Adverse effects of Immunotherapy

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Financial Disclosures

- None

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Objectives

- Understand intensity of the AEs.
- Understanding unique side-effects .
- Develop effective monitoring and management guidelines.

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Tumor Immunotherapy possible?

- “It would be difficult to reject the right ear and leave the left ear intact, as it is to immunize against cancer”.

W.H Woglom, Cancer Research 1929

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Diversity

- Cytokine therapies that induce capillary leakage to vaccines associated with low levels of autoimmunity .
- Cell therapies that can induce damaging cross-reactivity with normal tissue .
- Checkpoint protein inhibitors that induce immune-related adverse events that are autoinflammatory in nature.

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TOXICITIES OF CANCER VACCINES

- associated with minimal toxicity.

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TOXICITIES OF CANCER VACCINES

Complicated

- variety of antigens targeted.
- diversity of formulations.
- adjuvants used.
- combination with immunomodulators that may induce autoimmune phenomenon.

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TOXICITIES OF CANCER VACCINES

- Vaccines for melanoma targeted against melanocyte differentiation antigens.
- Vitiligo after administration of melanoma vaccines and is associated with a beneficial outcome

Cancer Immunol Immunotherapy 60:433-442, 2011
Ann. Oncol. 21:409-414, 2010

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TOXICITIES OF CANCER VACCINES

- adverse events (AEs) in trials of cancer vaccines administered with various adjuvants.
- 239 phase I and II studies performed between 1990 and 2011, with a total of nearly 5,000 patients.
- A total of 162 grade 3 and five grade 4 AEs were attributed to vaccination.

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J Immunol 168:4231- 4240, 2002

TOXICITIES OF CANCER VACCINES

- Local injection site reactions, constitutional symptoms such as myalgia and flu-like syndromes were the most common toxicities seen.
- Of the three cancer vaccine trials that reported reaching a dose-limiting toxicity, two used live attenuated bacterial vectors.
- Hypotension was dose limiting.

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Clin Cancer Res 20:4758-4767, 2014

Why low AEs?

- Targeted tumor-associated antigen proteins- markedly overexpressed in cancer cells but are found at low or undetectable levels in normal cells.
- T-cell response against overexpressed self-proteins selectively elicit tumor-specific immunity but not immunity against non malignant tissues expressing the targeted protein.

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BMC Cancer 14:270, 2014
J Clin Oncol 26:1452-1458, 2008

- Sipuleucel-T, -favorable toxicity profile.
- transient chills, fatigue, and fever commonly seen within 24 hours of an injection
- less than 4% of AEs were grade 3 or 4.
- Back pain and chills were the most common overall grade 3 to 4 AEs -2% .

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Cancer 115:3670-3679, 2009
J Clin Oncol 22:1916-1925, 2004
N Engl J Med 363:411-422, 2010

- the use of antigen-specific cancer vaccines in conjunction with checkpoint inhibitors –no additive or enhanced toxicity

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Lancet Oncol 13:501-508, 2012

TOXICITIES OF CYTOKINES

- Recombinant human interferon alfa (IFN).

❖Constitutional symptoms >80%

❖fever and fatigue, headache and myalgias

❖Neuropsychiatric issues

❖Pancytopenias

❖Autoimmunity, Myocarditis, Neurotoxicity

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- High doses of the cytokine interleukin-2 .

❖ICU monitoring and hemodynamic support delivered by an experienced team.

❖fever, chills, and GI Aes ie nausea, vomiting, anorexia, diarrhea, transaminitis, cholestasis with hyperbilirubinemia.

❖fluid retention ie pleural effusions and occasionally pulmonary edema, hypotension, and prerenal azotemia.

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TOXICITIES OF ADOPTIVE CELL THERAPY

- Preparative chemotherapy regimen for lymphodepletion causes 7 to 10 days of neutropenia and thrombocytopenia, which reverses spontaneously.
- Sepsis remains the dominant cause of the 1% to 2% rate of treatment-related mortality with cell therapy that includes lymphoid depletion.

