Immuno-Oncology: A Revolution in Cancer Therapy

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Disclosures

Consultant:   Bristol-Myers Squibb
             Merck
             Amgen
Objectives

• Describe principles of cancer immunotherapy and the mechanisms underlying recently developed immuno-oncology drugs
• Summarize the clinical activity of these agents across tumor types
• Assess a given patient’s suitability for therapy with an immuno-oncology drug
• Discuss optimization of patient outcomes by appropriate management of immune-mediated adverse events associated with immuno-oncology drugs
What is Immuno-Oncology?

• Immuno-Oncology focuses on harnessing the tremendous power of the human immune system to detect and destroy cancer.

• Why is the human immune system potentially the ultimate anti-cancer therapy?
  – **Specificity**: virtually infinite antigen recognition
  – **Adaptability**: based on tumor genetic & epigenetic changes
  – **Memory**: durable responses even after drug discontinuation
FDA-approved Immune Checkpoint Blockade Antibodies

- **CTLA-4 antibody**
  FDA-approved for patients with advanced and high-risk resected melanoma

- **PD-1 antibody**
  FDA-approved for patients with advanced melanoma, lung and kidney cancers (nivo)

*Ipilimumab + nivolumab*: approved for patients with advanced melanoma
Immune Checkpoint Blockade: Mechanism of Action

T cell

GO

Tumor cell or APC

STOP (aka: immune checkpoints CTLA-4, PD-1, PD-L1, etc.)
CTLA-4 Blockade: Long-Term Melanoma Remissions

Ipilimumab: Pooled Survival Analysis From Phase 2/3 Trials in Advanced Melanoma; N = 1,861
3-year OS rate = 22%

Nivolumab (anti-PD-1) in Melanoma: Overall Survival

4-year OS = 32%

No. at Risk
Total: 107 97 86 71 64 55 51 50 49 47 43 39 35 23 19 16 16 15 13 5 2 1 1 0

Objective responses to anti-PD-1/L1

- Melanoma
- Lung
- Kidney
- Bladder
- Head and Neck
- Biliary tract
- Skin squamous cell
- Hepatocellular
- Merkel cell carcinoma
- Glioblastoma
- Thymic
- Gastric
- Ovarian
- Cervical

Ongoing advances in immuno-oncology will continue to dramatically change how we treat patients with multiple tumor types.
A 58-year-old woman with advanced cancer progresses following standard targeted therapy. She has a recent history of systemic lupus erythematosus. Would you consider this patient a candidate for a clinical trial with an immune checkpoint inhibitor?

A. No – clinical data suggest that immune checkpoint therapy is not effective cancer therapy beyond the first-line setting.
B. No – prior targeted therapy is a contraindication
C. No – a recent history of an autoimmune disease would likely disqualify enrollment in a clinical trial
D. Yes – this patient would likely be eligible for a checkpoint blockade inhibitor clinical trial
Patient selection

1. Tumor burden / rapidity of growth
   • Anti-tumor impact of immune checkpoint blockade therapy can take several weeks

2. Immunologic comorbidities
   • Caution with underlying immune dysregulation (e.g., autoimmune conditions, organ transplant)

3. Overall ability to tolerate immune-related toxicity
Case Presentation

- 51 y.o. man with stage IV melanoma
- Low disease burden: several small (1-2cm) subcutaneous and pelvic lymph node metastases; no CNS involvement
- BRAF V600E
- Medical history: hyperlipidemia
- Medications: statin x 1 year
- Occasional EtOH

Vote: Immunotherapy vs targeted agent vs chemo
Preparing Patients for Immune Checkpoint Blockade Therapy

1. Tumors may appear to grow before they shrink
Immune-related response to nivolumab (anti-PD-1) in a patient with lung cancer

Preparing Patients for Immune Checkpoint Blockade Therapy

1. Tumors may appear to grow before they shrink

2. **Toxicities:**
   - Immune-related adverse events (irAEs) can affect any organ system
   - Keeping in close touch with the health care team is crucial
   - Immune-related toxicities can occur even after therapy has ended
Monitoring for irAEs

• Prior to each dose:
  – Careful review of systems & clinical evaluation including assessment for common immune-related toxicities
  – CBC w/ diff, CMP, TFTs, cortisol, lipase

• Careful clinical and laboratory assessments should occur at regular intervals after cessation of therapy
Immune-Related Adverse Events

• Drug-related inflammatory processes potentially affecting any organ system
• Distinct mechanism of action from traditional chemo-related side effects
• Evaluation and management are unique to this class of drugs
Select immune-related toxicities

Hypophysitis
Thyroiditis
Adrenal Insufficiency
Enterocolitis
Dermatitis

Pneumonitis
Hepatitis
Pancreatitis
Motor & Sensory Neuropathies
Arthritis
Less common immune-related toxicities

- **Hematologic** (hemolytic anemia, thrombocytopenia)
- **Cardiovascular** (myocarditis, pericarditis, vasculitis)
- **Ocular** (blepharitis, conjunctivitis, iritis, scleritis, uveitis)
- **Renal** (nephritis)
Case 1: 51 y.o. man with stage IV melanoma, s/p 3 doses of pembrolizumab, c/o diarrhea

- Reports increased stool output, 7-8 per day, 1 episode of incontinence. Mild abdominal discomfort, no blood in stool, no fevers. Mild anorexia and nausea.
- Reports no sick contacts; sushi for dinner
- On exam: afebrile, non-toxic appearing, vitals stable, mild epigastric tenderness, normoactive bowel sounds
Approach to potentially immune-mediated symptoms

