But I Don't Dispense Those! A Community Pharmacist's Guide to Immuno-Oncology Agents

David Frame, PharmD

Home Study Webcast
4 Slides Per Page
But I Don't Dispense Those! A Community Pharmacist's Guide to Immuno-Oncology Agents

ACTIVITY DESCRIPTION
The promise of the immune system in helping to treat cancer has finally become a reality in the past few years. The immune system is designed to differentiate between normal cells and foreign cells. To do this, it uses "checkpoints" – molecules on certain immune cells that need to be activated (or inactivated) to start an immune response. Cancer cells often may look like normal cells and may evade the immune system recognition. An important molecule in this process is CTLA4 and thus a CTLA4 antagonist has been developed to help T cells recognize cancer cells better. Once the T cells finds the cancer cell another checkpoint is the molecule PD-1 on the T cell which binds to the PD-L1 receptor on the Cancer cell which will cause destruction of the T cell. This appears to be a major reason why T cells have difficulty killing cancer cells. Both PD-1 and PD-L1 inhibitors have now been established and have good effects in a variety of cancers including melanoma of the skin, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, Hodgkin lymphoma, bladder cancer, non-small cell lung cancer, and Merkel cell skin cancer. Since these drugs inhibit normal checkpoints the problem is they may allow T cells to now recognize normal cells as being foreign, which can lead to serious side effects commonly behaving as autoimmune disease.

The newest agents in the immunology-oncology field are Chimeric Antigen Receptor T cells, in which the patient's own T cells are genetically modified to produce a receptor for a target on the T cell. Currently approved agents express CD19 and are approved for relapsed/refractory ALL and DLBCL. These are extremely exciting agents which may have the potential for long term remission of cancer. One problem is if the T cells expand too rapidly they release cytokines, called "Cytokine Storm" which can be life threatening. Thus it is critical pharmacists have a good understanding of the mechanisms and adverse events associated with all of these therapies and a good understanding of how to manage the side effects.

TARGET AUDIENCE
The target audience for this activity is pharmacists and nurses in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES
After completing this activity, the pharmacist will be able to:

- Identify current FDA approved PD-1, PD-L1 and CTLA4 Inhibitors as well as Chimeric Antigen T cells and their indications and their place in therapy.
- Describe the mechanism of action of these immunologic agents
- Describe the symptoms of the adverse events of these agents and potential management strategies
- Understand the pharmacist's role in communicating recommendations in caring for patients on these agents

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ABOUT THE AUTHOR
David Frame is a Clinical Pharmacist in Hematology/Immunohematology and BMT at the University of Michigan. He is also an Assistant Professor at the University of Michigan College of Pharmacy. David has extensive experience in the field being a clinical pharmacist in Oncology for almost 20 years. Recently he has been helping in developing the CAR-T cell therapies at the University of Michigan and is working on new ways to evaluate and personalize immunosuppressive therapies. Always open to new endeavors, after his child was diagnosed with CDKL5, a rare neurologic disorder, David has also developed the scientific program for the International Foundation for CDKL5 Research where he has helped to bring together a coalition of scientists from around the world and is now designing the first clinical study being translated from the basic science.

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Learning Objectives

1. Identify current FDA approved PD-1, PD-L1 and CTLA4 Inhibitors as well as Chimeric Antigen T cells and their place in therapy
2. Describe the mechanism of action of these immunologic agents.
3. Describe the symptoms of the adverse events of these agents and potential management strategies.
4. Understand the Pharmacists role in communicating recommendations in caring for patients on these agents.