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Cytokine syndrome

- When systemic IL-2 is given with T cells, the syndrome onset is more rapid and is likely a direct consequence of the IL-2.
- Without IL-2, it may appear later (day 5 through 7 after T-cell infusion).

- Autoimmunity induced by administered T cells may occur. This has observed when a receptor targeting a normal self-protein is retrovirally engineered into autologous PBLs.

CHECKPOINT PROTEIN INHIBITORS

Table 1. PD-1 and PD-L1 Antibodies in Clinical Development

Target and Agent	Class
PD-1	
Nivolumab (MDX1106, BMS-936558)	IgG4 fully human Ab
Pembrolizumab (MK-3475)	IgG4 engineered humanized Ab
Pidilizumab (CT-011)	IgG1 humanized Ab
PD-L1	
BMS935559 (MDX-1105)	IgG4 fully human Ab
MPDL3280A	IgG1 engineered fully human Ab
MEDI4736	IgG1 engineered fully human Ab
MSB0010718C	IgG1 fully human Ab
PD-1–positive T cells	
AMP-224	Fc of human IgG–PD-L2 fusion

Abbreviations: Ab, antibody; IgG, immunoglobulin G; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein 1 ligand.

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CHECKPOINT PROTEIN INHIBITORS

Anti-CTLA-4 Antibodies

Antibody	Investigational Names	Manufacturer	Antibody Type	Plasma Half-Life (days)
Ipilimumab (Yervoy)	MDX-010	Medarex/Bristol-Myers Squibb	Human	15
	BMS-734016		IgG1	
Tremelimumab	CP-275206	Pfizer	Human	22
	Ticilimumab		IgG2	

- Abbreviations: IgG1, immunoglobulin G1.

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- Boosting the immune system leads to toxicities that are derived from the hyperstimulation of our immune system.
- Incidence and severity of these toxicities - dose related.
- Relationship between dose and toxicity that has been observed with ipilimumab is not noted with anti PD1.

Check point AEs

- On- and off-target.
- Cell and metabolic toxic effects that need to be carefully monitored.

