Treatment of Renal Cell Carcinoma (RCC) in the Era of Targeted Agents

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Conflict of Interest

- None

Learning Objectives

1. Outline the pathophysiology of RCC and how this impacts drug selection.
2. Review the use of targeted agents in the adjuvant treatment of RCC.
3. Analyze the trial data to make appropriate first-line treatment recommendations for metastatic RCC.
4. Given patient specific information select appropriate medications to treat metastatic RCC; including the appropriate sequencing of agents for patients who have progressed on initial therapy.
5. Describe the mechanism of action, adverse reactions, and monitoring parameters of targeted agents used to treat RCC.

Epidemiology

- The highest incidence occurs in North Americans & Scandinavians
- Renal cell carcinoma rarely occurs before the age of 40
- Median age of diagnosis in the 60’s

<table>
<thead>
<tr>
<th></th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>31,590</td>
<td>8,080</td>
</tr>
<tr>
<td>Women</td>
<td>19,800</td>
<td>4,810</td>
</tr>
<tr>
<td>Total</td>
<td>51,190</td>
<td>12,890</td>
</tr>
</tbody>
</table>

Pathophysiology

- 80 - 85% of kidney tumors: renal cell
  - 75 - 85% clear cell
  - 12 -14% chromophilic
  - 4 - 6% chromophobic
  - 2 - 4% oncocytic
  - 1% collecting duct
- 15 - 20% Transitional cell
- Wilm’s tumor (children)

Pathogenesis

- The classic cytogenetic abnormality in renal cell carcinoma is loss of the short arm of chromosome 3 (between p14-p26)
- Von Hippel-Lindau disease is also associated with deletion in the short arm of chromosome 3p
  - Von Hippel-Lindau gene is a tumor suppressor gene
- Other genetic abnormalities distinct from the Von Hippel-Lindau gene occur in renal cell carcinomas
- Multiple genetic abnormalities in renal cell carcinoma are associated with a poor outcome

Molecular Pathways and Targeted Therapies in Renal-Cell Carcinoma

**VEGF: A Key Mediator of Angiogenesis**

- Environmental factors\(^1\)
  - Hypoxia, pH
- Growth factors, hormones\(^1\)
  - EGF, VEGF, PDGF, IGF-1, IL-1α, IL-6, estrogen
- Genes involved in tumorigenesis\(^3\)
  - p53, p73, vHL, src, ras, bcn, abl

**mTOR in Renal Cell Cancer**

- The mammalian target of rapamycin (mTOR) signaling pathway functions as an important intermediary in a variety of cell signaling events to regulate cell growth and cell proliferation and angiogenesis.
- mTOR is a serine/threonine kinase that lies downstream of the PI3K pathway.
- mTOR controls the cell replication process by controlling the progression of the cell cycle through the G1 to the S phase.
- Also, leads to biosynthesis of HIF-1.

**Natural History: Renal Cell Carcinoma**

- Patients with T1 or T2 lesions confined to renal parenchyma and undergo a radical nephrectomy are cured > 80% of the time.
- 20% present with metastatic disease.
  - Lung 50 - 60%
  - Bone 30 - 40%
  - Liver 30 - 40%
  - Brain 5%
- Only 1 - 3% of tumors occur bilaterally.

**Case 1**

MJ is 60 year-old male diagnosed with Stage I (due to the T1a lesion) renal cell cancer. All CT scans are negative for metastatic disease. He undergoes a partial nephrectomy because of the solitary mass, and the concern that the contra-lateral kidney is threatened by a long standing history of hypertension.

**Case I**

- Standard of care would be observation with scans of the abdomen and pelvis.
  - every 6 months for first 2 years
  - yearly thereafter
- Patients should be offered entry into an adjuvant clinical trial.
**Surgical Therapy: Renal Cell Carcinoma**

- Only surgery is curative
- Radical nephrectomy
  - At surgery the kidney, adrenal gland, & perirenal fat, and regional lymph nodes resected
  - May be used in Stage IV disease
- Partial nephrectomy
  - Indicated in pts. for whom a radical nephrectomy would result in permanent dialysis
  - Mainly used in patients in whom the contralateral kidney is threatened by a second disease (e.g. DM, HTN, etc.)

