Phase I Study of Sorafenib and Stereotactic Body Radiotherapy (SBRT) for Advanced Hepatocellular Carcinoma

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Hepatocellular Carcinoma (HCC)

- HCC occurs frequently in the setting of liver cirrhosis (hepatitis B/C virus, alcohol, metabolic)
- 3rd leading cause of cancer death world wide (9th in US, fastest increasing)
  - Global 5 year survival < 10%
- Local therapy can be curative but co-morbidity and late diagnosis make treatment delivery challenging
- Sorafenib (targeted therapy, an oral inhibitor of tyrosine kinases VEGFR-2, PDGF-beta, Raf, c-kit)
- Sorafenib improves survival in patients with very advanced HCC ineligible for local therapies with good liver function (Child-Pugh Class A):
  - Median overall survival 10.7 vs 7.9 months (Llovet NEJM 2008)
SBRT for Advanced HCC

• Stereotactic body radiotherapy (SBRT) to liver has shown promise in locally advanced, heavily pre-treated HCC pts
  – Median OS 16.8 months post SBRT (Bujold et al, ASTRO 2011)
• Lab tumour models suggest combining sorafenib with radiation may improve tumour control
• This study evaluated concurrent sorafenib and SBRT (6 fractions in 2 weeks) in patients with advanced HCC
  – Primary Objective: Determine maximum tolerated dose (MTD) and acute toxicity of sorafenib in combination with SBRT

**Trial Schema**

**Strata I – Small tumour(s) volume (<40% of liver)**

**Strata II – Large tumour(s) (40-60% of liver)**

Radiotherapy

Sorafenib

Wk 1  Wk 2  Wk 3  Wk 4  Wk 8
Combining SBRT and Sorafenib

- Patients had unresectable HCC, good performance status, good liver function (Child-Pugh Class A), >800 cc of non-tumor liver, and adequate hematologic, liver and kidney function, minimal extrahepatic disease
- 16 patients started therapy: strata I-small volume: II-large volume 4:12
  - Dose range strata I:II – 39-54 Gy/ 6 : 30-33 Gy/ 6
- 3 patients completed study therapy as planned
- 1 patient died due to tumour rupture pre-RT
- 4 patients discontinued Sorafenib < 4 wks: tumor progression (2), toxicity (2)
- 3 Dose Limiting Toxicities (drug/radiation related) were observed within 12 weeks: (small bowel obstruction Gr 4, lower GI bleed Gr 3, upper GI bleed/tumour rupture Gr 5) in Strata 2 => sorafenib dose de-escalated
- Strata 1- small volume: MTD not reached (study closed early, 200 mg bid appeared tolerable)
- Strata 2- large volume: MTD 200 mg sorafenib daily, completed
## Results

### Demographics

<table>
<thead>
<tr>
<th>Age (range)</th>
<th>Child score 5</th>
<th>Hepatitis (B/C/EtOH)</th>
<th>Tumor thrombus</th>
<th>Extrahepatic disease</th>
<th>Multiple lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>61.5 (52-79)</td>
<td>62.5%</td>
<td>43/38/38%</td>
<td>62.5%</td>
<td>19%</td>
<td>62.5%</td>
</tr>
</tbody>
</table>

### Change in Liver function (Child Pugh Score/Class) and Grade 3 + Toxicity

<table>
<thead>
<tr>
<th>CP Class Decline</th>
<th>Biochem/Liver</th>
<th>Hematologic</th>
<th>Other</th>
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<tr>
<td>36%</td>
<td>12.5%</td>
<td>25%</td>
<td>19%</td>
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### Response to Treatment

**Strata 1 (small volume), n=4**

- CR: 0
- PR: 2
- SD: 2
- PD: 0

*RR 50%*

**Strata 2 (large volume), n=11**

- CR: 0
- PR: 4
- SD: 7
- PD: 0

*RR 36%*
Conclusion

• Concurrent use of sorafenib and RT is challenging
• Reduced drug dose and irradiated volume are key factors in toxicity risk
• Despite advanced tumour burden and toxicity, response rates are impressive (40%)
• Concurrent sorafenib/ SBRT is not recommended for locally advanced HCC outside clinical trials
• Sequential SBRT followed by sorafenib will be tested in the RTOG 1112 phase III trial