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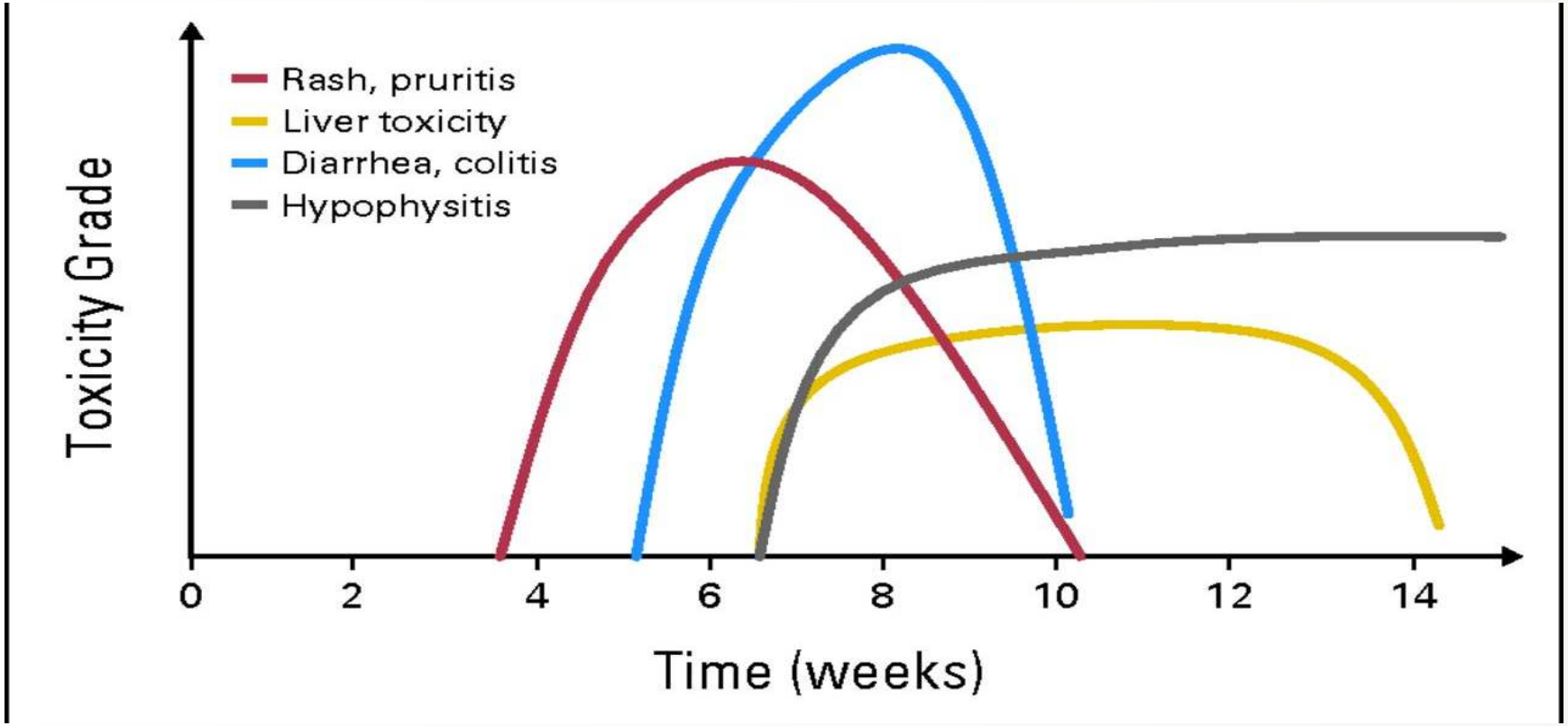
Kinetics of Appearance of irAEs With Checkpoint Blockade



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Kinetics of Appearance of irAEs With Checkpoint Blockade

- The kinetics of onset of irAEs, particularly with ipilimumab, follow a predictable pattern.
- Skin-related toxicities occur first; colitis appears next, after one to three doses.
- hepatitis and endocrinopathies occur last, often after the third or fourth dose of ipilimumab.
- Endocrinopathies occur late and have been seen between weeks 12 and 24. The same phenomenon has been observed with nivolumab and pembrolizumab, with rashes and GI toxicity seen early and liver toxicity or endocrinopathies seen later .

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Summary of CTLA-4 Blockade Immune-Mediated Toxicities

- Toxicity related to ipilimumab appears to be dose related
- Toxicity-related death occurred in < 1% of cases

Common (> 20%)

- Rash, pruritus
- Fevers, chills, lethargy
- **Diarrhea/colitis**

Occasional (3% to 20%)

- Hepatitis/liver enzyme abnormalities
- Endocrinopathies: hypophysitis, thyroiditis, adrenal insufficiency

Rare (< 2%)

- Episcleritis/uveitis
- Pancreatitis
- Nephritis
- Neuropathies, Guillain-Barré, myasthenia gravis
- Lymphadenopathy (sarcoid)
- Thrombocytopenia
- Toxic epidermal necrolysis, Stevens-Johnson syndrome

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ASSOCIATION OF irAEs WITH CLINICAL BENEFIT

- Data from early ipilimumab trials suggested that there was an association between irAEs and clinical benefit.
- In one trial in which 56 stage IV patients were treated with ipilimumab and a peptide vaccine, 36% of patients with a grade 3 or 4 irAE achieved a clinical response (complete response [CR] or partial response), whereas only 5% of patients without an irAE responded.

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Proc Natl Acad Sci U S A ***100****:8372–8377.*

AE's are dose related

- CTLA-4–blocking antibody ipilimumab, toxicities are dose related, -rate of grade 3 to 4 drug-related serious AEs increased from 5% to 18% when the dose was increased from 3 to 10 mg/kg and was 0% at a dose of 0.3 mg/kg.
- toxicities of PD-1 blockade with nivolumab are similar at doses ranging from 0.3 to 10 mg/kg.