Tumor Immunology Overview

1. Release of Cancer Cell Antigens
2. Cancer Antigen Presentation by Antigen Presenting Cell
3. Activation of T cells
4. Trafficking T cells to Tumor
5. Infiltration of T cells into Tumor
6. Recognition of Cancer Cells by T cells
7. Killing of Cancer Cells by T cells
"Normal" T-Cell Activation and Response

Immature Antigen-Presenting Cell (APC) → Antigen Uptake → Activated APC → MHC/TCR + Co-stimulation → ACTIVATION

"Normal" T-Cell Checkpoint: CTLA4

Immature Antigen-Presenting Cell (APC) → Antigen Uptake → Activated APC → CTLA4 → MHC/TCR + Co-stimulation = ACTIVATION

Immune Checkpoint #2: PD-1/PD-L1

Immature Antigen-Presenting Cell (APC) → Antigen Uptake → Activated APC → PD-L1 → PD-1 → CTLA4 → MHC/TCR + Co-stimulation = ACTIVATION

Checkpoint Inhibitor Immunotherapies FDA Approved

- CTLA4 antagonists
  - Ipilimumab (Yervoy)
- PD-1 Anagonists
  - Nivolumab (Opdivo)
  - Pembrolizumab (Keytruda)
- PD-L1 Antagonists
  - Atezolizumab (Tecentriq)
  - Avelumab
  - Durvalumab
Checkpoint Inhibitors Are Active Across Many Tumor Types

- Types of cancers approved for therapies
  - melanoma, metastatic NSCLC, head and neck squamous cancers, urothelial carcinoma, gastric adenocarcinoma, mismatch-repair-deficient solid tumors, classic Hodgkin lymphoma, hepatocellular, and renal cell carcinoma, Merkel cell carcinoma
- The combination of ipilimumab and nivolumab for patients with advanced melanoma
- The indications for use are increasing rapidly
- Development of combinations with cytotoxic chemotherapy is being developed with the first FDA approval of Pembolizumab + Caroaplatin/Pemetrexate approved for NSCLC

Immune Checkpoints Help Recognize “Self vs Non-Self”

Adverse Effects: Autoimmune-Like Conditions

NCCN and ASCO Guidelines Summary for Checkpoint Inhibitors

- In general, agents can be continued with close monitoring for mild (grade 1) toxicities, with the exception of neurologic and some hematologic toxicities.
- For moderate (grade 2) toxicities, agents should be held until symptoms and/or lab values revert to grade 1 levels or lower.
  - Corticosteroids may be offered.
- For severe (grade 3) toxicity, patients should receive high-dose corticosteroids for at least 6 weeks. Extreme caution when restarting immunotherapy after a grade 3 toxicity is recommended, if it is restarted at all.
- In general, very severe (grade 4) toxicity necessitates stopping therapy permanently.
Immune-Mediated Dermatitis

- Incidence: 30-50%
  - Pruritus 14-19% (PD-1); 24-36% (CTLA-4); 33-47% (combo)
  - Vitiligo 7.5-11% (PD-1); 1.5-8.5% (CTLA-4); 6.5-11% (combo)

- Onset
  - Mean 3-5 weeks (2 weeks with combo)
  - Vitiligo: several months

- Presentation
  - Maculopapular rash
  - Trunk +/- extremities +/- pruritus

Immune-Mediated Dermatitis: Symptom Management

<table>
<thead>
<tr>
<th>Skin effect</th>
<th>Treatment backbone</th>
<th>Hold</th>
<th>Permanently discontinue</th>
<th>Consult Dermatology</th>
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</thead>
<tbody>
<tr>
<td>Rash</td>
<td>Topical steroids, Oral steroids (G3)</td>
<td>Grade 3</td>
<td>MAYBE grade 4</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Bullous dermatoses</td>
<td>Topical steroids, Oral steroids (G2)</td>
<td>Grade 2</td>
<td>Grade 4</td>
<td>Grade 2</td>
</tr>
<tr>
<td>SCARs (no grade 1)</td>
<td>Topical steroids, Oral steroids (G2)</td>
<td>Grade 2</td>
<td>Grade 4</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Pruritis</td>
<td>Topical steroids, Oral steroids (G2) Oral antihistamines</td>
<td>Grade 2 (consider)</td>
<td>Grade 4?</td>
<td>Grade 3</td>
</tr>
</tbody>
</table>

Immune-Mediated Dermatitis

- Inflammatory Dermatitis
- Exfoliative Dermatitis
- Erythema multiforme
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Vitiligo
- Alopecia
- Lichen Planus

