From the frontlines: Adverse Effects of Immune Checkpoint Blockade

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Stage IV esophageal adenocarcinoma with neuroendocrine features, involvement of lower 1/3 esophagus and axillary/supraclavicular nodes, PDL1 positive.

Clinical trial regimen capecitabine with the immune checkpoint inhibitor pembroluzimab vs placebo initiated 10 weeks prior, last cycle 8 d prior to visit.

Progressive dyspnea, worse on exertion, as well as progressive peripheral neuropathy.

Room air sats 87%, HR 90, BP 137/61, T97.8. Chest clear, decreased at bases. WBC 9.4. Hgb 9.6. Cr 1.3. CTA ordered to rule out PE.
But wait...what *is* an immune checkpoint inhibitor?
Therapeutic strategies to activate T-Cells in treating cancer

# Immune Checkpoint-Blocking Antibodies Approved by the Food and Drug Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target*</th>
<th>Indication</th>
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<td>Ipilimumab (Yervoy)</td>
<td>CTLA-4</td>
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<td></td>
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<td>Nivolumab (Opdivo)</td>
<td>PD-1</td>
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<td>• Head and Neck Squamous Cell Cancer</td>
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<td>• Classical Hodgkin Lymphoma</td>
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<td>• Urothelial Carcinoma</td>
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<td></td>
<td></td>
<td>• Colorectal Cancer with Microsatellite Instability-High Cancer or Mismatch Repair Deficient</td>
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<td>• Hepatocellular Carcinoma</td>
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<td>• Merkel Cell Carcinoma</td>
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<td>Cemiplimab (Libtayo)</td>
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<td>Atezolizumab (Tecentriq)</td>
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<td>• Non-Small Cell Lung Cancer</td>
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</tbody>
</table>

* Cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1)

1. [http://www.accessdata.fda.gov](http://www.accessdata.fda.gov)
Organs Affected by Immune Checkpoint Blockade

- Encephalitis, aseptic meningitis, hypophysitis, uveitis
- Thyroiditis, hypothyroidism, hyperthyroidism, dry mouth, mucositis
- Pneumonitis, rash, vitiligo
- Thrombocytopenia, anemia, myocarditis
- Hepatitis, pancreatitis, autoimmune diabetes
- Adrenal insufficiency, nephritis, vasculitis, colitis, arthralgia, enteritis, neuropathy
Timing of onset of irAE variable, most commonly within first 3 months of rx, can occur >6 months post last dose.

The ultimate internist challenge: diagnosis of immune mediated adverse events (irAE):

- Symptoms nonspecific (eg fatigue)
- Any organ may be involved
- Strive for equipoise between two contradictory thoughts:
  - 1. “There should be a high level of suspicion that new symptoms are treatment related.” [American Society of Clinical Oncology guidelines]
  - 2. Diagnosis of exclusion:
    - related to underlying cancer
    - infection, including opportunistic secondary to prior cytotoxic chemorx
    - other unrelated organ dysfunction
- Multidisciplinary involvement: oncology and non-oncology specialists (at a minimum to rule out non-irAE etiologies)
Examples:

- **Dyspnea:** ?pneumonia ?pulmonary embolism ?pneumonitis ?myasthenia gravis or Guillain barre ?myocarditis ?arrhythmia ?pericarditis (cancer or irAE), ischemic cardiac event?

- **Fever and weight loss:** ?infection ?cancer ?thyroiditis

- **Headache:** ?CNS cancer involvement ?hypophysitis ?encephalitis (irAE or infectious or paraneoplastic) ?meningitis (infectious or irAE)

- **Fatigue:** ?all of the above ?if endocrine, primary or secondary?


- **New severe constipation:** ?narcotics ?hypothyroid ?myenteric plexus neuropathy
Most common organ systems adversely affected by immune checkpoint blockade

- Skin: maculopapular, vitiligo, severe inflammatory (Stevens-Johnson, TEN, DRESS) less common
- GI tract: colitis, mucositis, pancreatitis
- Endocrine: thyroid, hypophysitis, diabetes
- Liver: hepatitis
- Rheumatologic/musculoskeletal: arthritis, myalgia, myositis less common
- Pulmonary: pneumonitis, sarcoid, reactivation tb
Lower frequency organ involvement from immune checkpoint blockade

- Central Nervous System: encephalitis, transverse myelitis, myasthenia gravis, Guillain Barre, polyneuropathy, enteric neuropathy, posterior reversible leukoencephalopathy, demyelination
- Cardiovascular: myocarditis, pericarditis, arrhythmia, vasculitis
- Hematologic: hemolytic anemia, ITP, aplastic anemia
- Renal: interstitial nephritis, RPGN
- Ocular: uveitis, episcleritis
Four possible physiologic mechanisms of immune related adverse events (irAE)