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Lancet Oncol 11:155-164, 2010
N Engl J Med 366:2443-2454, 2012

- Toxicities with PD-1/PD-L1 agents may be slower to resolve than with ipilimumab, so long-term surveillance is advised.

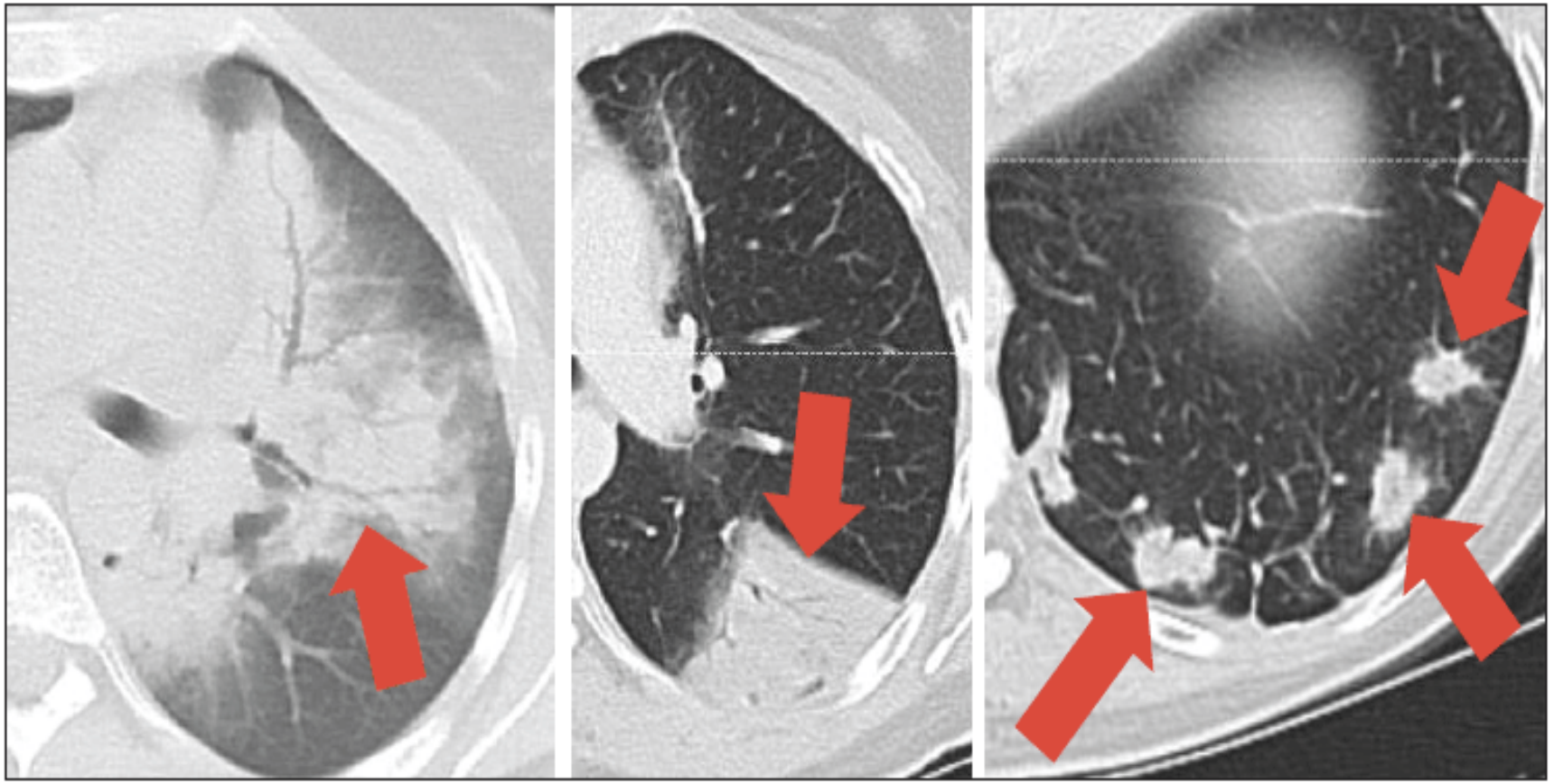

Figure 3: Different Radiographic Patterns of Checkpoint Blockade–Associated Pneumonitis Seen on CT