Pharmacist Considerations

- Skin care, moisturize, Lotion/creams for dry skin (CeraVe, Eucerin, etc)
- Counsel on sunscreen, avoid sun
- Pruritis: antihistamine, oatmeal baths
- Review full list of patient medications to rule out other drug-induced cause for photosensitivity or other drugs reactions
  - Example: Voriconazole
- Have patient consider monitoring with use of serial photography
- Duration may be as long as 6-8 weeks
May Lead to Improved Responses in Metastatic Melanoma

- Nivolumab
  - Overall survival, rash: hazard ratio: 0.423; vitiligo: 0.184
- Pembrolizumab
  - Objective response rate with vitiligo: 71% vs 28%, p=0.002
- Meta-analysis
  - Overall survival with vitiligo: hazard ratio=0.25 (p=0.003)

Gastrointestinal Tract (Diarrhea and Colitis)

- Abdominal pain
- Nausea
- Cramping
- Blood or mucus in stool or changes in bowel habits
- Fever
- Abdominal distention
- Obstipation
- Constipation

Gastrointestinal Tract
(Diarrhea and Colitis)

- Incidence
  - Diarrhea=54% (with CTLA-4 +/- PD-1)
  - Colitis= 8-27%
- Onset often 5-10 weeks
- Risk factors
- Consider infectious work-up (C. diff, etc)

GI Grading and Treatment

- Grade 1: 1-3 stools over baseline/day
  - Could consider holding
  - Consult GI if long lasting
- Grade 2 (4-6 stools over baseline/day)& higher: hold and consult GI
  - Consider permanently d/c if from CTLA-4
  - Corticosteroid 1 mg/kg/day
- Grade 3: 7 or more stools over baseline/day
  - Permanently d/c CTLA-4
  - Could restart PD-1/PD-L1 once grade 1 or less
- Grade 4: Urgent and life threatening
  - 2 mg/kg/d methylprednisolone until improve to G1, and then taper over 4-6 wks
  - Consider early infliximab 5-10 mg/kg if symptoms refractory within 2-3 days
Pharmacist Considerations

- Counsel for OTC anti-diarrheals
- PPI therapy
- Pre/Probiotics
- NSAID use with ipilimumab increases rate of colitis (31% vs 5%, p=0.003)

Immune-Mediated Hepatitis Symptoms

- Yellowing of skin or whites of the eyes
- Severe nausea or vomiting
- Pain on the right side of the abdomen
- Drowsiness
- Dark urine (tea colored)
- Bleeding or bruising more easily than normal
- Feeling less hungry than usual

Immune-Mediated Hepatitis

- Incidence: 25-30% (combination therapy); 15% grade 3
- Onset: 6-12 weeks
- Presentation: may often be asymptomatic
- Consider checking HIV, Hepatitis A & B

Immune-Mediated Hepatitis: Grading

<table>
<thead>
<tr>
<th>LFT</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>&gt; ULN to 1.5 x ULN</td>
<td>&gt; 1.5 to 3.0 x ULN</td>
<td>&gt; 3.0 to 10.0 x ULN</td>
<td>&gt; 10.0 x ULN</td>
</tr>
<tr>
<td>ALT/AST</td>
<td>&gt; ULN to 2.5 x ULN</td>
<td>&gt; 2.5 to 5.0 x ULN</td>
<td>&gt; 5.0 to 20.0 x ULN</td>
<td>&gt; 20.0 x ULN</td>
</tr>
<tr>
<td>Albumin</td>
<td>&lt; LLN to 3 g/dL</td>
<td>&lt; 3 to 2 g/dL</td>
<td>&lt; 2 g/dL</td>
<td>--</td>
</tr>
</tbody>
</table>
Immune-Mediated Hepatitis: Management

- Grade 1: Monitor closely
- Grade 2: hold
  - Prednisone 0.5-1 mg/kg/day
  - Stop any potential hepatotoxic drugs
- Grade 3: permanently d/c
  - Methylprednisolone 1-2 mg/kg
  - Persistent >3 days: MMF or azathioprine
- Grade 4: consult hepatology

