methylprednisolone or equivalent
  • Grade 3-4 irAEs: 1-2 mg/kg/oral prednisone or day IV methylprednisolone equivalent

• Patients should have significant clinical improvement within the initial 2-3 days. If no improvement is observed either increase dose of steroids up to 2mg/kg/day or add a second line immunosuppressive agent.

• Whenever second line immunosuppression is planned again re-evaluate for other causes of the toxicities (GI, liver or other organs).

• For myocarditis and CNS toxicities strongly consider higher dosage of methylprednisolone of 1 gm/day from 3-5 days
Supportive care with steroids

• When beginning corticosteroid therapy, patients should be specifically counseled about potential toxicities, including hyperglycemia, mood disturbances, insomnia, gastritis, weight gain, and opportunistic infections

• There is potential for overlapping toxicities from steroids and ICIs (diabetes, musculoskeletal)

• Infection prophylaxis may vary by institutional practice, but must be considered early on in steroid therapy
Steroid-Resistant
immune-related adverse events
Steroid-refractory colitis

High-grade colitis
Initial: prednisone 1-2 mg/kg/day
Grade 4: IV corticosteroids

If no improvement within 3-5 days:
Administer infliximab. If necessary can give up to 3 doses of infliximab (5 mg/kg) at 0, 2, and 6 weeks.

If symptoms persist after two doses of infliximab:
Hold the third dose of infliximab
Administer up to 3 doses of vedolizumab (300 mg) at 0, 2, and 6 weeks
Steroid-refractory hepatitis

High-grade hepatitis

Grade 2 hepatitis
Initial: IV or po prednisone 0.5-1.0 mg/kg/day

Grade 3-4 hepatitis
Initial prednisone 1.0-2.0 mg/kg/day

If no improvement within 3-5 days:

Administer Mycophenolate mofetil
Initial at 500mg BID
then 1000mg BID

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Steroid-refractory pneumonitis

High-grade pneumonitis

Grade 2: 1-2 mg/kg/day prednisone
Grade 3+: 1-2 mg/kg/day methylprednisolone

If no improvement within 72 hours:

- **Mycophenolate mofetil**: 1-1.5 g twice daily (LE: 3)
- **hdIVIG**: 2 g/kg in divided doses over 2-5 days (LE: 4)
- **Infliximab**: 5 mg/kg, one dose with optional second dose 2 wk later (LE: 4)
- **Cyclophosphamide**: 600 mg/m² for 6 infusions (LE: 3)
- **Tocilizumab**: 4 mg/kg (LE: 4)

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Steroid-refractory myocarditis

Suspected myocarditis

1000 mg methylprednisolone IV or equivalent daily for 3-5 days or until troponin normalizes

If no improvement within 24-48 hours:

- Mycophenolate mofetil
- Antithymocyte globulin (ATG)
- Abatacept (in planned clinical trial)
- Alemtuzumab

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Steroids and second-line immunosuppressives

• If a patient is started on steroid treatment for an irAE but then warrants second-line immunosuppression, how do you handle the steroids (taper, etc)?
  • Once irAE is controlled then taper steroids over 2-4 week period
• Are there any precautions one should take at this time?
• Does this preclude further immune checkpoint therapy?
Types of adverse events

- **Adverse events**
  - **Not due to treatment**
    - Other factors
      - Disease progression
      - Infectious etiology
      - Non-immune drug toxicity
    - Critical to R/O other causes adverse events
      - For example - stool w/u (c dif, C & S, etc)
      - Pneumonitis- bacterial or viral pneumonia, pulmonary infarct, cancer (lymphangitic)
  - **Treatment-related adverse events**
    - **Non-immune related adverse events**
    - **Immune-related adverse events** (irAEs)
      - Can result from all ICIs
      - Can impact any organ system
Pneumonitis: immune- or radiation-associated?

