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Lessons Learned in Addressing Immune-Related Adverse Events: A Practical Guide

Jeffrey Weber, MD, PhD
Deputy Director, Laura and Isaac Perlmutter Cancer Center
Professor of Medicine, NYU-Langone School of Medicine
New York City
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• I hold equity in CytoMx, Biond and Altor
• I am on scientific advisory boards for Celldex, CytoMx, Incyte, Biond, Protean, CV6 and Sellas
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• Don’t blame me, I didn’t vote for Donald Trump
Are there Unique Toxicities with Checkpoint Protein Inhibitor (CPI) Therapies?

Yes, they induce Immune-Related Adverse Events (irAEs)

Unchecked immune response

Organ-specific events
- Skin
- Gastrointestinal
- Liver
- Pulmonary
- Endocrine system
- Cardiovascular

Immune-related adverse events (auto-inflammatory toxicities)

General events
- Fatigue
- Pyrexia, chills
- Infusion reactions

Corticosteroids

Immunotherapy

Immune self-tolerance
Toxicities with Checkpoint Protein Inhibitors (continued)

- Most irAEs are reversible with steroids or other immune suppressants.
- Early recognition and treatment will reduce risk of complications.
- Consultation with an available team of specialists is critical.
- Little evidence that type of irAE varies across histologies except pneumonitis in lung CA, vitiligo in melanoma.

Incidence vs. Months on treatment:

- Rash
- Diarrhoea
- Endocrine
- Liver
- Pneumonitis
Kinetics of Onset and Resolution of Select Treatment-Related AEs With Nivolumab: Any Grade

The beginning and end of each curve represent the median time to onset and median time to resolution, respectively. Each peak reflects incidence of the AE. Weber, J et al J Clin Oncol 2017
Onset of immune related toxicities with IPI + NIVO versus NIVO alone

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†
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Management of Immune-Related Adverse Events (irAE) with CPI

<table>
<thead>
<tr>
<th>Grade</th>
<th>Steroids</th>
<th>Study Treatment</th>
<th>Persistent/ Recurring</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Treat symptomatically; No systemic steroids</td>
<td>Can continue</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Steroids for selected irAEs and for recurrent irAEs</td>
<td>Continue Hold for selected AEs*</td>
<td>Systemic steroids; Consider withholding; discontinue if ≥12 weeks</td>
</tr>
<tr>
<td>3</td>
<td>Systemic Steroids, prolonged tapers</td>
<td>Withhold or discontinue¹</td>
<td>Systemic steroids and discontinue</td>
</tr>
<tr>
<td>4</td>
<td>Systemic steroids</td>
<td>Discontinue (unless endocrine irAE)</td>
<td>Add other immune suppressants</td>
</tr>
</tbody>
</table>

Selected AEs: colitis, pneumonitis, liver/renal toxicity, hypophysitis, neurologic

Systemic steroids (PO or IV): 1–2 mg/kg/d prednisone or equivalent
- Slow taper over ≥4 weeks is recommended.
- Several courses may be necessary if symptoms worsen when dose decreased.

*Discontinue for G3/4 irAEs renal toxicity, pneumonitis and infusion reactions; question for liver grade 3.
Risk factors for development of irAEs

• Patients with a history of autoimmune disease, or who are being actively treated for an autoimmune disease, are at risk for worsening of their autoimmune disease while on immune checkpoint blockade [1].

• Similarly, patients that have had irAEs on ipilimumab are at risk of developing irAEs following anti-PD-1 treatment and vice versa [2].

• Results from these retrospective series showed a higher rate of grade 3 to 4 toxicity in patients treated with ipilimumab following anti-PD-1 (up to 35%) and patients with grade 3 to 4 toxicity on ipilimumab followed by anti-PD-1 developed grade 3 to 4 irAEs in > 20% of cases.