**Adjuvant Therapy: Renal Cell Carcinoma**

![Graph showing Median Recurrence-Free Survival and Overall Survival for different therapies](image)

- **Observation (n=143)**
  - Median Recurrence-Free Survival: 3.0 yrs.
  - Median Overall Survival: 7.4 yrs.
- **IFN-alpha NL (n=140)**
  - Median Recurrence-Free Survival: 2.2 yrs. (p=0.33)
  - Median Overall Survival: 5.1 yrs. (p=0.09)

**ASSURE Trial (ECOG 2805)**

- Eligibility Criteria:
  - pT1b, G3-4; pT2-4; N+ disease, no metastatic disease
  - Confirmed clear cell or non-clear cell RCC
  - Intermediate-high risk or very high-risk disease
  - Prior radical or partial nephrectomy

- Treatment repeats every 6 weeks for up to 9 courses in the absence of disease progression or unacceptable toxicity

**Targeted Agents in the Adjuvant Setting**

- **ASSURE**
  - Status: Closed
  - Arms: Sunitinib or Sorafenib
  - Design: MC, DB, R, PC
  - Stratification: At least intermediate-high-risk UISS, ECOG PS= 0 or 1, clear or non-clear cell RCC

- **ATLAS**
  - Status: Recruiting
  - Arms: Axitinib
  - Design: PC
  - Stratification: High-risk UISS, ECOG PS= 0 or 1, predominant clear cell histology

- **PROTECT**
  - Status: Recruiting
  - Arms: Pazopanib
  - Design: PC
  - Stratification: Modified UISS, Karnofsky performance scale of at least 80, clear cell or predominant clear cell histology

- **SORCE**
  - Status: Recruiting
  - Arms: Sorafenib
  - Design: PC
  - Stratification: Intermediate- and high-risk SSIGN, ECOG PS= 0 or 1, clear or non-clear cell RCC

- **S-TRAC**
  - Status: Closed
  - Arms: Sunitinib
  - Design: PC
  - Stratification: High risk UISS, ECOG PS= 0-2, predominant clear cell histology

- **SWOG-S0931**
  - Status: Recruiting
  - Arms: Everolimus
  - Design: PC
  - Stratification: Pathological high or very high risk, no further details available, ECOG PS= 0 or 1

**Adjuvant Therapy:**

**Median Overall Survival**

- **Observation (n=143)**: 7.4 yrs.
- **IFN-alpha NL (n=140)**: 5.1 yrs. (p=0.09)

**Advanced RCC**

**Metastatic RCC Prognosis: MSKCC Risk-Factor Model**

- Greater number of risk factors is associated with worse prognosis*
  - 0 risk factors (164 patients, 30 alive): 29.6m**
  - 1 or 2 risk factors (245 patients, 23 alive): 10.3m**
  - 3, 4, or 5 risk factors (144 patients, 1 alive): 4.9m**

*Risk factors: no prior nephrectomy, KPS >80, low HGB, high corrected calcium, high LDH, intHemoglobin, KPS-Hemoglobin, LDH-Mate, daptomycin.

**Internal from initial RCC Dx to IFN α Therapy**

**Overall Survival in the Era of Targeted Agents**

- Favorable: 0 factors (mOS 44 mos)
- Intermediate: 1-2 factors (mOS 21 mos)
- Poor: 3-6 factors (mOS 8 mos)

\[ p<0.0001 \]

Heng et al. ASCO 2011

**Cytoreductive Nephrectomy**

- Cytoreductive Nephrectomy (CN) is independently associated with an improved overall survival in metastatic RCC patients treated with VEGF-targeted agents
- Cytoreductive nephrectomy in era of targeted therapy may produce superior OS when adjusted for known prognostic factors
- The benefit seems to be marginal in patients in the poor-risk group/poor KPS
- Prospective clinical trials in progress


**RCC Consortium Database**

- Consecutive 645 patients with median follow up 25 months.
- Metastatic RCC, any histology.
- Treated with anti-VEGF agents:
  - Sunitinib
  - Sorafenib
  - Bevacizumab
- No prior VEGF-targeted agents.
- Data collected using uniform data collection software and standardized definitions.
- Excluded N=331 (s/p nephrectomy, but not cytoreductive).