Scanning in a Single Patient Treated With Ipilimumab and Nivolumab—Pneumonitis secondary to ipilimumab is shown in the left-hand panel, and pneumonitis secondary to nivolumab is shown in the center and right-hand panels. Red arrows indicate areas of radiologic abnormality.

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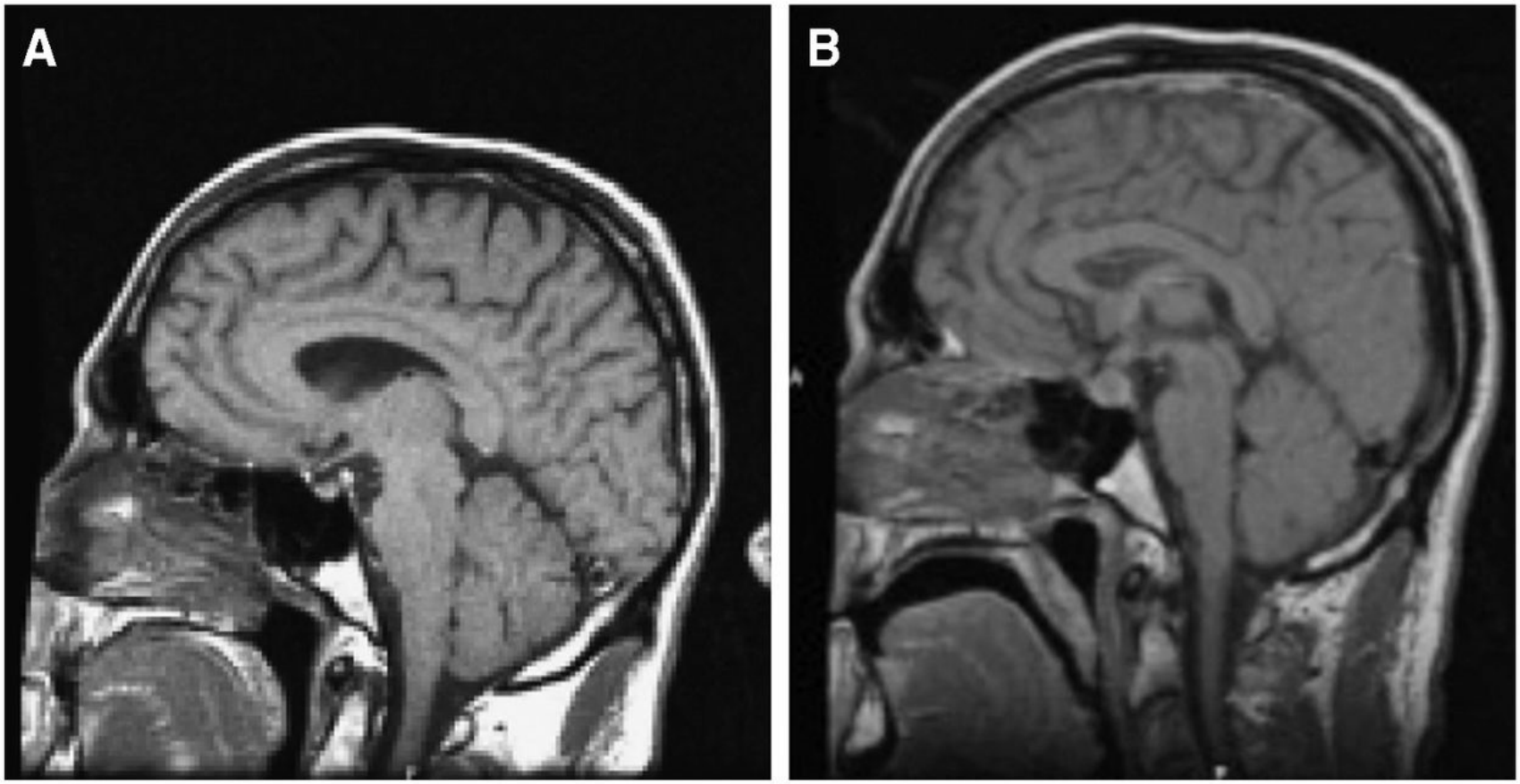
Colitis

