Recognizing and Managing the Toxicities of Treatment for Renal Cell Carcinoma

Emily Feld, MD
Fellow, Hematology/Oncology
University of Pennsylvania
Classes of Therapy for Metastatic Renal Cell Carcinoma (RCC)

- Vascular Endothelial Growth Factor Tyrosine Kinase Inhibitors (VEGF-TKIs)
- mTOR Inhibitors
- Immunotherapy
Common Therapies for Metastatic RCC

- **VEGF-TKIs**
  - Sorafenib
  - Sunitinib
  - Pazopanib
  - Axitinib
  - Lenvatinib
  - Cabozantinib

- **Immunotherapies**
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
  - Avelumab

- **mTOR Inhibitors**
  - Everolimus
  - Temsirolimus
Mechanism of VEGF-TKIs

VEGF-TKI Toxicities

• **Skin:** Hand-foot syndrome, changes in hair or skin color
• **Oral:** Inflammation of the oral mucosa, taste changes, dry mouth
• **GI:** Diarrhea, nausea
• **Cardiovascular:** Hypertension, heart failure, heart attack, blood clots
• Delayed wound healing—must hold therapy for procedures
• **Protein in the urine**
• **Bleeding**
• **Low blood counts**
• **Thyroid dysfunction**
• **Weight loss, decreased appetite**
• **Fatigue**
Hand-Foot Syndrome

• Aka “palmar-plantar erythrodysesthesia”

• Symptoms:
  • Localized, tender lesions which often appear as blisters in areas of trauma or friction
  • Tingling, burning
  • Decreased tolerance to hot temperatures
  • Callus formation

• Often occurs within the first 2-4 weeks of therapy

• Occurs in 40% of patients receiving cabozantinib

Images from R. Motzer, MD
Prevention is Key!
Prevention of Hand-Foot Syndrome

**P:** Always pedicure/remove calluses BEFORE treatment

**O:** Fatty ointments 3 times daily (fragrance- and alcohol-free moisturizers—urea cream 20-40%)

**P:** Use patches on all areas of increased calluses

**S:** Use shoes with soft insoles
- Wear shoes that are not constrictive, thick socks
- For hands: thick cotton gloves

And, avoid exposure of hands and feet to hot water
Management of Hand-Foot Syndrome

• For mild symptoms: Numbness, tingling, redness, or painless swelling not affecting daily activities
  • Liberal use of moisturizers
  • Reduce pressure to affected areas

• For moderate symptoms: Painful redness and/or swelling affecting daily activities
  • Add topical corticosteroid (clobetasol 0.05% ointment twice daily)
  • For discomfort, topical 2% lidocaine, topical DMSO, gabapentin
  • May require temporary VEGF-TKI dose reduction

• For severe symptoms: Peeling, blistering, erosions, or severe pain causing inability to work or do daily activities
  • Discontinue treatment for at least one week (or until symptoms improve)
  • Resume treatment at dose reduction
Oral Toxicity

- Mucositis/stomatitis
  - Inflammation of oral mucous membranes
  - Often occurs 1 month after initiation of treatment
- Oral pain and sensitivity without ulcers
- Altered taste
- Dry mouth
- Most common with sunitinib and cabozantinib (up to 50%); least common with pazopanib or axitinib (~15%)
- Also a common toxicity with mTOR inhibitors
  - Can occur rapidly (<5 days)
  - Most often involves mucosa of the lips, lateral tongue, buccal mucosa and soft palate
  - Dose-effect relationship
Management of Oral Toxicity

• Mouthwash
  • Dexamethasone swish and spit 0.5mg twice daily
    • Do not swallow as this can impair VEGF-TKI absorption!
  • Topical analgesics: magic mouthwash (Lidocaine, Benadryl, Maalox), viscous lidocaine 2%, benzocaine

• Oral hygiene
  • Avoid agents containing alcohol, hydrogen peroxide, and iodine
  • Avoid spicy food
  • Dose interruption and/or modification
Hypertension

- Up to 80% of patients develop high blood pressure (either de novo or worsening of pre-existing hypertension)
- Can develop within hours to days of starting treatment
- An acute rise in BP can precipitate acute end-organ complications:
  - Stroke, heart attack, heart failure, acute kidney injury
- **Need to monitor closely**
  - Home blood pressure cuff
- Requires treatment if BP≥140/90
Posterior Leukoencephalopathy