**Case I (Cont): MJ**

- MJ refused to participate in the ASSURE trial and unfortunately he now has metastatic disease 11 months after his initial diagnosis
- His hemoglobin, LDH, neutrophils, and platelets are within normal range
  - ECOG PS is 0
  - Corrected calcium is 13.6 mg/dL

Schaub M, ed. Encyclopedia of Cancer. 3rd edition. Springer-Verlag Berlin Heidelberg 2012, pp 552-565 (Figure 5).

**Cytoreductive Nephrectomy by KPS**

- Median OS: 23.3 vs. 16.5 months \( p=0.01 \)
- Cytoreductive Nephrectomy by KPS

**Mechanism of Action of Current VEGF Inhibitors**

Schaub M, ed. Encyclopedia of Cancer. 3rd edition. Springer-Verlag Berlin Heidelberg 2012, pp 552-565 (Figure 5).
**Targets and Inhibitors**

**Signal Transduction Inhibitors**

- **Sorafenib (BAY 43-9006)-TARGET Trial**
  - Phase II trial in RCC demonstrated 40% RR (> 25% reduction in mass size) & 30% stable disease
  - 400 mg PO BID without food
  - Randomized, phase III trial in RCC pts. who received one prior systemic therapy

<table>
<thead>
<tr>
<th>Response Rate</th>
<th>TTP</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>10%</td>
<td>5.5 months</td>
</tr>
<tr>
<td>Placebo</td>
<td>2%</td>
<td>(p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p&lt;0.001)</td>
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<tr>
<td></td>
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<td>(p=0.146)</td>
</tr>
</tbody>
</table>


**Signal Transduction Inhibitor**

- **Sunitinib (SU 11248)**
  - 50 mg po daily x 4 weeks, then two weeks off
  - Approved based upon 2 phase II trials
  - Compared to interferon in a phase III trial
    - Adverse Events: Skin (rash, hand-foot syndrome, dry skin), hypertension, and diarrhea
    - Neutropenia: Grade III (11%) and grade IV (1%)
    - Hepatotoxicity, decreased LVEF, prolonged QT interval and hemorrhagic events
    - Other anti-VEGF adverse effects (proteinuria, wound healing)

<table>
<thead>
<tr>
<th>Response Rate</th>
<th>Progression Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>31%</td>
<td>11 months</td>
</tr>
<tr>
<td>IFN</td>
<td>6% (p&lt;0.001)</td>
<td>5 months (p&lt;0.001)</td>
</tr>
</tbody>
</table>


**Pazopanib**

- Compared to interferon in a phase III trial
- 800mg PO daily without food
- QOL indices also improved
- Benefit greater in cytokine naïve patients
- Grade 3 (10%) and 4 (2%) ALT elevations seen

<table>
<thead>
<tr>
<th>Response Rate</th>
<th>Progression Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib</td>
<td>30%</td>
<td>9.2 months</td>
</tr>
<tr>
<td>IFN</td>
<td>3%</td>
<td>4.2 months</td>
</tr>
</tbody>
</table>


**Pazopanib**

- Compared to sunitinib in the first-line setting
- Lower rate of adverse effects (fatigue, hand-foot syndrome) and increased patient QOL reported

<table>
<thead>
<tr>
<th>Progression Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib</td>
<td>8.4 months</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>9.5 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response Rate</th>
<th>Progression Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>19%</td>
<td>6.7 months</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>9%</td>
<td>4.7 months</td>
</tr>
</tbody>
</table>

Axitinib

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>All Grades, %</th>
<th>Grades 3/4, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>55</td>
<td>11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40</td>
<td>16</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39</td>
<td>11</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>PPE</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>Anemia</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Constipation</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>19</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Everolimus vs. Placebo in Metastatic Renal Cell Cancer (mRCC) Patients Previously Treated with TKIs

Randomized 2:1, stratified by MSKCC risk criteria and previous VEGF-TKI therapy (1 vs. 2)

Treatment until progression or intolerance

- Everolimus 10 mg/day PO + BSC (n = 272)
- Placebo + BSC (n = 136)

Everolimus

- Oral inhibitor of mTOR
- FDA approved for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib
- Dose is 10 mg once daily with or without food
- For patients with Child-Pugh class B hepatic impairment, reduce dose to 5 mg once daily
- CYP3A4 substrate
- May increase dose in 5 mg increments to a maximum of 20 mg once daily if patient on a “strong” inducer