- Grade 3 to 4 colitis occurs in 6% to 14% of patients receiving ipilimumab, but in only <1% of those receiving PD-1/PD-L1 antibodies.
- High doses of corticosteroids are required for severe colitis. Infliximab should be administered to patients whose colitis fails to resolve within 3 days of high-dose cortico-steroids or to those who experience a relapse of colitis symptoms with corticosteroid taper.

- Immune-related hematologic and neurologic toxicities
- Encephalitis, Guillain-Barré syndrome, and a myasthenia gravis–like syndrome
- Bone marrow suppression is rare and likely on an autoimmune basis for ipilimumab

Endocrinopathy

- A specific concern in patients with endocrinopathies is the difficulty in delivering subsequent IL-2 therapy, including as a component of adoptive cell therapy, to patients with inadequate adrenal function on replacement corticosteroids.



6/30/04 - Baseline (4.5 mm)

12/3/04 - Headache/fatigue (10.8 mm)

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Jeffrey S. Weber et al. JCO 2012;30:2691-2697

- Thyroid function studies, complete blood counts, and liver function and metabolic panels at each treatment and at intervals of 6 to 12 weeks for the first 6 months after finishing treatment.

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- ACTH, cortisol, and in men, testosterone - in patients who develop fatigue and nonspecific symptoms.
- Follow-up testing - to increase in frequency based on individual response and AEs that occur.
- Corticosteroids can reverse nearly all of the toxic manifestations of these drugs, only for grade 3 to 4 or prolonged grade 2 immune-related AEs.

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3 QUESTIONS

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- Which Immune related adverse effect is the first to appear with CTLA 4 Antibodies?
  1. Endocrinopathy.
  2. Colitis.
  3. Skin changes.
  4. Hepatitis.

Answer: Colitis.

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- **A 69-year-old man with recurrent metastatic melanoma is currently receiving pembrolizumab 2 mg/kg IV every 3 weeks. Between cycles 2 and 3, he calls complaining of mild diarrhea with 4 bowel movements per day and a low-grade fever.**
- **On examination, the patient indicates that he has had continued fatigue but his weight is stable and he has not had any abdominal pain. Laboratory results reveal elevated amylase (1.6 x ULN) and lipase (1.7 x ULN).**

1. Continue Rx and monitor.
2. Hold Rx until resolved to Grade 1 and then restart.
3. Hold Rx, initiate steroids and restart after resolution of symptoms to Grade 1.
4. Permanently discontinue Rx and initiate steroids.

Answer- Hold Rx, initiate steroids and restart after resolution of symptoms.

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Which of the following is true?

1. CTLA-4 antibody Ipilumumab causes symptomatic pneumonitis in the range of 10%.
2. The kinetics of onset of irAEs, particularly with ipilimumab, follow a predictable pattern and Skin-related toxicities occur first.
3. Infliximab should not be administered to if colitis fails to resolve within 3 days of high-dose corticosteroids .
4. Toxicities with PD-1/PD-L1 agents are faster to resolve than with ipilimumab.

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Answer 2-The kinetics of onset of irAEs, particularly with ipilimumab, follow a predictable pattern and Skin-related toxicities occur first.