Optimal Management of RCC in the elderly: systemic therapies

Dr. Ravindran Kanesvaran
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National Cancer Centre Singapore
Outline

• Demographics
• Geriatric Assessment
• Systemic therapies
• Data in elderly
• SIOG Taskforce
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Demographics

- Over 200,000 new cases and over 100,000 deaths worldwide per year
- Median age is 64 years
- 24.2% are in patients 74 years and over
- Up to 30% are metastatic at time of diagnosis

Metastatic RCC in NCCS GU clinic

• Subspeciality GU oncology practice (RCC, prostate, bladder, testicular Ca, penile Ca etc)

• No of new mRCC patients treated a month: 5 patients (about 60 new patients/ year)

• Agents available for mRCC: Sunitinib, Pazopanib, Sorafenib, Everolimus, Temsirolimus, IL2, Bevacizumab + Interferon

• Clinical Trials
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What is a Comprehensive Geriatric Assessment (CGA)?

• Multidisciplinary evaluation of older persons in which their multiple problems are uncovered, described and explained

• CGA has been used by both geriatricians and oncologists to understand these group of patients better
Components of CGA

- Functional Status (ECOG-PS, ADL, IADL, GUG Test)
- Affective Status (GDS)
- Cognitive Status (Clock drawing test, MMSE)
- Nutritional Status (BMI, DNI)
- Comorbidity (CCI)
- Geriatric Syndromes
- Pharmacy
The role of CGA

• Some components of the CGA have been shown to be prognostic in Western populations independent of performance status alone

• Intervention based on CGA evaluation has been shown to prolong survival in elderly cancer patients
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Treatment options for patients with mRCC have been revolutionised in a short period of time…

<table>
<thead>
<tr>
<th>Setting</th>
<th>Patients</th>
<th>Therapies with level 1 evidence</th>
<th>Other Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good or intermediate risk</td>
<td>Sunitinib, Pazopanib, Bevacizumab+IFN</td>
<td></td>
<td>High dose IL-2 in highly select patients, Sorafenib, Clinical Trial, Observation in select patients</td>
</tr>
<tr>
<td>Poor risk</td>
<td>Temsirolimus</td>
<td></td>
<td>Other VEGF inhibitors, Clinical Trial</td>
</tr>
<tr>
<td><strong>Second Line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior cytokines</td>
<td>Sorafenib, Axitinib, Pazopanib</td>
<td></td>
<td>Sunitinib, Clinical Trial</td>
</tr>
<tr>
<td>Prior VEGF</td>
<td>Axitinib, Everolimus</td>
<td></td>
<td>Targeted therapy not previously used</td>
</tr>
<tr>
<td>Prior mTOR</td>
<td>No data</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Third Line</strong></td>
<td></td>
<td></td>
<td>Heng &amp; Choueiri ASCO Educational Book 2012</td>
</tr>
</tbody>
</table>
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Sunitinib prolongs overall survival in good/intermediate risk RCC.


Retrospective analysis from 6 clinical trials in patients <70 vs >=70 showed similar efficacy but more adverse events (fatigue, decreased appetite, LOW).

Huston TE et al ASCO 2011 abs
PFS with dose attenuation (37.5mg daily- 4 weeks on)

HS Tan et al, Pending review
AVOREN trial: bevacizumab and interferon prolongs PFS

Benefit not statistically significant for patients >65 years

Overall Survival Pazopanib Registration trial

Hazard Ratio = 0.73
95% CI (0.47, 1.12)
P value = 0.02 (1-sided)

Median OS
Pazopanib: 21.1 mo
Placebo: 18.7 mo

48% of placebo patients received pazopanib after PD
Benefit seen even in the elderly 65 years and above

O'Brien-Fleming boundary for futility / superiority: \( P = 0.201 / 0.004 \) (1-sided)
Sternberg C, et al. 2009 ASCO Annual Meeting; Abstract 5021
ARCC trial: Temsirolimus prolongs overall survival in poor-risk RCC

No OS benefit seen in patients 65 years and older

TARGET: Sorafenib prolongs OS in cytokine refractory RCC

Sorafenib (n=451) = 17.8 months
Placebo (n=452) = 14.3 months

HR (sorafenib/placebo) = 0.78
95% CI: 0.62–0.97
P=0.0287**

Same benefit for both <65 and >=65 years old with marginally higher incidence of adverse events