  • Note: Infliximab not recommended, risk of idiosyncratic liver failure

Pharmacist Considerations

- Evaluate other drugs for related changes in LFTs
- Counsel on preventive care
- Comprehensive medication and disease evaluation
- If Mycophenolate used for treatment, counsel on enterohepatic recirculation

Immune-Related Pneumonitis: Signs and Symptoms

- Shortness of breath
- Dry cough
- New or increasing oxygen requirements
- May be detected just on imaging

Immune-Mediated Pneumonitis

- Incidence: 0-10% (higher in combo therapy)
  - All grades: NSCLC vs melanoma, 1.43 odds ratio
  - RCC vs melanoma. 1.59 odds ratio
  - Most treatment deaths from pneumonitis are in NSCLC
  - Smokers: 56%, never smokers: 44%

- Onset Median: 3 months (2-24 months)
**Immune-Mediated Pneumonitis**

- Fairly uncommon, but potentially serious
  - Deaths have been reported
  - Need to carefully monitor pts
- Pts at increased risk for pneumonitis
  - NSCLC in the setting of chronic lung inflammation
  - Heavily pretreated pts
  - Combination of CTLA-4 and PD-1 agents
  - Prior radiation to lung
  - History of COPD

**Grade 1:** Asymptomatic
- confined to one lobe of the lung or
- 25% of lung parenchyma
- clinical or diagnostic observations only

**Grade 2:** Symptomatic
- involves more than one lobe of the lung or
- 25%-50% of lung parenchyma

**Grade 3:** Severe symptoms, hospitalization required
- involves all lung lobes or > 50% of lung parenchyma
- Oxygen required
- Grade 4: Life threatening

**Pharmacist Considerations**

- Consider supportive prophylaxis medications (>12 weeks on steroids)
  - Proton pump inhibitor for GI prophylaxis
  - Bactrim for Pneumocystis prophylaxis
  - Antifungal prophylaxis
  - Calcium + vitamin D
  - Inhalers

**Immune-Mediated Pneumonitis**

- Grade 1: Hold
  - Get imaging
- Grade 2: Hold
  - Start prednisone 1-2 mg/kg/day
  - Taper by 5-10 mg/week
  - Consider bronchoscopy and/or empiric antibiotics
- Grade 3: permanently d/c
  - Methylprednisolone 1-2 mg/kd/day
  - Refractory (>48 hours)
    - Infliximab 5 mg/kg or MMF or IVIG or Cyclophosphamide

**Grade 1:** Hold
- Get imaging

**Grade 2:** Hold
- Start prednisone 1-2 mg/kg/day
- Taper by 5-10 mg/week
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**Grade 3:** permanently d/c
- Methylprednisolone 1-2 mg/kd/day
- Refractory (>48 hours)
  - Infliximab 5 mg/kg or MMF or IVIG or Cyclophosphamide
Immune Mediated Endocrinopathies

- Organs involved
  - Adrenal insufficiency
  - Autoimmune thyroid disorders (hypo or hyperthyroidism)
  - Type 1 diabetes mellitus
  - Hypophysitis

- Incidence: 10-11.2%
- Onset: 6-24 weeks

Endocrine System: Symptoms

- Headaches that will not go away or unusual headache patterns
- Vision changes
- Rapid heartbeat
- Increased sweating
- Extreme tiredness or weakness
- Muscle aches
- Weight gain or weight loss
- Dizziness or fainting
- Feeling more hungry or thirsty than usual
- Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- Feeling cold
- Constipation
- Voice gets deeper
- Urinating more often than usual
- Nausea or vomiting
- Abdominal pain
- Hair loss

Primary Hypothyroidism

- Can hold at any grade based on symptoms
  - Recommend holding for grade 3
  - Grade 3 or 4: endocrine consult
- Treatment
  - Levothyroxine 1.6 mcg/kg/day
    - If elderly or frail can start at 25-50 mcg
- Monitor TSH, free T4 every 4-6 weeks
- Correct adrenal dysfunction first (if co-exists)
- May stay on/rechallenge immunotherapy