• A rare complication of hypertension + VEGF TKI therapy

• Insidious onset of headache, confusion, decreased level of consciousness, visual changes, seizures with associated characteristic neuroimaging findings

• Contact your primary oncology team immediately
  • Requires emergency management

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Hypertension as a Biomarker

Rini et al. JNCI 2011
Management of Other Toxicities

Fatigue

- Light exercise
- Short naps
- Dose modification, including night time dosing

- Imodium: 4 mg, followed by 2 mg after each loose stool (max: 16 mg/day)
- Creon

- Nutritional supplements (Boost, Ensure 2-3x/day)
- Frequent, small high-calorie meals

- Mirtazapine
- Marinol

- Zofran 8 mg every 8 hours as needed
- Compazine 10 mg every 6 hours as needed

- Dose modification
Common Therapies for Metastatic RCC

**VEGF-TKIs**
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- Pazopanib
- Axitinib
- Lenvatinib
- Cabozantinib

**Immunotherapies**
- Nivolumab
- Pembrolizumab
- Ipilimumab
- Avelumab

**mTOR Inhibitors**
- Everolimus
- Temsirolimus
Mechanism of immune checkpoint blockade
Immunotherapy Toxicities

- Fatigue
  - Uncommon, but may be severe and life threatening
  - Time-limited and reversible
  - Highly steroid responsive
Risk of Toxicity

- Ipilimumab
- Nivolumab or Pembrolizumab
- Ipilimumab/Nivolumab
**Rash**

- Most common immune-related toxicity
- For mild symptoms:
  - Topical corticosteroids
    - Clobetasol propionate, betamethasone dipropionate for body
    - Hydrocortisone, aclometasone desonide for face
  - Oral anti-histamines
    - Non-sedating: Claritin, Zyrtec
    - Sedating: Hydroxyzine or Benadryl at bedtime
- Severe rashes may require oral steroids and holding therapy
Colitis (Inflammation of the Colon)

• Symptoms
  • Diarrhea
  • Abdominal pain/cramping
  • Blood or mucous in stool

• Immediately report changes in bowel movements
Management of Colitis

• Rule out other causes (i.e. c.difficile infection)

• **Mild (Bowel movement <4x above baseline)**
  • Supportive care (fluids, bland diet, Imodium)

• **Moderate (4-6x above baseline)**
  • Hold treatment, consider steroids
  • Consider colonoscopy

• **Severe (>7x above baseline or other complications)**
  • Permanently discontinue treatment, start steroids
  • Hospitalization may be warranted
  • If no improvement even with IV steroids, consider infliximab
Pneumonitis (Inflammation of the Lungs)

- Symptoms: Cough, shortness of breath, low O2
- Also can occur with mTOR inhibitors
Management of Pneumonitis

• **Asymptomatic**
  • Can continue treatment with close observation vs hold therapy for 2-4 weeks

• **Symptomatic**
  • Hold treatment, start steroids
  • If severe symptoms or low O2:
    • Hospitalization, steroids, consideration of bronchoscopy
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mTOR Inhibitor Toxicities

• Fatigue
• Mucositis
• Low blood counts
• Nausea, vomiting, diarrhea
• Swelling
• Poor wound healing
• Inflammation of the lungs
• Elevated blood sugar
• Elevated cholesterol
Elevated Blood Sugar and Cholesterol

- Affects up to 70% of patients
- Requires intervention if ≥ grade 2
- Baseline lipid profile and continued monitoring necessary
- Very high triglycerides (≥ 500 mg/dl) require prompt treatment with fibrates (pancreatitis risk)
Summary

• Treatment with VEGF-TKIs, immune checkpoint blockade, and mTOR inhibitors requires close monitoring for the development of toxicities.

• VEGF-TKIs and mTOR inhibitors can produce a range of severe effects warranting aggressive supportive care and sometimes dose interruptions or treatment holidays.

• Immune checkpoint blockade can cause unique immune-related side effects, which are often steroid-responsive, but in rare cases can be life-threatening.

• Always contact your primary oncology team with any new symptoms.
Thank you!