Inpatient Management of Oncology Specialty Drugs
New Agents, Opportunities, and Challenges
Jennifer Swank, PharmD, BCOP

Disclosure
Do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation

Pharmacist Objectives
- Identify common toxicities of oral oncology therapies in the internal medicine patient
- Describe management of oral oncology therapy toxicity balanced with internal medicine complications
- Discuss the identification and treatment of immune related adverse events in the internal medicine patient

Technician Objectives
- Recognize oncology therapies by brand/generic name
- Identify storage and dispensing issues with these medications
- Apply proper disposal techniques for these medications in daily practice

Vascular Endothelial Growth Factor (VEGF)
- Glycoprotein that activates intracellular signaling by binding to VEGF receptor
- Key role in the maintenance of vascular homeostasis
  - Mediation of the production of vasodilator nitric oxide
  - Decreased vascular resistance through the generation of new blood vessels
- VEGF inhibition
  - Prevention of angiogenesis
  - Promotion of apoptosis
  - Causes endothelial dysfunction and increased endogenous sFlt1 and endothelin-1 production


Inhibiting Tyrosine Kinase Signaling
**VEGF Toxicity Management**

- Rash: severe dermatologic toxicity rare
- Diarrhea: maintain appropriate hydration and treat symptomatically
- Myocardial infarction: use with caution in patients with significant cardiac history
- Thrombosis: monitor for symptoms of clots and treat if identified
- Heart failure: monitor for symptoms of HF or EF reduction. If symptoms obtain ECHO and discontinue therapy if EF <50% or 10% in baseline EF
- QTc prolongation: baseline EKG, maintain appropriate electrolytes
- Myocardial infarction: use with caution in patients with significant cardiac history
- Impaired wound healing
- Proteinuria/nephrotic syndrome

**Bevacizumab (Avastin®)**
- Impaired wound healing
- Discontinue therapy of at least 28 days prior to surgery and continue to hold for 28 days post surgery and until wound is healed
- Thromboembolism
- Risk factors include h/o of thrombosis, diabetes, >65 years of age
- GI perforation
- Higher incidence with tumors involving the bowel
- Hemorrhage
- Avoid use in patients with recent hemorrhage or hemoptysis
- Proteinuria/nephrotic syndrome
- withheld treatment for ≥2 g proteinuria/24 hours, discontinue if nephrotic syndrome

**Mammalian Target of Rapamycin (mTOR) Inhibitors**
- mTOR pathway plays a central role in the control of the growth of cells
- When activated it induces mRNA transcription and translation of numerous proteins stimulating cell cycle progression, division, and inhibiting apoptosis
- mTOR inhibitors halt cell cycle at G1 phase and blocking downstream phosphorylation of ribosomal proteins; exhibits anti-angiogenesis activity by reducing levels of hypoxia inducible factors (HIF) and VEGF

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**Table**

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<th>Drug</th>
<th>Indication</th>
<th>Toxicity</th>
<th>Monitoring</th>
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**mTOR Inhibitor Toxicity**

- **Drugs**
  - Temsirolimus (Torisel®)
  - Everolimus (Afinitor®)
- Electrolyte abnormalities
  - Hypokalemia, hypomagnesemia, hypophosphatemia
- Hyperglycemia
- Hypercholesterolemia
- Mucositis
- Interstitial pneumonitis
- Monitor for respiratory symptoms and start inhaled corticosteroids
- Treatment: Prednisone 40mg daily and taper by 10mg every 2 weeks
- Permanently discontinue mTOR therapy

**References:**

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**T Cell Antitumor Response**

1. Tumor antigens released by tumor cells
2. Tumor antigens presented to T cells
3. T cells recognize tumor antigens
4. T cells kill tumor cells

**References:**

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**Tumor Mechanism to Evade Immune System**

1. Inhibition of tumor antigen presentation (e.g., down-regulation of MHC-I)
2. Recruitment of immunosuppressive cell types (e.g., Tregs)
3. Inhibition of attack by immune cells (e.g., inhibition of cytokine pathways)
4. Secretion of immunosuppressive factors (e.g., TGF-β)

**References:**

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**T-Cell Checkpoint Regulation**

- T-cell responses are regulated through a complex balance of inhibitory (“checkpoint”) and activating signals
- Tumors can dysregulate checkpoint and activating pathways, and consequently the immune response
- Targeting checkpoint and activating pathways is an evolving approach to cancer therapy, designed to promote an immune response

**References:**
Mechanism of Action of Checkpoint Inhibitors

- Anti-PD-1 therapies are designed to bind to PD-1 on activated T cells in tumor microenvironment. Anti-CTLA-4 agents are designed to act by binding to CTLA-4 on activated T cells in the lymph nodes.

