Integrating systemic and locoregional therapies in a patient with advanced hepatocellular carcinoma (HCC)

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Disclosures

• Ch. Verslype receives research funding from
  – Bayer
  – Sirtex
Case 1: male patient, 47 yr

- 1/2013: abdominal pain, no signs of chronic liver disease
- Imaging: 2 hypervascular liver lesions (both > 5 cm)
- Excellent liver synthetic function
- Normal serum alfa-foetoprotein
- No portal hypertension
• 3/2013: central hepatectomy (s.4a + 4b + 5)
  – RO-resection
  – Well-differentiated HCC < β-catenin mutated adenoma?
  – Non-cirrhotic liver
• 3/2013: central hepatectomy (s.4a + 4b + 5)
  – RO-resection
  – Well-differentiated HCC < β-catenin mutated adenoma?
  – Non-cirrhotic liver

• 1/2014
  – rise in serum AFP
  – multifocal intrahepatic recurrence
  – no extra-hepatic spread
Male patient, 47 yrs

• Multifocal bilobar recurrence of HCC
  – 1 year following central hepatectomy
  – No extrahepatic spread
  – Excellent liver function

• Therapeutic options?
Male patient, 47 yrs

- Multifocal bilobar recurrence of HCC
  - 1 year following central hepatectomy
  - No extrahepatic spread
  - Excellent liver function

- Therapeutic options?
  1. Liver transplantation
  2. Transarterial chemoembolization
  3. Sorafenib
  4. Radioembolization
  5. Other
Hepatocellular Carcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment, and Follow-up†

* Poor liver synthetic function due to tumor involvement of the liver.
° Only Child–Pugh A.

Guidelines versus clinical practice

• 101 patients with newly diagnosed, previously untreated HCC in BCLC stage B

  – 55%: transarterial locoregional therapy
    • TACE/TAE: 38%
    • Y90-RE: 17%
  – 35%: radical therapy
    • RFA: 4%
    • Resection: 9%
    • LTx: 25%
  – 5%: systemic therapy
  – 5%: best supportive care

SORAMIC

**Imaging Sub-Study**

1⁰ endpoint
- Non-inferiority (1ˢᵗ step) or superiority (2ⁿᵈ step) of Primovist-MRI vs. CE-CT

Contrast-enhanced CT
- Primovist®-enhanced MRI

Assign to study arm
- Off Study
  - BCLC 0
  - BCLC D

**Local Ablation Group**
(<4 tumours; <5 cm each)

Randomise
1:1
n = 290
- RFA

Palliative Group

Randomise
n = 375
- SIR-Spheres

**1⁰ endpoint**
- sorafenib
  - Time to Recurrence
  - Overall Survival
- placebo
- sorafenib

Off Study
- BCLC 0
- BCLC D
HCT116 xenograft tumor growth delay: sorafenib alters radiation response

Plastaras, Cancer Res 2007
Case 1 (continued)

- SORAMIC trial
  - randomized in combination arm
  - sequential treatment of right and left liver lobe with $^{90}$Y-resin microspheres
  - Day 3 post-SIRT, start sorafenib
    - Half dose (400 mg/day)
    - After 1 week: full dose (800 mg/day)

- Tolerance: grade 2 fatigue and skin rash
2 months post SIRT + sorafenib
LIVER CANCER

Safety and toxicity of radioembolization plus Sorafenib in advanced hepatocellular carcinoma: analysis of the European multicentre trial SORAMIC

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Planned safety analysis for the first 40 patients in the SORAMIC trial

Table 2. Treatment characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sorafenib + radioembolization</th>
<th>Sorafenib only</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily sorafenib dose, mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>528</td>
<td>574</td>
<td>0.647</td>
</tr>
<tr>
<td>Median</td>
<td>614</td>
<td>557</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>45–793</td>
<td>284–792</td>
<td></td>
</tr>
<tr>
<td>Duration of sorafenib treatment, months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>9.4</td>
<td>8.8</td>
<td>0.776</td>
</tr>
<tr>
<td>Median</td>
<td>8.5</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>Activity RE total, GBq</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.87</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.54–2.35</td>
<td>n.a.</td>
<td></td>
</tr>
</tbody>
</table>

n.a., not applicable.
Planned safety analysis for the first 40 patients in the SORAMIC trial

<table>
<thead>
<tr>
<th>Adverse event (%)</th>
<th>Sorafenib + RE</th>
<th>Sorafenib only</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grade</td>
<td>Grade 3/4/5</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>74 (14 of 19)</td>
<td>21/0/0</td>
<td>0.405</td>
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<tr>
<td>Hand-foot skin reaction</td>
<td>35</td>
<td>20/0/0</td>
<td>1.000</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>55</td>
<td>20/0/0</td>
<td>1.000</td>
</tr>
<tr>
<td>Infection</td>
<td>10</td>
<td>5/0/0</td>
<td>0.014</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40</td>
<td>15/5/0</td>
<td>0.748</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5</td>
<td>0/0/0</td>
<td>0.092</td>
</tr>
<tr>
<td>Weight loss</td>
<td>70</td>
<td>5/0/0</td>
<td>1.000</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>5/0/0</td>
<td>1.000</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>0/0/0</td>
<td>0.231</td>
</tr>
<tr>
<td>Rash/Desquamation</td>
<td>10</td>
<td>5/0/0</td>
<td>1.000</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>5</td>
<td>0/0/5</td>
<td>0.605</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory-related events</th>
<th>Sorafenib + RE</th>
<th>Sorafenib only</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grade</td>
<td>Grade 3/4/5</td>
<td></td>
</tr>
<tr>
<td>Elevated GGT</td>
<td>95</td>
<td>25/5/0</td>
<td>1.000</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>90</td>
<td>0/0/0</td>
<td>1.000</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>60</td>
<td>0/0/0</td>
<td>1.000</td>
</tr>
<tr>
<td>Ascites</td>
<td>25</td>
<td>10/0/0</td>
<td>1.000</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>40</td>
<td>5/0/0</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypoalbuminaemia</td>
<td>45</td>
<td>0/0/0</td>
<td>0.748</td>
</tr>
<tr>
<td>Anaemia</td>
<td>60</td>
<td>5/0/0</td>
<td>0.741</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>90</td>
<td>5/0/0</td>
<td>0.127</td>
</tr>
<tr>
<td>Increased INR</td>
<td>20</td>
<td>0/0/0</td>
<td>0.288</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.
Conclusions

• The benefits of combined systemic and liver-directed treatments in inoperable intermediate- or advanced-stage hepatocellular carcinoma (HCC) have yet to be defined

• Early safety analysis of SORAMIC study is promising