Questions: Immune related toxicities in immuno-oncology

- At what point and for how long should one be treated with steroids for toxicity of checkpoint inhibitors? When to use infliximab or mycophenolic acid?
- Can patients with a grade 3 or 4 immune-related adverse event ever be re-treated with a checkpoint inhibitor?
- For which patients are there absolute contraindications for the use of checkpoint inhibitors? Allograft transplant? Pre-existing autoimmune disease?
Dermatitis With Checkpoint Inhibition

Back:
Confluent red rash

Right upper arm:
Vacuolar changes (magnification x20)

Back:
Papular lesions (Close up)

Anti-CD8 staining:
Extensive epidermal exocytosis (magnification x20)

Arch Dermatol 2006 Feb;142(2):166-72
Cutaneous irAE etiology and management

- 285 patients with 427 ircAEs included pruritus (32%), maculopapular rash (28%), psoriasiform rash (5%), others (34%).
- 88 ircAEs (20%) were managed with systemic immunomodulators.
- In 7 patients with corticosteroid-refractory ircAEs, improvement resulted from targeted biologic immunomodulatory therapies.
- Serum interleukin-6 (IL-6) was elevated in 34 (52%) of 65 patients; grade 3 or greater ircAEs were associated with increased absolute eosinophils (odds ratio, 4.1) and IL-10 (odds ratio, 23.8).
- Mean immunoglobulin E serum levels were greater in higher-grade ircAEs: 1,093 kU/L (grade 3), 245 kU/L (grade 2), and 112 kU/L (grade 1; \( P = 0.043 \)).

Phillips, GS et al J Clin Oncol 2019
Colitis and Enteritis with Checkpoint Inhibition

- Diarrhea is a common irAE (37% all grade and 12% grades 3/4) with IPI; less common with PD-1 blockade
- Colonoscopy or sigmoidoscopy shows diffusely erythematous, friable, and occasionally ulcerated mucosa
- Colon biopsy usually demonstrates inflammatory colitis with CD4>CD8 infiltrate in interstitium
- Most cases respond to symptomatic treatment or high-dose steroids with a long taper (over a month)
- Infliximab is used in steroid-refractory cases
- Can rarely lead to gastrointestinal perforation (1%), profound ileus or megacolon requiring surgery
Hepatitis with Checkpoint Inhibition

- Liver function tests (LFT) must be assessed prior to each dose of ipilimumab or PD-1/PD-L1 drugs
- LFT elevations in patients may be associated with symptoms of hepatotoxicity (jaundice, right upper quadrant pain, vomiting) or may be completely asymptomatic; many patients have other non-specific symptoms (fever, malaise)
- Often elevated LFTs are of long duration
- All subjects must meet LFT criteria before each dose of ipilimumab
  - With no liver mets < 2.5X ULN for AST, ALT
  - Liver mets; < 5X ULN for AST, ALT, < 2.5X ULN for total bilirubin
Hepatitis irAE Management – Grade 3/4

- LFTs >5x or total bilirubin >3x ULN
  - Permanently discontinue therapy
  - Intensified monitoring; labs every 1-3 days until begin to resolve
  - High dose steroids, eg, methylprednisolone 1-2 mg/kg/day; if LFTs decrease convert to oral steroids
  - If after 3 days, no improvement or rebound, add mycophenolate 1 gram PO BID
  - Consult with a hepatologist and consider a liver biopsy
  - If no improvement in 5-7 days, add tacrolimus 0.1 to 0.15 mg/kg/day IV (trough level 5-20 ng/ml) or anti-thymocyte globulin (ATG); Infliximab is not recommended

Endocrine irAE Management

• Hold checkpoint inhibitors if moderate-severe symptoms
• Methylprednisolone 1mg/kg/day IV with a taper over ≥ 4 weeks if CNS symptoms
• Obtain endocrine consult
• Replace deficient hormones
  – Replace hydrocortisone 1 week before thyroid hormone supplement
• Symptoms will resolve with treatment
  – Slow return of some endocrine function
  – Most patients require life-long hydrocortisone supplement
• Use stress dose hydrocortisone in perioperative period and critical illness
  – Educate patient about stress dose steroid, emergency hydrocortisone injection, and medical alert bracelet

12/3/04- Headache/Fatigue
Pituitary size = 10.8 mm.

Sagittal MRI section from patient 7 at the time of clinical symptom onset.

Endocrinopathies with checkpoint inhibition
Scott et al Eur J Endocrin 2017

• 18% of combination immunotherapy pts developed an endocrine immune related adverse event (thyroid dysfunction 14%, hypophysitis 6% and autoimmune diabetes 0.6%)

• Combination immunotherapy was more likely to result in a single or multiple endocrinopathy compared to anti-PD-1 monotherapy (27% vs 9% and 7% vs 0% respectively, P<0.01).

• Endocrinopathies occurred after a median of 8 weeks from treatment commencement (range 12-225 days), with combination immunotherapy resulting in significantly earlier onset compared to ipilimumab (median 30 vs 76 days, P=0.046).