- Drug induced irAE **always** included in differential, often diagnosed by exclusion
  - Rule out other etiologies (e.g., infection, other drugs, neoplasm, metabolic causes)
- Can affect **any** organ system
- Early recognition, evaluation and treatment are **critical for patient safety**
Immune-related toxicity management: General principles

- Grade 1: supportive care; +/- withhold drug

- Grade 2: withhold drug, consider re-dose if toxicity resolves to ≤ Grade 1. Low dose corticosteroids (prednisone 0.5mg/kg/day or equivalent) if symptoms do not resolve within a week

- Grade 3-4: discontinue drug; high dose corticosteroids (prednisone 1-2mg/kg/day or equivalent) tapered over ≥ 1 month once toxicity resolves to ≤ Grade 1.
Diarrhea: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<tr>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
<td>Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline</td>
<td><strong>Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL</strong></td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
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Assess severity not only by the number of stools per day, but also by clinical symptoms such as cramping, fever, malaise, blood in stool, etc.
Case 1: 51 y.o. man with stage IV melanoma, s/p 3 doses of pembrolizumab, c/o diarrhea

Which of the following may be appropriate?

A. Discontinue pembrolizumab
B. Check stool cultures, ova & parasites, *c. difficile*
C. Consider GI consult for scope with colon biopsies and rapid pathologic review
D. Start systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent); administer IV fluids
E. Consider CT abd; check Quantiferon

F. All of the above
Colonoscopy performed on a 51-year-old man with metastatic melanoma who developed watery diarrhea after receiving immune checkpoint therapy.

Images courtesy of Animesh Jain, MD
Johns Hopkins University School of Medicine
Case 1: 51 y.o. man with stage IV melanoma, s/p 3 doses of pembrolizumab, c/o diarrhea

- Colonoscopy well-tolerated, but patient reports further increase in stool output despite IV steroids
- Abdominal discomfort worse, endorses some blood-tinged watery stool
- No fevers, but feels “washed-out”
- Exam: abd soft, mild diffuse tenderness to palpation, no peritoneal signs; Quantiferon neg.
Case 1: 51 y.o. man with stage IV melanoma, s/p 3 doses of pembrolizumab, c/o diarrhea

Which of the following may be appropriate?
A. Administer IV fluids
B. Administer infliximab at 5mg/kg
C. Consider inpatient admission
D. Administer PJP prophylaxis
E. All of the above
Case 2: Pneumonitis

- Life-threatening immune-related toxicity
- Early recognition is critical
- Can vary significantly in presentation, both clinically and radiographically
- Relatively uncommon, but potentially serious
Case 2: 40 y.o. woman, stage IV cancer s/p 4 doses of nivolumab, c/o cough, SOB

• Reports no sick contacts
• On exam: afebrile, vitals stable, uncomfortable appearing due to unremitting cough
• Chest CT demonstrates left-sided fluffy infiltrates, air bronchograms
40 y.o. woman, stage IV cancer s/p 4 doses of nivolumab, c/o cough, SOB
Case 2: 40 y.o. woman, stage IV cancer s/p 4 doses of nivolumab, c/o cough, SOB

Which of the following is/are appropriate?

A. Continue nivolumab, administer antibiotics including coverage for atypical organisms and PJP; see patient again in 2 weeks to make sure pneumonia is resolving

B. Hold nivolumab, monitor symptoms daily, consider hospitalization, request pulmonary and ID consults, obtain STAT bronchoscopy with bronchoalveolar lavage and tissue biopsies, consider empiric antibiotics and/or corticosteroids.
Highly variable radiographic appearance of pneumonitis
A 60 y.o. woman with stage IV melanoma has received 2 doses of pembrolizumab. Her cutaneous lesions have increased in size and look more inflamed than on last exam. She reports that her fatigue has improved somewhat since starting therapy. What is the appropriate next step?

A. Discontinue pembrolizumab; tumor growth at this early stage certainly portends progressive disease.

B. Increase the dose of pembrolizumab to 10mg/kg

C. Continue pembrolizumab along with close monitoring of symptoms. Reassure patient that this early increase in tumor size may be followed by regression.
A 75 y.o. man with stage IV lung cancer is about to begin therapy with nivolumab. He tells you that he “knows all about the side effects of chemotherapy” after watching his wife go through breast cancer treatment. He says, “Don’t worry doc, I’m prepared for all that vomiting and diarrhea. I won’t bother you about it over the weekend, though. I’ve got Kaopectate at home – that always works for me.” What to tell him?

A. Side effects from nivolumab are very different from those his wife experienced, both in terms of what to expect and how they are treated.
B. It is crucial to keep in touch with his health care team to report symptoms such as vomiting or diarrhea right away.
C. Immune-related toxicities can affect any organ, so better to err on the side of caution and report all symptoms.
D. All of the above
Conclusions

• Immune checkpoint blockade has produced objective anti-tumor responses in multiple tumor types
• Treatment of patients with immune checkpoint inhibitors can be different than with conventional therapies, including
  – Unconventional responses
  – Immune-related adverse events
• Patient complaints related to any organ system are immune-related and drug-associated until proven otherwise
  – Rule out infections, metabolic causes, tumor effects, etc.
• Early recognition, evaluation and treatment are critical
Questions?

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