There are no randomized controlled trials on treatment of irAE from checkpoint inhibitors

- Case series
- Individual case reports
- Expert opinion
  - Guidelines:
    - National Comprehensive Cancer Network (NCCN) 2019
    - American Society of Clinical Oncology (ASCO) 2018
    - European Society of Medical Oncology (ESMO) 2017
    - Society for Immunotherapy of Cancer (SITC) 2017

- Disclaimer from ASCO relevant to all above except NCCN: “This information is not continually updated and may not reflect the most recent evidence.”
Pharmacologic management of irAE from ICI

• Hold or discontinue ICI therapy for all moderate to severe irAE
• Systemic steroids (prednisone or methylprednisolone) = primary rx
• Dosing:
  • .5 mg/kg for moderate (grade 2) if used
  • 1-2 mg/kg severe (grade 3-4)
• Duration:
  • Slow taper over ≥ 1 month after toxicity resolves to low grade or better
Management of steroid refractory severe irAE

- **Infliximab** (TNF inhibitor): Given if no response to high dose steroids within 48-72 hours, 5 mg/kg x 1; may give second dose 2 weeks after first if needed. *Not used in hepatitis currently.*
  - **Vedolizumab** (integrin antagonist): alternative to infliximab for colitis, inhibits migration of T-cells across endothelium, may avoid systemic immune suppression.

- **Mycophenolate**
- **IVIG**
- **Plasmapheresis**
Steroid refractory severe irAE, other agents

- Antithymocyte globulin (ATG)
- Rituximab
- Tacrolimus
- Tocilizumab
- Cyclosporine
- Cyclophosphamide
- DMARDs for rheum/arthritis (methotrexate, sulfasalazine, leflunomide)
- Abatacept (myocarditis, case report)
- Alemtuzumab (myocarditis, case report)
7 weeks after starting ipilimumab, different patient presents with abdominal cramping, watery diarrhea, > 8 bowel movements/d above baseline

- Colitis frequency: 25% CTLA-4, 5% PD-1/PD-L1
- Colitis grading:
  - Mild (G1): < 4 BM/d above baseline, no colitis sx
  - Moderate (G2): 4-6 BM above baseline, colitis sx, not interfering with ADLs.
  - Severe (G3-4): >6 BM above baseline, colitis symptoms, interferes with ADLs. May be hemodynamically unstable, serious complication (ischemic bowel, perforation, toxic megacolon).
- Colitis rx:
  - Mild (G1): Consider hold ICI, rx Imodium/Lomitil, hydrate, monitor.
  - Moderate: Hold ICI, rx prednisone 1 mg/kg, increase to 2 mg/kg if no improvement in 2-3 d
  - Severe: D/C ICI, inpatient care, iv methylpred 2 mg/kg/d, infliximab, consider vedolizumab.
New onset severe constipation/Ogilvie’s

61 year old woman with metastatic NSCLCA (nodes in neck, upper mediastinum, malignant pleural and pericardial effusions), PD-L1 90% positive, with excellent tumor resolibe by CT to cytotoxic chemotherapy plus pembroluzimab but irAE including hepatitis requiring steroids and recent hemorrhagic esophagitis/mucositis, as well as pulmonary emboli, presents with abdominal pain and new severe obstipation.

Consider: immune-mediated constipation secondary to myenteric ganglionitis.

Pneumonitis

- Classic presentation nonproductive cough, shortness of breath, hypoxia, absence of fever.
- Frequency: 2-5%
- Classic CT ground glass and/or interstitial thickening, but variable.
- Evaluation includes bronchoscopy.
- Rx: Prednisone/methylprednisolone 1-2 mg/kg/d, empiric abx. No better within 48 hours: Infliximab 5 mg/kg, may repeat in 14 days if needed.
Variable CT presentation of pneumonitis

Headache and hypotension following several cycles Ipilimumab (CTLA-4)
Hypophysitis following anti-CTLA-4 ICI

- Frequency: Up to 10% with anti CTLA-4
- Presentation:
  - Symptomatic adrenal insufficiency, +/- hypothyroid (+/- hypogonatotrophic hypogonadism): fatigue, hypotension.
  - If acute/early onset phase: headache, photophobia, dizziness, nausea, visual field cuts.
- Evaluation: AM cortisol, ACTH, TSH, free T4, FSH, LH, testosterone, estradiol, Na, K. If acute sx (HA): MRI brain/sella +/- contrast
- Rx: Replacement dose steroids (hydrocortisone 10-20 mg am, 5-10 mg pm). If concurrent hypothyroid, initiate steroids first to avoid adrenal crisis. If inflammatory sx, higher dose steroids initially considered.
- Duration: Destructive process, life-long replacement generally required.
• Frequency: Up to 30%, occurs early
• Presentations:
  • Most common maculopapular rash on trunk, proximal limbs, generally pruritic
    • Rx topical steroids, antihistamines if mild
    • Severity grading based on BSA, systemic steroids if severe
  • Vitiligo common in melanoma patients
  • Rare severe inflammatory (Stevens-Johnson, TEN, DRESS)
    • Hospitalize, derm consult, etc.
66 yo woman with metastatic lung cancer presented with ptosis, diplopia, subacute painful paresis proximal muscles post 3 doses of nivolumab. Now complains of chest pain...

