Updates in Toxicity Management and Educational Resources

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Overview, Current State in RCC

- Seven FDA approved treatments since December 2005
- Improved clinical outcomes
- Adverse effects impact every organ system
- Treatment is chronic
- Toxicities are cumulative
- Side effect management is anecdotal
- CTCAE grading is inadequate
Management of mRCC: Strategies for Today

- How can we optimize outcomes with current therapies in the treatment of mRCC?

Multiple targeted agents → Effective therapy management → Improved patient outcomes

- Dose optimization
- Maximize treatment duration
- Adverse event management
Side Effects Cause

- Reduced quality of life
- Diminished treatment adherence
- Multiple dose adjustments
- Treatment interruptions
- Premature discontinuation of therapy
- Compromised therapeutic efficacy
Patient Assessment

• Review medical history and medications
  - Cardiac, Endocrine, Renal
  - CYP34A inhibitors and inducers
    - http://medicine.iupui.edu/flockhart/
  - Previous TKI and/or mTOR therapy
  - Prior XRT
  - Anti-coagulation therapy

• Stabilize co-morbidities before treatment
  - Hypertension for VEGFR
  - Diabetes for mTOR
  - Correct coagulopathy
Patient Education

- Reinforce treatment goals & schedule
- Proactive interventions to treat toxicity
- Connect patient with treatment team
- Prompt intervention of side effects
- Foods to avoid (grapefruit, star fruit, papaya, pomegranate)
- Dosage instructions (DO NOT CRUSH, DISSOLVE OR OPEN CAPSULE)
- Inform doctor, nurse and pharmacist about OTC, herbal or vitamin supplements
Current Medical Therapies in RCC

- **Immunotherapy**
  - Interferon
  - Aldesleukin (HD IL-2)
- **Tyrosine kinase inhibitors**
  - Sorafenib
  - Sunitinib
  - Pazopanib
  - Axitinib
- **VEGF-ligand inhibitor**
  - Bevacizumab +/- IFN
- **mTOR inhibitors**
  - Temsirolimus
  - Everolimus
- **Investigational (i.e. examples) plus many others**
  - PD-1, PD-L1, Cabozantinib
Lessons from Immunotherapy

- HD IL-2 treatment guidelines exist
- Side effect management is well coordinated and predictable
- Nursing education of drug delivery
- Assessment of patient risk factors prior to treatment
- Post-treatment guidelines exist
- Could this past experience provide guidance for new immune check-point inhibitors?
Previous trials have told us…..

• **Sunitinib (Sutent)**
  - New dosing regimens are evolving that decrease Grade 3 & 4 toxicities and maintain efficacy
  - Black box warning for liver toxicity
  - HBP as a biomarker for tumor response

• **Pazopanib (Votrient)**
  - Hepatotoxicity
  - Lower incidence of HFS, fatigue, mucositis compared to Sutent (COMPARZ)
  - Better tolerability yields better QOL

• **Axitinib (Inlyta)**
  - Fast recovery (short half-life)
  - Difficult to maintain dosing due to adverse events
Most Common Side Effects with Targeted Therapies

• TKI
  ➢ Diarrhea*
  ➢ Fatigue*
  ➢ Hypertension
  ➢ Hand foot skin reactions*
  ➢ Stomatitis*

• mTOR
  ➢ Metabolic effects (↑glucose, cholesterol and triglycerides)
  ➢ Pneumonitis—rare but potentially serious*
  ➢ Anemia
  ➢ Fatigue*
  ➢ Rash
  ➢ Aphthous stomatitis*

* Frequently requires a dose reduction and or interruption
Challenges in RCC Therapy

• CTCAE grading system less useful with chronic AE’s
  ➢ Toxicities wax and wane

• Inexperience leads to less effective treatment and frequent dose modifications

• Dosing regimens modified by both patient and physician

• Coverage for treatment varies by health insurance

• Lack of Category 1 studies for supportive care

• Oral therapies decrease patient/nurse interaction while phone calls, email and websites usage increase

• Differences in patient population (age, gender, genetics, race)
TKI Case Study

- 65 year old male, ECOG–0, clear cell mRCC, no cardiac hx.
- Sunitinib 50 mg 4/2 schedule
- First set of scans show a 27% decrease in pulmonary metastases
- Cycle 4  Day 18. Pt. sends picture of his hands and feet and informs RN of the following.
  - Watery diarrhea  X 7 episodes per day
  - Fatigue, unable to participate in ADL’s
  - Mouth is burning
  - BP log 180/ 98
  - Painful hands and feet, unable to walk