• The majority of endocrinopathies were identified in asymptomatic patients with lab screening.
Endocrinopathies Type 1 Diabetes Mellitus

- Rare, <1%, more common with anti-PD-1/PD-L1
- May occur with rapid onset anytime during therapy
- Monitor serum glucose at baseline and prior to each cycle of checkpoint inhibitor
- Obtain endocrine consult
  - C-peptide and diabetes related autoantibodies*
- Require life-long insulin therapy
- Role of high-dose steroid unclear
  - Exacerbate hyperglycemia
  - No data to suggest high-dose steroid can prevent total β cell loss
- Resume checkpoint inhibitors once blood sugar well-controlled

*Glutamic acid decarboxylase 65 (GAD-65) antibody; Tyrosine phosphatase islet 2 antibody (IA-2); Insulin autoantibody (IAA)

Managing pneumonitis with PD-1 abs

- Fairly uncommon: 0.5 to 3% of patients at grades 2-3
- Uncommon with PD-L1 antibodies; higher with IPI/NIVO
- We routinely check pulse oximetry in all PD-1/PD-1/IPI pts
- Get a chest X-ray in anyone on PD-1 ab with SOB, chronic cough, increased sputum, and have a low threshold for obtaining a CT of the chest and pulmonary consultation!
- High dose steroids with at least 45-60 day tapers with starting doses of at least 1-2 mg/kg are required
- CT findings will lag behind the patient’s symptoms
- 86% of all cases show resolution with immunosuppressants
- Steroids may need to be re-tapered if symptoms return
- Use infliximab at 5 mg/kg if without relief in 72-96 hrs

Neurological irAEs with checkpoint inhibition

• Relatively infrequent (<1% all grades) with IPI or PD-1
• Symptoms:
  – Numbness, tingling, foot drop and localized muscle weakness, or generalized ascending motor and diaphragmatic weakness
• Observed so far:
  – Myesthenia-gravis like syndrome; Guillan-Barré Syndrome
  – Peripheral neuropathy
  – Encephalitis
• Management: get a neurologic consult!
  – for grade 2 or more, discontinue antibodies, work-up including labs and brain MRI, high dose corticosteroid administration with a prolonged taper, neurology consultation, EMG if appropriate
  – Hospitalize if MG-like syndrome
  – Consider rapidly moving to IV Ig and infliximab if grades 3-4 and without resolution of symptoms within 24-48 hours

Cardiotoxic irAEs

- Rare, <1%
- Myocarditis, pericarditis, arrhythmias, cardiomyopathy, and impaired ventricular function have been reported
- Incidence higher with combination
  - Ipilimumab + nivolumab (0.27%)
  - Nivolumab monotherapy (0.06%)
- Early consult with cardiology
- High-dose corticosteroids
- Escalation to other immunosuppressants may be necessary
  - Infliximab
  - Mycophenolic Acid
  - Anti-thymocyte Globulin

Rheumatic irAEs with checkpoint inhibition

• The “dirty little secret” of CPI
• Arthralgias, myalgias and arthritis often present after 12 months of therapy\(^1\)
• Most often seen with PD-1 blockade
• Myositis also an issue at 0.27% of all pts
• Recent data suggested that 2 patients treated with nivolumab died of myocarditis and CHF\(^2\)
• For mild arthralgia, start NSAIDs, and if no improvement, consider low dose steroids (10–20 mg prednisone). In the case of severe polyarthritis, consult a rheumatologist and start prednisone 1 mg/kg. Sometimes infliximab is required for improvement of arthritis
• No clear utility of ANA, sed rate, antibody levels

Other irAEs with checkpoint inhibition

- **Pancreatitis**
  - Amylase/lipase elevation, abdominal pain low, and out of proportion to elevation of lab tests

- **Uveitis**
  - Redness, change in vision; ophtho evaluation
  - Topical corticosteroid eye drops

- **Nephritis (rare)**
  - CT scans show stranding = inflammation
  - Consider steroids if Cr > 2.0
Kinetics of resolution of irAEs with combination checkpoint inhibition

Published in: Mario Sznol; Pier Francesco Ferrucci; David Hogg; Michael B. Atkins; Pascal Wolter; Massimo Guidoboni; Celeste Lebbé; John M. Kirkwood; Jacob Schachter; Gregory A. Daniels; Jessica Hassel; Jonathan Cebon; Winald Gerritsen; Victoria Atkinson; Luc Thomas; John McCaffrey; Derek Power; Dana Walker; Rafia Bhore; Joel Jiang; F. Stephen Hodi; Jedd D. Wolchok; JCO Ahead of Print DOI: 10.1200/JCO.2016.72.1167 Copyright © 2017 American Society of Clinical Oncology
Are irAEs associated with outcome?