- Troponin T 1616; CK 1,400; N-terminal pro BNP 4,172
- Normal coronary arteries on angiography
- Cardiac MRI showed...

Myocarditis

- Frequency: Uncertain, 1% in one large series, less in others but likely underreported.
- Co-occurrence with myasthenia gravis and myositis common
- Common initial symptoms: weakness, fatigue, followed by dyspnea, atypical chest pain.
- High mortality, often from refractory VT with normal EF
Myocarditis less common irAE, most fatal

65 yo woman with atypical chest pain and dyspnea 12 days 1st dose ipilimumab/nivolumab for metastatic melanoma

- CK 17,720, Troponin I 4.7 rising to 51.3
- Prolonged PR rapidly progresses to complete heart block within 24 hours
- EF 73% on echo
- Methylprednisolone 1 mg/kg
- Progressive multiorgan failure and refractory VT from which could not be resuscitated
NCCN management recommendations for severe/life-threatening myocarditis

• Immediate cardiology consultation and admission with cardiac monitoring
• Diagnostic evaluation to include echo, cardiac MRI, cardiac and inflammatory biomarkers (CK, troponin, ESR, CRP, WBC)
• Permanently discontinue immunotherapy
• Methylprednisolone pulse dosing 1 g/day x 3-5 days then high dose prednisone 1-2 mg/kg/d until improved then taper over 4-6 weeks
• If no improvement in 24 hours: consider infliximab, consider anti-thymocyte globulin
First-line treatment: 6 cycles of carboplatin-pemetrexed

Second-line treatment: 3 doses of nivolumab, 240 mg/15 days

Thoracic imaging

Cancer diagnosis

Thoracic imaging

Myocarditis diagnosis

Cardiac MRI and echocardiography

Thoracic imaging

Electrical instability

Echocardiography

Thoracic imaging

Echocardiography

24-Hr Holter monitoring

ULN—Upper limit of the normal range

Grade 4

Grade 3

Grade 2

Grade 1

Immune-related adverse events

Intravenous

Oral

Plasma exchange

Abatacept injection

Development of irAE may correlate with tumor response to immune checkpoint inhibitor (ICI)

Correlation between development of vitiligo and tumor response to melanoma treated with PD-1 blockade

Diarrhea following ICI rx may correlate with improved overall survival [though severe colitis most common fatal irAE]

Patients developing rheumatologic irAEs may have higher tumor response rate than those with no irAEs

Lo et al. JAMA Oncol 2015
Sanlorenzo M et al. JAMA Dermatology 2015
Thompson JA et al. NCCN Guidelines 2019
Fatigue: an immune mediated adverse event?

• 7 patients with longstanding chronic fatigue syndrome developed malignant disease (Hodgkin lymphoma, DLCB-cell lymphoma, breast ca) and independently reported resolution of CFS with cyclophosphamide/ifosfomide/rituximab

• Open label trial rituximab in 30 pts with CFS, 50% pts improved

• 151 pts with CFS randomized rituximab vs placebo, no effect

• But still….why DO patients on ICI treatment get so tired?


Antoni Ribas, and Jedd D. Wolchok Science 2018;359:1350-1355
Back to our first patient with PD-1 positive esophageal cancer treated with cytotoxic chemo plus pembrolizumab vs placebo….

• CT read: “Significant bilateral groundglass and interstitial opacities, basilar predominant, with small bilateral pleural effusions. Constellation of findings most likely represent pulmonary edema. Infectious, alveolar, or inflammatory etiologies are also within the differential but considered less likely. No PE.”
On admission...

- Complains of dyspnea. No cough, fever, chest pain.
- PMH: Aortic stenosis post replacement, HTN, depression, CKD, GERD, BPH, Hx CVA no residual, peripheral neuropathy
- Meds: ASA, atorvastatin, buproprion, fluoxetine, losartan, omeprazole, tamsulosin, trazadone
- T 97.8  BP 112/52  HR 77  SaO2 92% 2L
- Chest clear, cardiac exam unremarkable, extremities without edema
- BNP 143, Troponin .02. Procalcitonin low, flu neg, CRP 134
- Echo with EF 50-55%, anteroseptal and anterior wall motion abnl. EKG nl.
- Admitting impression: HFpEF vs viral pneumonia vs checkpoint inhibitor toxicity.
- Rx: Furosemide.
Pembroluzimab induced pneumonitis

