Updates in Renal Cell Cancer in Older Patients

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Disclosures

- None
Renal Tumors

Epidemiology

- Malignant tumors of the kidney account for 2% of all cancers
- Median age at diagnosis is 66 years and median age at death is 70 years
  - 25% aged > 75
- Autopsy incidence is ~2-5%
- Incidental tumor detection: 70%
- 30-40% of patients will present with or eventually develop metastatic disease
Patients ≥ 75 with Metastatic RCC

Shorter survival

Less Treatment
More likely to discontinue due to toxicities and preference

Pal et al., JGO 2012
Treatment Options for Metastatic Disease

- Nephrectomy in Metastatic Disease
- Immunotherapy Alone
- Targeted Therapies
Nephrectomy for Metastatic Disease

Abern et al., Anticancer Research, 2014
Cytoreductive Nephrectomy in RCC

Conclusions for patients ≥ 75

- 504 older patients vs 2796 younger patients
- Perioperative mortality (PM) was 4.8% in older patients vs 1.9% in the younger patients
- Blood transfusions (29.8 vs 21.5%)
- Postoperative complications (27.8 vs 22.8%)
- Prolonged length of stay (45.0 vs 32.0%)
- In multivariable analysis, older patients were 2.2 more likely to experience perioperative mortality

Sun et al. BJU Int, 2012
# Immunotherapy Meta-analysis

- 58 Trials involving 6,880 evaluated patients

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Overall Response Rate</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunotherapy (IL2 and Interferon α)</td>
<td>6752</td>
<td>12.4%</td>
<td>13 months</td>
</tr>
<tr>
<td>Non-immunotherapy (Control)</td>
<td>6752</td>
<td>2.4%</td>
<td>9.5 months</td>
</tr>
</tbody>
</table>

*Toxicities are significant

Coppin et al. Cochrane Database Syst Rev. 2005
Targeted Therapies
First Phase III Trials

- Sorafenib (400 mg bid) vs placebo
  - All subtypes, low or intermediate grade, one systemic treatment allowed
  - 30% >65 years
  - 17.8 months vs 14.3 months
  - HR: 0.78, p=0.02

- Sunitinib (50 mg 4/2 vs IFN-α)
  - Clear cell, all risk groups, no prior treatment
  - 36% >65
  - 26.4 months vs 21.8 months
  - HR: 0.82, p=0.05

Esudier et al. JCO, 2009
Motzer et al. NEJM, 2007; Motzer et al. JCO 2009
HRQOL (time to deterioration) in Older Patients on Sorafenib

Eisen, JNCI, 2008
Sunitinib in Patients ≥ 70

- Retrospective analysis (6 trials)
  - N=1059, 202 ≥70 (19%)
- Sunitinib dosing
  - 50 mg 4/2, 37.5 daily
  - Older patients had more: dose interruptions (68% vs 59%) and dose reductions (57% vs 42%)

<table>
<thead>
<tr>
<th></th>
<th>Sunitinib</th>
<th>IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS HR</td>
<td>11 mths</td>
<td>7.9 mths</td>
</tr>
<tr>
<td></td>
<td>0.62 (0.41-0.93)</td>
<td>P=0.02</td>
</tr>
<tr>
<td>OS HR</td>
<td>25.5 mths</td>
<td>17.5 mths</td>
</tr>
<tr>
<td></td>
<td>0.71 (0.49-1.02)</td>
<td>P=0.06</td>
</tr>
</tbody>
</table>

Hutson et al. BJC., 2014
Phase III: Pazopanib vs Sunitinib
median age=61 (40% ≥65)

- Clear cell RCC
- No prior therapies
- Adequate organ function
- Exclusion
- Brain mets
- Poorly controlled HTN
- Recent cardiovascular event

Randomize

- Pazopanib 800 mg daily
  N = 557

- Sunitinib 50 mg 4/2
  N = 553

Motzer, NEJM, 2013
Outcomes

Non-inferior PFS and OS

Better HRQoL and satisfaction

Motzer, NEJM, 2013
Preferences

- Patients preferred Pazopanib
  - 70% vs 22%
  - Less fatigue
  - Better HRQoL
- Physicians preferred Pazopanib
  - 61% vs 22%

Escudier, JCO, 2014
RECORD-1

Phase III: Everolimus vs Placebo

- Clear cell component
- All risk groups (15% poor risk)
- Progression on sunitinib, sorafenib, or both

Randomize

Everolimus 10 mg daily
N = 272

Placebo
N = 138

Motzer et al. Lancet 2008
Exploratory Analysis

n=416, 36% ≥ 65, 17.5% > 70

HR for PFS: 0.33, p<.001
5.4 months vs 2.2 months

- Well tolerated
- More common in older patients:
  - Peripheral edema
  - Cough
  - Rash
  - Diarrhea