Primary Hyperthyroidism

- Grade 2
  - Consider hold & endocrine consult
  - Beta blocker
  - Steroids usually not beneficial
  - Usually transient & self resolving
Primary Adrenal Insufficiency

• Definition: decreased morning cortisol & increased morning ACTH
  • Also hyponatremia & hyperkalemia
  • Orthostasis & volume depletion
  • Lose both mineralcorticoid & glucocorticoid
• Grade 1
  • May hold
  • Replace with prednisone 5-10 mg or hydrocortisone
  • May need fludrocortisone 0.1 mg/d
  • May stay on/rechallenge immunotherapy

Pharmacist Considerations

• Always start corticosteroids several days before thyroid hormone to prevent precipitating adrenal crisis
• Follow FT4 for thyroid hormone replacement titration (TSH is not accurate)
• Should administer insulin for T1DM (or as default therapy if there is confusion about type)

Hypophysitis

• Definition: low morning ACTH & cortisol
  • Often low/normal TSH & low free T4
  • Low testosterone or estradiol (+ low LH & FSH)
• Grade 1
  • Consider holding
  • Treat with hydrocortisone 10-20 mg po Qam & 5-10 mg po Qpm
  • Endocrine consult
• Grade 3/4 (severe symptoms)
  • May need high dose steroids tapered over 1-2 weeks

Muscular Skeletal: Inflammatory Arthritis

• Incidence: 40%
  • More common in PD-1/PD-L1 treatment
• Grade 1 (based on symptoms)
  • Acetaminophen and/or NSAIDs
• Grade 2
  • Hold
  • Increase pain medications
  • Prednisone 10-20 mg/day x 4-6 weeks with slow taper
  • If pt can’t do <10 mg of prednisone after 3 months consider DMARD & refer to rheumatology
Pharmacist Considerations

- Counsel on not doing strenuous work-out routines on therapy
- Counsel on signs of muscle breakdown and rhabomyolysis
- Clarify use of NSAIDS and potential for increased renal dysfunction

Neurological

- Headache
- Dizziness
- Weakness/lack of energy
- Numbness/tingling

Immune Mediated Encephalitis

- Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture
- Withhold therapy in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes.
- If other etiologies are ruled out, administer corticosteroids and permanently discontinue therapy for immune-mediated encephalitis.

Renal: Nephritis

- Reduced urine production
- Edema
- Increased creatinine
Immune Mediated Nephritis and Renal Dysfunction

- Administer corticosteroids for Grades 2-4 increased serum creatinine.
- Withhold therapy for Grade 2 or 3.
- Permanently discontinue for Grade 4 increased serum creatinine.

Pharmacist Considerations

- Evaluate any other medications cleared renally for appropriate dosing.
- Evaluate any other nephrotoxic medications, esp NSAIDS.

Comparison of Toxicities Between CTLA4 and PD-1 Inhibition

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab All Grades (%)</th>
<th>Ipilimumab Grades 3-4 (%)</th>
<th>Pembrolizumab All Grades (%)</th>
<th>Pembrolizumab Grades 3-4 (%)</th>
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</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>45</td>
<td>2.6</td>
<td>20</td>
<td>0</td>
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<tr>
<td>GI</td>
<td>33</td>
<td>9.1</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Endocrine</td>
<td>4.5</td>
<td>3</td>
<td>10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1.6</td>
<td>1.1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>2.9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nephritis</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
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</tbody>
</table>
Steroid Management

- Steroids are generally first line therapy for more severe reactions to help quickly shut down T cell function
- For most reactions the initial steroid dose will be 1-2 mg/kg/day of prednisone equivalent
- Steroid taper will depend on severity of symptoms
- Antibodies half-life is approximately 3-5 weeks so effects can be long which can slow the steroid taper, watch closely for symptoms to restart when tapering
- Steroids most likely will decrease or stop immune effects of the agent on the cancer so often will try and be tapered quickly if possible