• Ninety-eight of 290 patients (34%) experienced any grade irAEs among those receiving PD-1 antibodies at MD Anderson.

• Among the 15 (5.2%) patients with grade ≥ 3 irAEs, the most common irAEs were dermatitis and enterocolitis. Although 80% of the patients with grade ≥ 3 irAEs required systemic corticosteroids, all 15 patients recovered from the irAEs.

• On re-challenge, 4 of the 5 patients who had received systemic corticosteroids for irAE continued to respond. There were no irAE-related deaths.

• Patients with grade ≥ 3 irAEs had improved overall response rate (25 vs. 6%; p = 0.039) and longer median time to progression (30 weeks vs. 10 weeks; p = 0.0040) when compared to those without grade ≥ 3 irAEs.

Fuji, T Invest New Drugs 2017
Are irAEs associated with outcome?

- 389 pts receiving PD-1 were enrolled with ORR 23.1%.
- At median f-u of 12 mos, median PFS was 4.5 months.
- Any grade and grade 3-4 drAEs reported in 124 (32%) and 27 (7%) of pts, respectively; no treatment-related deaths.
- Of the 22 drAEs inducing treatment discontinuation, 10 (45%) were irAEs. Pts with drAEs had a significantly longer OS than those without, (median OS 22.5 versus 16.4 months, p = 0.01).
- Pts with irAEs versus without irAEs had a more significant survival benefit (median OS not reached versus 16.8 months, p = 0.002), confirmed at the landmark analysis at 6 weeks.
- The occurrence of irAEs displayed a strong association with OS in univariable (HR 0.48, p = 0.003) and multivariable (HR 0.57, p = 0.02) analysis.

Verzoni, E et al JITC 2019
Are irAEs associated with outcome?

- 559 NSCLC pts enrolled; 231 pts (41.3%) developed irAEs of any grade and 50 patients (8.9%) G3/G4 events.
- In multivariate analysis, higher ORR was related to irAEs of any grade ($P < .0001$), "single-site" irAEs ($P < .0001$), endocrine ($P = .0043$) and skin irAEs ($P = .0005$).
- Longer PFS was related to irAEs of any grade ($P < .0001$), "single-site" irAEs ($P < .0001$), "multiple-site" irAEs ($P = .0374$), endocrine irAEs ($P = .0084$) and skin irAEs ($P = .0001$).
- Longer OS was related to irAEs of any grade ($P < .0001$), "single-site" irAEs ($P < .0001$), endocrine irAEs ($P = .0044$), gastrointestinal irAEs ($P = .0437$), skin irAEs ($P = .0006$), and others irAEs ($P = .0378$).
- At the 6-week landmark analysis, irAEs of any grade was confirmed an independent predictor of higher ORR, longer PFS, and longer OS

Cortellini, A et al Clin Lung Ca Res 2019
Association of irAEs and Clinical Outcome?

- 7 trials with 1747 patients with urothelial cancer for registration
- Related AESI was reported in 64% of responding patients and in 34% of patients who did not respond to anti-PD-1/L1 antibody
- Related imAE occurred in 28% and 12% of patients who did and did not respond to study drug, respectively.
- In a responder analysis, an increase in overall survival was seen in patients with related AESIs compared with those with no related AESIs (hazard ratio, 0.45; 95% CI, 0.39 to 0.52).
- Fifty-seven percent of responding patients with a related AESI reported the AESI before documentation of response.
- Patients who responded to treatment with an anti-PD-1/L1 antibody were more likely to report a related AESI or related imAE.

Maher, VE et al J Clin Oncol 2019
Are irAEs associated with outcome??

No different in RFS in CheckMate-238 patients who had or did not have any (A) or select (B) irAEs by week 12 as a landmark analysis

Mandala, M et al ASCO 2019
Problems related to management of irAEs

• Waxing and waning symptoms?
• Multiple irAEs in the same patient
• Not waiting too long before starting infliximab?
• Should we be using low dose steroids to treat lingering grade 2 toxicity?
• Using mycophenolic acid to treat lingering amylase/lipase elevations?
• When to start TPN with steroid-resistant colitis?
• Proper dosing (under-dosing) of steroids?
• Slight increase in irAEs for PD-1 vs PD-L1 blockade?
Are there biomarkers, clinical or lab based, associated with development of irAEs?