- Imaging findings may be similar
- Patients with prior thoracic radiotherapy may have pre-existing lung changes
- Immune-mediated pneumonitis should respond to immunosuppression
COVID-19

- Imaging findings of pneumonitis from ICIs may be similar to those of severe COVID-19 infection
- Management of the two conditions are different, making accurate diagnosis critical
Determining which Agent in Combination Therapy: (other ICI or TKI, or Ctx) is the etiology of the toxicity

• Some chemotherapy or targeted therapy AEs may have similar presentation to irAEs, so identifying the causative agent is important for proper treatment
  • Gastrointestinal and dermatologic events also common with taxanes and VEGFR inhibitors, but root causes are different

• Pembrolizumab + axitinib (approved for RCC) tends to cause higher incidence of grade 3+ irAE. TKI and ICI toxicities overlap especially diarrhea, other toxicities are very different

• Several clinical trials of IO + targeted therapies were discontinued due to high rates of toxicity

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Practical pearls for combination treatment toxicities

• Differences in timing of onset
• Chronic and irregular inconsistent clinical course
• Stop targeted agent first and look for immediate resolution
• Many toxicities are unique to each agent
  • TKI- hypertension, palmer-plantar dyserythrodynesthesia, irregular diarrhea
  • Immune checkpoint inhibitor- hypophysitis, pneumonitis, encephalitis
Myasthenia gravis an irAE with a high morbidity/mortality

Diagnosis

• Not very common, but high potential for patient fatality
• Patients may present with:
  • Fatigable or fluctuating muscle weakness, often in proximal muscles
  • Ptosis
  • Facial weakness
  • Difficulty swallowing
  • Respiratory compromise
• May co-occur with myositis and/or myocarditis

Management

• Discontinue ICIs
• Frequent pulmonary assessments
• Corticosteroids and pyridostigmine with IVIG or PLEX
• Grade 3+: hospital admission and potential ICU-level monitoring
Immune checkpoint therapy can be resumed in some cases....

- Hypophysitis with physiologic hormone replacement therapy
- Thyroiditis without thyrotoxicosis
- Colitis/diarrhea grade 2-3 controlled with steroids over 4-6 weeks
  - Even consider after Colitis/diarrhea with infliximab given and rapid response??
  - Can resume therapy as long as steroid taper << 12 weeks
  - Can consider repeat colonoscopy prior to g
- Hepatitis with AST, ALT < 8 x ULN, Direct bilirubin elevation, 2xULN?
  - Use of mycophenalate largely should be a situation where treatment should not be resumed
- Grade 2 pneumonitis, completely resolved
- Patients recovered from combination of anti-CTLA-4 and anti PD-1 now proceeding to single agent anti-PD-1
Endocrinopathies are unique

• Continuation of treatment is generally free from additional problems
• These toxicities are generally
• Many have non-specific and/or overlapping cancer-related symptoms (fatigue, headache, malaise)
• Usually late-onset
• Assumed to be long-lasting or chronic
• Include:
  • Primary or secondary **thyroid dysfunction**
  • Hypophysitis
  • **Secondary adrenal insufficiency** (primary AI is exceedingly rare)
  • **Type 1 diabetes mellitus** (rare but life threatening)
Clinical Scenarios where retreatment is likely too high a risk

Myocarditis, completely resolved

- Retreatment could easily be fatal
- Frequently myocarditis can leave long standing cardiac abnormal function or electrophysiologic status

- Myasthenia gravis, completely resolved
  - Potential recurrence can lead to persistent deficit or be fatal
  - Consider association with myocarditis and myositis
  - Can lead to respiratory depression or failure
Re-challenging with ICIs after irAEs

- Patients should not be re-challenged until irAE resolved to grade ≤1
- Re-challenge with anti-PD-1/L1 after anti-CTLA-4 + anti-PD-1 likely safe
- Caution in re-challenging with same ICI in patients who previously had grade 3-4 irAEs

Association of irAEs and survival

- Some studies associate irAE development with PFS or OS
- Certain types of irAE may correlate more with outcomes
- This trend is not consistent across settings, agents or studies

Haratani, JAMA Oncol 2018
Chen, Front Oncol 2021
Conclusions

• Do not continue to administer front line steroids alone if no response in 3-5 days but instead switch to higher dose of steroids or second line immunosuppression.

• Immune checkpoint inhibitors can be given to patients with autoimmune disease especially if controlled with caution.

• Generally all irAE are treated with high dose steroids but
  • Endocrine toxicities generally are simply treated with replacement of hormonal deficit in most situations except in specific situations.
  • Situations include patients with severe headache from enlarged pituitary or thyrotoxicosis and local effects.
  • Myocarditis and severe neurologic toxicities are frequently treated with 1gm methylprednisolone x 3-5 days.

• Always evaluate patients for other causes of toxicities even after steroids are ineffective.

• Retreatment is feasible in some situations but not all.
Case Studies in Immune Checkpoint Inhibitor-related Adverse Events

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