Other Possibilities for AE Management

- TNF Inhibitors
  - Most likely would want to use a short acting agent like etanercept (Enbrel) rather than an antibody like adalimumab (Humira) or infliximab (Remicade)
- IL-6 Inhibitors
  - Only long acting available, tocilizumab (Actemra) or siltuximab (Sylvant)
  - Value shown in Cytokine Release Syndrome
- Calcineurin Inhibitors
  - Cyclosporine (Neoral, Sandimmune) or tacrolimus (Prograf, Astagraf XL, Envarsus XR)
- Mycophenolate
Introducing the CAR-T Cell

• The Idea
  • Put the entire T-cell stimulation process in 1 transmembrane receptor
  1. Create antigen receptor
  2. Apply it to cytotoxic T-cells
  3. Link it DIRECTLY to T-cell intracellular cascades
  • No need for co stimulation or any other pathway.
• FDA Approved Agents
  • Tisagenlecleucel (Kymriah)
  • Axicabtagene Ciloleucel (Yescarta)

Cytokine Release Syndrome
Management

<table>
<thead>
<tr>
<th>CRS Severity</th>
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| **Resistant CRS:**
  No clinical improvement in 12 to 18 hours, or worsening at any time, despite prior management. | Multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. |
| **Prodromal Syndrome:**
  Low-grade fever, fatigue, anorexia | Observe; exclude infection; administer antibiotics per local guide if neutropenic |
| **Overt CRS (one or more of the following):**
  - High fever
  - Hypoxia
  - Mild hypotension | Administer antipyretics, oxygen, intravenous fluids and/or low-dose vaspressors as needed. |
| **Severe or Life-Threatening CRS (one or more of the following):**
  - Hemodynamic instability despite intravenous fluids and vasopressor support
  - Worsening respiratory distress
  - Rapid clinical deterioration | Administer high dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. Administer tocilizumab. Pt weight < 30 kg: 12 mg/kg IV over 1 hour - Pt weight > 30 kg: 8 mg/kg IV over 1 hour (maximum dose 800 mg). |

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Drug Interactions
Drug Interactions

- Unlike most drugs there is not an interaction with cytochrome P450
- Most interactions are going to be with drugs that effect the immune system:
  - TNF Inhibitors (such as Humira, Enbrel, Cimzia, Simponi, Remicade)
  - IL-6 Inhibitors (such as Actemra)
  - IL-1 Inhibitors (such as Kineret, Arcalyst and Ilaris)
  - JAK Inhibitors (such as Xeljanz XR and Jakafi)
- Clinically difficult with patients that have autoimmune conditions at baseline

Complimentary Therapies that Could Decrease Cancer Response

- Curcumin may decrease inflammatory cytokines
- High doses of Vitamin D may decrease activated T cells
- Fish oils- have anti-inflammatory fatty acids
- Green tea
- Flavones- apigenin, luteolin
- Melatonin- enhances IL-10
- Rose Hip
- Alpha-lipoic acid

Complimentary Therapies that Could Increase Autoimmune Effects

- Echinacea
- Spirulina platensis
- Ginseng
- Mistletoe
- Mushroom extracts
- Elderberry
- Cistanche

A Community Case Scenario

A patient with melanoma is taking pembrolizumab. They come into your pharmacy with a script for flexeril from their PCP for muscle spasms. When counseling they tell you that it feels like the flu, they hurt all over and that their urine is really dark and its been getting worse over the past 3 weeks since getting the last dose of pembrolizumab. They have been taking NSAIDs with little relief.

- Do you think this patients symptoms could be related to the immunotherapy?
- What concerns do you have about dispensing the new prescription?
- How do you proceed?
Summary

• T cells are one of the most important cells to attack cancer
• Activation of T cells requires co-stimulatory molecules and this can be potentiated with CTLA-4 Inhibitors
• Cancer cells may have the ability to shut down T cells by PD-L1 so blocking PD-L1 or PD-1 receptors can help T cells kills cancer cells
• Immune Checkpoints help to recognize self vs non-self thus inhibiting these checkpoints can lead to auto-immune like conditions which must be recognized and treated quickly
• The pharmacist should be aware of therapies that can interact with the immune system and these agents