*Statistically significant: O’Brien–Fleming threshold for statistical significance α=0.037
*P censored at 30 June 2005, approx. start of crossover
Everolimus vs Placebo: PFS by Central Radiology Review

- **Hazard ratio**: 0.30
- **95% CI**: (0.22, 0.40)
- **Log-rank**: $P<0.0001$

- **Median PFS**
  - Everolimus: 4.0 mo
  - Placebo: 1.9 mo

**PFS better in patients < 65 years old**

Phase III trials of approved RCC drugs

<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>
</tr>
</thead>
<tbody>
<tr>
<td>Sutent(^6)</td>
<td>62</td>
<td>87</td>
<td>39.5%</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Sorafenib(^6)</td>
<td>58</td>
<td>86</td>
<td>57%</td>
<td>5.5</td>
<td>19.3</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>
</tr>
<tr>
<td>Pazopanib(^10)</td>
<td>59</td>
<td>85</td>
<td>68.3%</td>
<td>9.2</td>
<td></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>
</tr>
<tr>
<td>Everolimus(^7)</td>
<td>61</td>
<td>85</td>
<td>64%</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Quivy A et al. Clin Interventions in Aging 2013
COMPARZ
COMParing the efficacy, sAfety and toleRability of paZopanib vs. Sunitinb
Primary endpoint: Pazopanib is non-inferior to sunitinib (independent review)

PFS HR (95% CI): 1.047 (0.898-1.220)

<table>
<thead>
<tr>
<th></th>
<th>Median months PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib</td>
<td>557 8.4 (8.3-10.9)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>553 9.5 (8.3-11.1)</td>
</tr>
</tbody>
</table>

1. Motzer R, et al. ESMO 2012 oral presentation; abstract LBA8_PR.
Relative Risk in Adverse Events

AE occurrence ≥10% in either arm where the 95% CI for RR does not cross 1

**Adverse event***

- Hair colour change
- Weight decreased
- Serum ALT increased
- Alopecia
- Upper abdominal pain
- Serum AST increased
- Fatigue
- Hash
- Pain in extremity
- Constipation
- Taste alteration
- LDH increased
- Serum creatinine increased
- Peripheral oedema
- Hand-foot syndrome
- Dyspepsia
- Pyrexia
- Leukopenia
- Hypothyroidism
- Epistaxis
- Serum TSH increased
- Mucositis
- Neutropenia
- Anaemia
- Thrombocytopenia

**Relative risk (95% CI)**

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The medical treatment of metastatic renal cell cancer in the elderly: Position paper of a SIOG Taskforce

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Accepted 15 August 2008
<table>
<thead>
<tr>
<th>Factors</th>
<th>Possible consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological</td>
<td>Ageing body systems</td>
</tr>
<tr>
<td></td>
<td>Higher risk of toxicity and poor tolerability</td>
</tr>
<tr>
<td>Pathological</td>
<td>Comorbidities</td>
</tr>
<tr>
<td>Pharmacological</td>
<td>Drug interactions</td>
</tr>
<tr>
<td></td>
<td>Ditto</td>
</tr>
<tr>
<td></td>
<td>Ditto; less effective treatment</td>
</tr>
<tr>
<td>Psychological</td>
<td>Less (or possibly greater) acceptance of toxicity,</td>
</tr>
<tr>
<td></td>
<td>with implications for compliance</td>
</tr>
<tr>
<td>Professional</td>
<td>Could clinician bias or lack of available clinical</td>
</tr>
<tr>
<td></td>
<td>trial data and guidelines be limiting the treatment</td>
</tr>
<tr>
<td></td>
<td>options?</td>
</tr>
</tbody>
</table>

Bellmunt et al CROH 2009
1. Conclusions and recommendations

On the limited information available, which comes mostly from retrospective analysis of subgroups in controlled and uncontrolled clinical trials, it would appear that patients aged over 65 years benefit as much from targeted therapies as younger patients and do not experience more frequent or severe toxicity. However, no data are available for patients aged over 85 years.

Bellmunt et al CROH 2009
Thank you

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