• HOSPITAL DAY 2
  • Initial subjective improvement with diuresis
  • Oxygen requirement increased to 8L, faint basilar crackles on exam.
  • CXR extensive reticular densities, mainly peripherally.
  • Oncoming hospitalist concerned for pembrolizimab induced pneumonitis
  • Discussed with primary oncologist
  • Prednisone 1 mg/kg = 80 mg, oral furosemide

• HOSPITAL DAY 3
  • Oxygen requirements increased to high flow
  • Clinical trial unblinded confirming had received pembrolizumab
  • Methylprednisolone 2 mg/kg substituted for prednisone 1 mg/kg, plan for infliximab if not improving within 24 hours
  • Pulmonary consult, empiric antibiotics, bronchoscopy following day: no evidence malignancy, neg cytology, inflammatory cells, gram stain c/w normal flora
Fatal pneumonitis, complicated by pembroluzimab mediated ITP and pulmonary hemorrhage

- Received infliximab 5 mg/kg x 2 doses 14 days apart (1st dose 48 hrs post steroids begun)
- Empiric antibiotics discontinued
- Methylprednisolone increased to 125 mg q 6 hours prior to taper
- ICU transfer observed on BiPap, no intubation
- O2 requirement improved to 6L NC, prednisone down to 60 mg/d,
- Sub-cutaneous emphysema and pneumomediastinum
- Thrombocytopenia to plts 17 K, HIT negative, HIV/Hep C neg, rx’d IVIG for possible ITP, bone marrow considered, progressively weak and tired
- Frank hemoptysis, abrupt worsening respiratory status, goals transitioned to comfort
- Died hospital day #30
Fatal toxic effects associated with immune checkpoint inhibitors: JAMA oncology 2018

Table 1. Spectrum of Fatal Immune-Related Adverse Events in Viglyteze

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
<th>Anti-PD-1/PD-L1 (n = 333)</th>
<th>Combination (n = 87)</th>
<th>P Value</th>
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<td>Types of cancer*</td>
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<td>Melanoma</td>
<td>136 (96)</td>
<td>59 (18)</td>
<td>49 (66)</td>
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<td>Lung cancer</td>
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<td>152 (54)</td>
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<td>Other</td>
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<td>78 (28)</td>
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<td>Type of fatal irAE</td>
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<td>Colitis</td>
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<td>3 (2)</td>
<td>14 (4)</td>
<td>2 (2)</td>
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<tr>
<td>Other (skin, thyroid, diabetes, other gastrointestinal)</td>
<td>13 (7)</td>
<td>24 (8)</td>
<td>7 (8)</td>
<td>.93</td>
</tr>
</tbody>
</table>

Other clinical features

| Median time to irAE, days | 40 | 40 | 14 | < .01 |
| >1 concurrent irAE, % | 27 (14) | 51 (15) | 24 (28) | < .01 |

Reporting year

| 2014 or before | 98 (51) | 3 (1) | 2 (2) | < .001 |
| 2015 | 45 (23) | 20 (6) | 9 (10) | < .001 |
| 2016 | 21 (11) | 88 (28) | 17 (20) | .001 |
| 2017 | 26 (13) | 192 (58) | 44 (51) | < .001 |
| 2018 (up to January 15) | 3 (2) | 30 (9) | 15 (17) | < .001 |

Abbreviations: irAE, immune-related adverse event; PD-L1, programmed death ligand-1; PD-1, programmed death-1.

* Percent of known 52 patients treated with ipilimumab, 53 with anti-PD-1/PD-L1, and 13 with combination did not list cancer types.
Quality improvement to consider for your institution

- Patient education (wallet cards)
- ER provider, primary care, and subspecialty education
- Pharmacy education, alert on inpatient rounds if history immunotherapy
- Electronic medical record: easily identify pts on ICI, consider irAE treatment order sets
- Participate in regional irAE multidisciplinary ground rounds
- Consider irAE consult service if you have volume/capacity
- Report immune related adverse events.
EMR strategy to easily identify patients who have received immune checkpoint inhibitors: color change

- All caring for patient have instant visual notification of risk for irAE
  - ER triage RN and MD
  - Hospitalist, subspecialist consult
  - Primary care
  - Radiologist
  - Pathologist

- Passive notification
  - Avoids alert fatigue
  - Needs no additional screen space
If you are treating a severe/life threatening irAE, consider asking your institutional pharmacy to report it

https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=professional.reporting1
References


• Few slides shared by Yelena Y. Janjigian MD, Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center.


• Hasalam A. Estimation of the percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor immunotherapy drugs. JAMA Network Open.2019;2(5):e192535

• Cole S et al. Managing immuno-oncology toxicity: top 10 innovative institutional solutions. 2019 ASCO Educational Book (asco.org/edbook)

References