Porta et al, Euro Urol, 2012
AXIS

Phase III: Axitinib vs Sorafenib

- Clear cell component
- All risk groups (10% poor risk)
- Progression on sunitinib (54%), bevacizumab+IFN (8%), temsirolimus (3%) or cytokine (35%)

Randomize

Axitinib 5 mg twice daily
N = 361

Sorafenib 400 mg twice daily
N = 362

Rini et al. Lancet 2011
Outcomes

Median age 61, 34% ≥ 65, oldest pt 82

Median PFS longer with Axitinib, OS not different

HRQoL comparable

Rini et al. Lancet 2011
Motzer, Lanc Onc, 2013
Cella, BRC, 2013
## Sequential Therapy

<table>
<thead>
<tr>
<th>Histology and setting</th>
<th>Risk group</th>
<th>Standard</th>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell first line</td>
<td>Good or intermediate</td>
<td>Sunitinib, bevacizumab (±IFN), pazopanib</td>
<td>Cytokines, sorafenib</td>
</tr>
<tr>
<td></td>
<td>Poor prognosis</td>
<td>Temsirolimus</td>
<td>Sunitinib, sorafenib</td>
</tr>
<tr>
<td>Clear cell second line</td>
<td>Post cytokines</td>
<td>Sorafenib, pazopanib, axitinib</td>
<td>Sunitinib</td>
</tr>
<tr>
<td></td>
<td>Post TKI</td>
<td>Everolimus, axitinib</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Clear cell third line</td>
<td>Post two TKIs</td>
<td>Everolimus</td>
<td></td>
</tr>
<tr>
<td>Non clear cell histology</td>
<td></td>
<td></td>
<td>Temsirolimus, sunitinib, sorafenib</td>
</tr>
</tbody>
</table>

Quivy, Clin Interv Aging, 2013
## Summary

<table>
<thead>
<tr>
<th>Phase 3 trial</th>
<th>Median age (years)</th>
<th>Age of oldest patient (years)</th>
<th>Clinical benefit%</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sutent(^6)</td>
<td>62</td>
<td>87</td>
<td>39.5%</td>
<td>11</td>
<td></td>
<td>Diarrhea, vomiting, hypertension, hand-foot syndrome, neutropenia, anemia, thrombocytopenia, cough, peripheral edema, fatigue, anorexia</td>
</tr>
<tr>
<td>Sorafenib(^7)</td>
<td>58</td>
<td>86</td>
<td>57%</td>
<td>5.5</td>
<td>19.3</td>
<td>Diarrhea, fatigue, rash, hand-foot syndrome, anorexia, anemia, hypertension</td>
</tr>
<tr>
<td>Bevacizumab + IFN-α(^8)</td>
<td>61</td>
<td>82</td>
<td>38.5%</td>
<td>10.2</td>
<td></td>
<td>Bleeding, hypertension, proteinuria</td>
</tr>
<tr>
<td>Pazopanib(^9)</td>
<td>59</td>
<td>85</td>
<td>68.3%</td>
<td>9.2</td>
<td></td>
<td>Diarrhea, vomiting, hypertension, hair color changes, nausea, anorexia, arterial thrombotic events, hemorrhagic events, ALT and AST elevation</td>
</tr>
<tr>
<td>Temsirolimus(^8)</td>
<td>58</td>
<td>81</td>
<td>32.1%</td>
<td>3.8</td>
<td>10.9</td>
<td>Rash, peripheral edema, stomatitis, nausea, hyperglycemia, hyperlipidemia, hypercholesterolemia, diarrhea, anemia, dyspnea</td>
</tr>
<tr>
<td>Everolimus(^7)</td>
<td>61</td>
<td>85</td>
<td>64%</td>
<td>4</td>
<td></td>
<td>Stomatitis, rash, fatigue, pneumonitis, diarrhea</td>
</tr>
</tbody>
</table>

Quivy, Clin Interv Aging, 2013
Outcomes of Ineligible Patients

Heng, Ann Onc, 2014
Compliance
Younger age and higher comorbidity predict higher compliance with pazopanib

Hackshaw, J Manag Pharm, 2014
Costs of Care

- Medicare-SEER
- Patients with AEs had higher costs over 30 days
  - Mean $13,944 [SD $14,529]) compared with those without mention of these events (Mean $1878 [SD $5264]).
  - Adjusting for differences in baseline characteristics, the mean (95% confidence interval) difference in costs between evented and non-evented patients was $12,410 ($9217–$16,522).

Hagiwara, J Med Econ, 2013
Conclusions

- Older patients benefit from RCC therapies
  - Review eligibility for each study when evaluating if a patient is a candidate
- More data needed for those who are not candidates for RCC therapies
  - Limited data for those aged 80 plus
  - Limited data for those who do not fit the eligibility criteria perfectly
- Include GA in trials designed for these populations
  - (Hurria, JCO 2014)