Temsirolimus for mRCC: Phase III Study Design

- Improved PFS median progression-free survival 4.9 [95% CI 3.7–5.5] vs. 1.9 [1.8–1.9] months
- Mostly stable disease
- No OS benefit
- Stomatitis, rash, and fatigue were the most commonly reported adverse events
- Pneumonitis (any grade) was detected in 22 (8%) patients in the everolimus group, 8 were grade 3
- The adverse event (AE) profile of the mTOR inhibitors includes hyperglycemia, hyperlipidemia, and hypercholesterolemia

Patient Case 2: KC

- KC is a 75-year old female with stage IV clear cell renal cancer. Upon work-up she is identified as having 4 poor risk factors according to the MSKCC risk stratification model.
- Chest CT scan reveals multiple pulmonary nodules; LDH is 4 times the upper-limit of normal; corrected calcium is 14 mg/dL and she has a KPS of 65
- Her other serum chemistries are within normal limits
Summary of Efficacy Measures

<table>
<thead>
<tr>
<th>End Point</th>
<th>Interferon</th>
<th>Temsirolimus</th>
<th>Interferon plus Temsirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival — mo (95% CI)</td>
<td>7.3 (6.1-8.8)</td>
<td>10.9 (8.6-12.7)</td>
<td>8.4 (6.6-10.3)</td>
</tr>
<tr>
<td>Median progression-free survival — mo (95% CI)</td>
<td>3.6 (2.6-4.5)</td>
<td>3.8 (3.6-5.2)</td>
<td>3.7 (3.3-4.3)</td>
</tr>
<tr>
<td>Site investigators’ assessment</td>
<td>1.5 (1.0–2.2)</td>
<td>3.8 (2.6–5.2)</td>
<td>3.7 (2.3–4.4)</td>
</tr>
<tr>
<td>Independent assessment</td>
<td>3.1 (2.2–3.9)</td>
<td>5.3 (3.9–7.0)</td>
<td>4.7 (3.5–6.3)</td>
</tr>
<tr>
<td>Median time to treatment failure — mo (95% CI)*</td>
<td>1.0 (0.7–1.3)</td>
<td>3.6 (2.5–4.5)</td>
<td>2.1 (1.5–3.4)</td>
</tr>
<tr>
<td>Objective response rate — % (95% CI)*</td>
<td>4.8 (2.7–7.1)</td>
<td>8.6 (6.0–12.6)</td>
<td>8.1 (4.4–12.8)</td>
</tr>
<tr>
<td>Clinical benefit (objective response or stable disease for ≥ 24 wks) — % (95% CI)*</td>
<td>13.5 (8.5–19.6)</td>
<td>32.1 (23.7–38.6)</td>
<td>28.1 (20.0–36.3)</td>
</tr>
</tbody>
</table>

*This category includes only patients who underwent tumor assessment after the baseline assessment: 131 patients in the interferon group (40%), 192 patients in the temsirolimus group (92%), and 188 patients in the combination therapy group (99%).

†The time to treatment failure was determined by the site investigators.

Comments

- Patients require diphenhydramine as a premed.
- Anemia, neutropenia, and thrombocytopenia were more common in the combination therapy.
- Hyperglycemia, hypercholesterolemia, and hyperlipidemia were more common in the temsirolimus group and may require therapy.
- 25 mg IV given over 30-60 minutes.
  - The mean weekly dose of temsirolimus was 23.1 mg, or 92% of the planned dose.

Summary of Targeted Agents

- Sunitinib, Temsirolimus, Bevacizumab + interferon, and Pazopanib approved for first line or second line use.
  - Temsirolimus has highest response in poor prognosis patients.
- Everolimus (after tyrosine kinase inhibitors, TKI’s) and TKI’s after cytokine therapy utilized in the second line setting.