Patients can find information about side effects of immunotherapy at cancer.net, or download an NCCN infographic.
• nal information is available at
Exam Questions:

1. Which of the following agents works by inhibiting CTLA4?
   a. Ipilimumab
   b. Pembrolizumab
   c. Durvalumab
   d. Atezolizumab

2. Which of the following mechanisms inhibit cancer cells from killing T cells?
   a. PD-1 inhibition
   b. CTLA-4 inhibition
   c. Chimeric antigen receptor development
   d. Both PD-1 and CTLA4 Inhibition

3. What appears to be the main reason for having Immune checkpoints?
   a. To assure tumor recognition
   b. To enhance T cell cytotoxic activity
   c. To decrease antigen presentation
   d. To recognize self vs non-self

4. Which of the following would have the highest risk of causing auto-immune like conditions?
   a. Pembrolizumab
   b. Atezolizumab
   c. Ipilimumab
   d. Ipilimumab plus nivolumab

5. Which of the following adverse effects is MOST likely with CTLA4 and PD-1 Inhibition?
   a. Dermatitis
   b. Colitis
   c. Endocrinopathy
   d. Pleuritis
6. Which of the following is one of the worst dermatologic side effects that can occur with immune checkpoint inhibitors?
   a. Macropapular rash
   b. Puritis
   c. Stevens Johnson Syndrome
   d. Vitiligo

7. If a patient with metastatic melanoma develops a rash on a checkpoint inhibitor
   a. It could result in increased response rate
   b. It would necessitate immediate steroid use
   c. The drug should immediately be stopped
   d. You should recommend prednisone

8. Mild Colitis (grade 1) from checkpoint inhibitor therapy
   a. Requires urgent follow up with physician
   b. Requires emergency room visit
   c. Could be started on loperamide
   d. Requires the agent to be stopped

9. First line therapy for a SEVERE adverse event from a CTLA4 or PD-1 Inhibitor should generally be
   a. Prednisone 0.25 mg/kg/day
   b. Prednisone 0.5 mg/kg/day
   c. Prednisone 1 mg/kg/day
   d. Prednisone 2 mg/kg/day

10. When high dose steroids are required for management of adverse effects of checkpoint inhibitors
    a. The agent must be stopped permanently
    b. The taper off steroids should be rapid
    c. There is no need to recommend bone health maintenance
    d. The agent should be stopped and steroids tapered slowly over at least 6 weeks

11. The half-life of most drugs that are monoclonal antibodies is generally about
    a. 1 Day
    b. 1 week
    c. 1 month
    d. 1 year
12. A newly described immunologic toxicity with checkpoint inhibitors is muscular toxicity. When counseling patients you should warn them
   a. It is common to see severe spasms
   b. They should not have heavy work-out routines while on therapy
   c. NSAIDS are most likely the best relief
   d. They will be sore but will not cause any severe muscular problems

13. Chimeric Antigen T cell therapies
   a. Are genetically modified T cells from the cancer patient
   b. Are part of the cells given an allogeneic stem cell transplant
   c. Do not have the capability of lasting a long period of time
   d. Are extremely safe

14. A patient who received CAR-T cells for lymphoma comes into your store and tells you she is having night sweats and low grade fevers through the day and is lightheaded at times. You counsel her to
   a. To keep taking her temperature
   b. To take Tylenol around the clock
   c. To call the clinic immediately and go to the emergency room
   d. To try NSAIDS to help prevent the fevers

15. A patient receiving pembrolizumab for metastatic melanoma presents to the pharmacy asking for your recommendation on a product to help with 4 or more diarrhea episodes per day for the last 2 days. Based on your knowledge of diarrhea in cancer patients receiving immuno-oncology agents, you would ____________.
   a. Recommend loperamide or bismuth salicylate
   b. Refer the patient to their physician for steroids
   c. Recommend probiotics and a bland diet
   d. Refer the patient to their physician for diphenoxylate-atropine
   e. Recommend electrolyte replacement fluids until diarrhea resolves