• For PD-1 antibodies, skin based immune-related adverse events and vitiligo are associated with anti tumor response and survival in melanoma\(^1,2\)

• For nivolumab, an association of any grade irAE with response\(^3\)

• Increased OS and response noted in patients who received immune modulators for irAEs

• Are there lab-based markers associated with irAEs?
  – 248 citations in PubMed on PD-1 toxicity with no papers exploring molecular mechanisms/biomarkers of toxicity
  – 91 citations on Ipilimumab toxicity

Can you resume PD-1 blockade after severe irAEs with combination immunotherapy?

- Eighty patients discontinued combination therapy due to irAEs, including colitis (41%), hepatitis (36%), and pneumonitis (4%).
- 96% received corticosteroids, and 21% received additional immunosuppression (e.g. infliximab).
- 14 (18%) had recurrent irAEs at a median of 14 days after therapy resumption (6 grade 1-2, 7 grade 3-4, 1 grade 5 Stevens-Johnson).
- Colitis was less likely to recur than other irAEs (6% vs. 28%, \( p=0.01 \)). Clinically significant but distinct toxicities occurred in an additional 17 (21%) patients (11 grade 1-2, 6 grade 3-4).
- Patients remaining on steroid therapy at anti-PD-1 resumption had higher rates of toxicities (55% vs. 31%, \( p=0.03 \)).
- One can resume therapy with PD-1 ab alone, but with caution!

Pollack, M et al Ann Oncology 2017
 Restart PD-1 blockade after grades 2-4 irAEs?

• 40 patients with grade 2-4 irAEs were re-challenged with the same anti-PD-1 or anti-PD-L1 agent; 53 were not

• The rechallenged and non-rechallenged groups did not differ in terms of median age, time to initial irAE, irAE severity (grade 2: 18 [47.5%] vs 27 [51%]; grades 3-4: 22 [52.5%] vs 26 [49%]; or steroid use (17 [42.5%] vs 32 [60%]).

• With a median follow-up period of 14 months, the same irAE or a different irAE occurred in 22 patients (55%).

• Shorter time to the initial irAE was linked to the occurrence of a second irAE (9 vs 15 weeks; P = .04).

• The second irAEs were not found to be more severe than the first.

Simonaggio, A et al JAMA Oncology 2019
Use of Tocilizumab to treat irAEs

• 87 patients treated with nivolumab, 34 were given tocilizumab
• All patients were on corticosteroids.
• Pneumonitis in 35.3%, serum sickness/SIRS in 35.3%, cerebritis in 14.7%
• C-reactive protein increased from a median of 23 mg/L (range 0.1–238.5) at baseline to 109.3 mg/L (21.5–350.4) at time of index irAE, with a decrease to 19.2 mg/L (0.25–149) after tocilizumab ($p < 0.00001$).
• Clinical improvement was noted in 27/34 patients (79.4%).
• Some patients (52.9%) required one dose, 38.2% required two, 8.8% required three and 1 patient required four doses.
• For the 53 doses of tocilizumab that were delivered when infliximab was an option, there was a cost savings of $141,048.72

Chipman, RG et al, J Clin Oncol Pharm Prac 2019
• Of 127 patients with lung cancer treated with at least one dose of nivolumab, 42 received the influenza vaccine, and 85 patients were not vaccinated.
• Median follow-up period was 118 days.
• In vaccinated and non-vaccinated patients, the incidence of irAEs was 26% and 22%, respectively, rate ratio 1.20 (95% confidence interval [CI] 0.51-2.65).
• The incidence of serious irAEs was 7% and 4%, respectively, rate ratio 2.07 (95% CI 0.28-15.43).
• Influenza vaccination during nivolumab did not result in significant differences in death, clinical toxicity or tumor response between the groups.

Wijn, DH et al Eur J Cancer 2018
Checkpoint Inhibitor Treatment and irAEs: Take-home points

• Most irAEs occur during the first 12 weeks of checkpoint inhibitor therapy, i.e. during the induction period
• Steroids can be used to manage almost all irAEs
• Prolonged steroid tapers are required
• irAEs can wax and wane, particularly colitis
• Late irAEs can occur: one episode has been seen at month 47 during maintenance
• Multiple irAEs can occur in any given patient
• Minimal evidence of permanent symptoms
• However, PD-1/PD-L1 blocking drugs are safe!