- How would you manage?
Management of Diarrhea

• Pharmacologic interventions
  ➢ Loperamide/ Diphenoxylate-standard dosing
  ➢ Tincture of opium, morphine or codeine
  ➢ Consider bulking agents to decrease frequency of stool

• Dietary
  ➢ BRAT diet (bananas, rice, applesauce, toast)
  ➢ Avoid spicy, dairy (?) if lactose intolerant, high fat, caffeine, fiber foods
  ➢ Aggressive oral fluid replacement
  ➢ Dietician referral as needed

• Time of dosing and diarrhea?
• Patient follow up
• Modify dosing for CTC Grade 3?
Management of Fatigue

• Investigate causes
  ➢ Anemia, hypothyroidism, cardiac, dehydration, disease progression, inflammatory processes
  ➢ Baseline energy and activity

• Provide coping strategies to motivate patients
  ➢ Energy conservation strategies
  ➢ Lifestyle changes

• Relaxation techniques and nutritional support
• Pharmacological management with psychostimulants
• Dose adjustments and interruptions for CTCAE Grade 3
Management of Stomatitis

- Baseline dental evaluation
- Avoid tobacco, alcohol and irritating foods
- Treat symptoms
- Widespread GI involvement
- Can be dose limiting, CTCAE Grade 3
- Associated with mTOR inhibitors
Hypertension Management

- Coordinate care with PCP and/or Cardiologist
- Typically appears within one month of therapy
- Assess at baseline (Goal is <140/90)
- No data favors one class over another in treating HBP
- BP log with daily readings
- Tx discontinued in RPLS or uncontrolled HBP
- If Grade 3 HBP develops, hold drug and resume once HBP is controlled
Management Hand Foot Skin Reaction

• Preventive measures
  ➢ Patient education regarding awareness
  ➢ Liberal use of moisturizers 2-3 times a day
  ➢ Wear socks, cotton gloves, footwear with extra padding/gel inserts
  ➢ Promptly report symptoms

• For painful lesions
  ➢ Decrease pressure and friction to affected areas: stay off feet
  ➢ Institute steroid cream, urea-based moisturizers
  ➢ Analgesics if necessary

• Interrupt TX and consider dose reduction for CTC Grade 3
The Case Study-A Case for Alternative Dosing?

• Chronic treatment, cumulative toxicities, quality of life impacted
• Interventions are anecdotal
• Patient was benefiting with regression of tumor
• C4 Day 18, patient sent a picture to the office instead of being evaluated in person
• The hand foot skin reaction & fatigue were Grade 3; the dose was interrupted and reduced
Alternative Sunitinib Schedules

- Modifying standard therapy (4/2) to (2/1) has been shown to maintain efficacy with decreasing severity of adverse events

Table 2. AEs before and at first followup after schedule modification

<table>
<thead>
<tr>
<th>AE</th>
<th>No. Before (%)</th>
<th>No. Followup (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>40 (64)</td>
<td>18 (29)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>24 (38)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (32)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>14 (22)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>9 (14)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>6 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (10)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5 (8)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Mouth sores</td>
<td>3 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Laboratory abnormalities:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>less than 1 K/μl/ml</td>
<td>3 (5)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Platelet count less than 100 K/μl/ml</td>
<td>2 (3)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Thyroid stimulating hormone greater than 4.20 IU/ml</td>
<td>2 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

Questions Remain Regarding Alternative Dosing Schedules

- Will this benefit carry over to other oral agents that treat mRCC?
- Does an individualized schedule lead to a maintained PFS and OS?
- Improved toxicity management will need to be evaluated in the context of prospective studies
Summary

• Alternate dosing: promising intervention to control adverse events with Sunitinib
  ➢ Prospective clinical trials are underway to further evaluate the benefit of alternate schedules
• TKI benefits; challenge is maintaining better outcomes
• Prompt management of side effects is essential
• Ensure coordination of patient with health care team
• Newer agents may have greater toxicities requiring optimal management skills to improve treatment outcomes
• Are adverse events prognostic/predictive markers in RCC?
Educational Resources

• KCA Nurse Advisory Board
• Kidneycancer.org
  ➢ Symptom management sheets
  ➢ Webinars symptom management
  ➢ “We have Kidney Cancer”
  ➢ Kidney Cancer Survivor Book
• OncologyEducation.com
• Kidney Cancer Home Page at cancer.gov
• Kidney-cancer-journal.com
• Cancernetwork.com

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