Monitoring Parameters

- All VEGF Inhibitors
  - Blood pressure, proteinuria, bleeding and wound healing issues, thrombotic events, rare reversible posterior leukoencephalopathy syndrome (RPLS).
- VEGF TKI’s
  - Rash and other skin effects (hand-foot syndrome), LFT’s (check prior to administration), effect of food, fatigue, GI (diarrhea).
- Drug-Interactions (CYP3A4 substrates)
- mTOR Inhibitors
  - Stomatitis, rash, and fatigue.
  - Hyperglycemia, hyperlipidemia, and hypercholesterolemia.
- Rare pneumonitis.
- Everolimus is a CYP3A4 substrate and hepatically metabolized.
  - Check for drug-interactions and LFT’s prior to use.
Published Second-line or greater data in Advanced RCC

Ongoing Clinical Trials in mRCC: Sequential Therapies

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Treatment Arms</th>
</tr>
</thead>
</table>
| AXIS: Phase III study comparing Axitinib vs. Sorafenib as 2nd line therapy | 540 | Axitinib
| Phase III study comparing Temsirolimus vs. Sorafenib in Sunitinib-refractory patients | 440 | Temsirolimus Sorafenib
| SWITCH: Phase III sequential study as second-line therapy | 540 | Sunitinib → Sorafenib Sorafenib → Sunitinib
| RECORD 3: Phase II sequential study as second-line therapy | 390 | Everolimus → Sunitinib Sunitinib → Everolimus

Diagram of assessable patients included in this study and their subsequent treatment. mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor.

Suggested approach to the management of (A) metastatic renal cell carcinoma (RCC), including (B) relapse or progressive disease.
Elevated Diastolic Blood Pressure May Predict Prolonged Survival With Axitinib

- Patients with cytokine- or sorafenib-refractory mRCC treated with axitinib

\[ \text{dBP=diastolic blood pressure.} \]

OS

<table>
<thead>
<tr>
<th>Survival Probability</th>
<th>Time (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
<td>0.8</td>
<td>50</td>
</tr>
<tr>
<td>0.6</td>
<td>100</td>
</tr>
<tr>
<td>0.4</td>
<td>150</td>
</tr>
<tr>
<td>0.2</td>
<td>200</td>
</tr>
<tr>
<td>0.0</td>
<td>250</td>
</tr>
</tbody>
</table>

Sunitinib overall survival (OS) by hypertension (HTN) status (post-cycle 1, day 1)

Clinical Outcome to Bevacizumab plus Interferon According to the Development of Grade 2 or Greater Hypertension (CALGB trial)*

<table>
<thead>
<tr>
<th></th>
<th>Pts. with ≥ Grade 2 HTN</th>
<th>Patients w/o ≥ Grade 2 HTN</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (months; 95% CI)</td>
<td>41.6 (28.3-55.1)</td>
<td>16.2 (14.2-18.7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PFS (months; 95% CI)</td>
<td>13.2 (10.6-15.5)</td>
<td>8.0 (5.9-8.6)</td>
<td>0.0009</td>
</tr>
<tr>
<td>ORR 13.1%</td>
<td>9.0% (6.3-18.9)</td>
<td>0.95</td>
<td></td>
</tr>
</tbody>
</table>

* Any relation to therapy according to CTC AE version 3.0

1. Which of the following is the most common genetic abnormality identified in renal cell cancer?
   1. Mutated p53
   2. BCL-2 overexpression
   3. Mutation Von Hippel-Lindau gene
   4. HER-2 overexpression
   5. Not sure

2. Which of the following is NOT used to predict prognosis in patients with metastatic renal cell cancer?
   1. Serum creatinine
   2. Calcium levels
   3. LDH levels
   4. Performance status
   5. Not sure

3. Which of the following agents approved for metastatic renal cell cancer targets mTOR?
   1. Bevacizumab
   2. Temsirolimus
   3. Sorafenib
   4. Axitinib
   5. Not sure
4. Which of the following regarding the comparison of pazopanib and sunitinib in metastatic renal cell cancer is correct?

1. Pazopanib demonstrated superior disease-free survival
2. Pazopanib demonstrated increased hand-foot syndrome
3. Pazopanib demonstrated improved quality-of-life
4. Pazopanib demonstrated improved overall-survival
5. Not sure

5. Which of the following parameters is commonly elevated in patients who receive mTOR inhibitors?

1. Blood glucose
2. Serum creatinine
3. Blood pressure
4. White blood cells
5. Not sure

QUESTIONS?