Available Agents

- Cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor
  - Ipilimumab (Yervoy®)
- Programmed cell death-1 (PD-1) inhibitors
  - Nivolumab (Opdivo®)
  - Pembrolizumab (Keytruda®)
- Programmed cell death ligand-1 (PDL-1) inhibitors
  - Atezolizumab (Tecentriq®)
  - Avelumab (Bavencio®)
  - Durvalumab (Imfinzi®)

Toxicity of Checkpoint Inhibitors

- Therapies designed to enhance the patient’s immune response against the tumor can result in novel spectrum of adverse events arising from the activation of the immune system.
- Termed “immune related adverse events (irAEs)"
- May be due to cytokine release by activated T cells
- May be unfamiliar to clinicians
- Can be serious and potentially fatal
- Requires prompt recognition and treatment
- Requires education of the patients and healthcare team

Role of Pharmacist

- Understanding irAEs:
  - Diarrhea is common with CTLA-4 inhibitors but less common with PD-1/PDL-1 therapies
  - Rash is common, but severe dermatitis is not
  - Endocrinopathies, hepatitis, and nephritis are uncommon
  - Infusion reactions are very rare
  - Pneumonitis and neurologic toxicities are very rare
- Early recognition of irAEs
  - Familiarity with side effects of newer therapies
  - Awareness of timing/onset of irAEs to ensure quick diagnosis and prompt initiation of treatment
- irAEs are dose-dependent, schedule-related, and cumulative

Kinetics of irAEs

- Rash, pruritis
- Liver toxicity
- Diarrhea, colitis
- Hypophysis

References:
- Tarhini A. Scientifica (Cairo) 2013; 2013:857519
Early Diagnosis and Management

- Systemic high-dose corticosteroids may be required for severe events
- Can be severe or life-threatening
- May involve various organs
- Early diagnosis and appropriate management is essential to minimize life-threatening reactions
- Patient education for early recognition

Cutaneous Toxicity Management

- Symptoms: erythematous and/or maculopapular rash, dry skin, pruritus, vitiligo, blisters, ulceration, bullae, necrotic or hemorrhagic lesions

Pulmonary Toxicity Management

- Symptoms: new/worsening cough, dyspnea, or chest pain
- Rule out other causes (ie. Infection, COPD exacerbation, PE)
- High resolution CT scan of chest or CT angiogram

Gastrointestinal Toxicity Management

- Symptoms: changes in bowel habits, abdominal pain, blood or mucus in stool, nausea
- Rule out other causes (ie. Infection)

Neurologic Toxicity Management

- Symptoms: neuropathies, myopathy, severe refractory constipation, aseptic meningsitis, Guillain-Barre syndrome, motor neuropathy, myasthenia gravis

Guidelines for irAE Treatment

- Assess symptoms and grade (see CTCAE guidelines)
- Initial treatment
  - Mild symptoms: anti-emetics, antihistamines, antipruritic agents, topical moisturizers, topical/oral antihistamines
  - Moderate (Grade 2)
    - Colitis: asymptomatic
      - Diarrhea: <4 stools/day
      - Colitis: asymptomatic
    - Diarrhea: 4-6 stools/day
    - Colitis: severe abdominal pain, ileus, interfering with ADL
  - Severe (Grade 3 /4)
    - Diarrhea: ≥7 stools/day, need hospitalization, infectious disease and pulmonary consults
    - Asymptomatic radiographic or endoscopic inflammation
    - Colitis: severe abdominal pain, ileus, interfering with ADL
    - Cognition, memory, mood, speech, coordination
    - Severe shortness of breath
    - Moderate (Grade 2)
      - Diarrhea: <10% BSA
      - Colitis: asymptomatic
    - Severe (Grade 3 /4)
      - Diarrhea: >30% BSA, blisters, ulceration, bullae, necrotic or hemorrhagic lesions
      - Pneumonia
      - Severe shortness of breath

Follow-up

- Discontinue immunotherapy if symptoms persist
- Infliximab 5mg/kg IV x 1 dose (may repeat in 1 week if responds to <grade 1)
- If symptoms improve then 4-6 week steroid taper
- If symptoms persist >3 days or relapse with steroid taper
- Influenza or tetanus prophylaxis
- Consider hospitalization
- Infectious disease and pulmonary consults
- Topical steroids (hydrocortisone/triamcinolone)
- Treat symptomatically: topical moisturizers, topical/oral antihistamines
- Re-image at least every 3 weeks

Endocrine Toxicity Management

- Taper high dose steroids over a minimum of 4 weeks
- Continue hormone replacement as needed
- Monitor endocrine labs as appropriate
- Repeat MRI as clinically indicated
- Rule out other etiologies
- Repeat endocrine labs in 1-3 weeks
- Initiate frequent patient follow-up
- Initiate short course (7 days) of high dose corticosteroids to reverse inflammation, dexamethasone 4 mg every 6 hours or equivalent
- Initiate hormone replacement to manage endocrinopathy
- Consult endocrinologist

Renal Toxicity Management

- Evaluate for other causes: recent IV contrast, medications, fluid status, etc
- Monitor BUN weekly and creatinine every 3-4 days
- Hold comedication if BUN >15 mg/dL or creatinine >2 mg/dL
- Hold BFI/IFN-α if BUN >15 mg/dL or creatinine >2 mg/dL
- Hold bortezomib, lenalidomide, melphalan, aspirin, celecoxib, etc.
- No requirement for a 17-day treat as Grade 1/2

Hepatic Toxicity Management

- Symptoms: yellowing of skin or whites of eyes, severe nausea/vomiting, pain in right side of abdomen, drowsiness, dark urine, bleeding or bruising more than normal, feeling less hungry
- Evaluate other causes: medications, infection, progression of disease

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