Hepatocellular Carcinoma (HCC) Patient Cases

Bruno Daniele
Department of Oncology
G. Rummo Hospital
Benevento - Italy
Disclaimer

• Consultant and lecture fees:
  – Bayer Schering Pharma
  – Daiichi-Sankyo
  – Novartis
Patient Case 1

- Female, 61 yrs old
- Chronic Hepatitis B treated with entecavir
- No evidence of liver cirrhosis (no esophageal varices, no thrombocytopenia, no US signs)
- February 2012: incidental discovery of a large (10 cm) liver mass (VII-VIII segments) with thrombus in the cava vein and in the right atrium. Several small (> 1 cm) nodules in the right lobe.
- AFP = 4691 ng/ml
Patient Case 1
What will you do for diagnosis?

- Contrast-enhanced MRI
- Liver biopsy
- Rely upon AFP value and imaging for diagnosis of HCC
**Diagnosis of HCC**

**In cirrothnic patients:**
- contrast uptake in the arterial phase and washout in the venous/late phase in nodules > 2 cm
- AFP dropped from the diagnostic algorithm

**In non-cirrhotic patients:**
- Pathological diagnosis of HCC is recommended for all nodules occurring in non-cirrhotic livers
Patient Case 1

Well differentiated HCC

Glypican 3 immunostaining
**Patient Case 1**

- Patient started sorafenib 400 mg p.o. b.i.d.
- No significant side effects (grade 1 HFSR)
- AFP value dropped to 3120 ng/ml in April 2012 and to 2410 ng/dl in June 2012
- Interval US examination indicated no changes in the size of the liver mass
- In July 2012 the patient was admitted to hospital because of abdominal pain and fever
- AFP value was 3482
- CT scan showed a slight increase in the size of the liver mass
Patient Case 1
What will you do?

- Continue sorafenib
- Increase sorafenib dosage
- Stop sorafenib and do best supportive care
- Stop sorafenib and enroll the patient in a clinical trial
From April 2007 to July 2008, 300 patients were prospectively treated with sorafenib 400 mg BID. At documented radiological PD, 101 patients (34%) were randomized: 49 patients (48.5%) to increased-dose sorafenib (600 mg BID) + BSC and 52 patients (51.5%) to BSC, respectively.

PD=radiological progression, PFS=progression-free survival.

Adapted from Pressiani T et al. Presented at: ASCO Annual Meeting; June 3-7, 2011; Chicago, IL.
### Overall Survival (OS)

- **HR sorafenib vs BSC, 0.71; CI 95% : (0.47-1.08); P value: .107**
- **Risk reduction of 29%**

<table>
<thead>
<tr>
<th></th>
<th>All Median (range)</th>
<th>Sorafenib Median (range)</th>
<th>BSC Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP (months)</td>
<td>6.11 (0.26-44.50)</td>
<td>7.55 (0.26-44.50)</td>
<td>5.89 (0.49-26.64)</td>
</tr>
</tbody>
</table>

Adapted from Pressiani T et al. Presented at: ASCO Annual Meeting; June 3-7, 2011; Chicago, IL.
Patient Case 1

Fibrosis and non neoplastic liver
Patient Case 1

Fibrosis with bile ducts proliferation
CK7 immunostaining of the bile ducts
Response assessment during sorafenib

• How do you define disease progression in your patients?
• What criteria do you assess?
  – Patient symptoms
  – Radiological scans
  – Other
Guidelines for evaluating response to treatment in solid tumours have evolved
Targeted agents can induce tumour necrosis, but not necessarily tumour shrinkage

Representative CT scans from a single patient included in a phase II study of 137 patients with inoperable HCC treated with sorafenib

<table>
<thead>
<tr>
<th>Reponse by mWHO</th>
<th>Baseline</th>
<th>Follow-up 1 (8 weeks)</th>
<th>Follow-up 2 (16 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (cm³)</td>
<td>295</td>
<td>341</td>
<td>285</td>
</tr>
<tr>
<td>% necrosis</td>
<td>2</td>
<td>53</td>
<td>51</td>
</tr>
</tbody>
</table>

CT, computed tomography
Disease progression

• Tumour response criteria are evolving, adding ambiguity to cross-trial comparisons
• Not all cancer therapies necessarily induce tumour shrinkage\(^1\text{–}^3\)
• Many targeted agents improve survival, but are associated with a low response rate according to RECIST\(^4\text{–}^6\)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Tumour type</th>
<th>Objective response (RECIST)</th>
<th>Survival benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib(^4)</td>
<td>NSCLC</td>
<td>9% (PR)</td>
<td>Yes</td>
</tr>
<tr>
<td>Sorafenib(^5)</td>
<td>HCC</td>
<td>2% (PR)</td>
<td>Yes</td>
</tr>
<tr>
<td>Temsirolimus(^6)</td>
<td>RCC</td>
<td>8% (PR)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; CRC, colorectal cancer.
Sorafenib has demonstrated benefit in advanced HCC according to mRECIST

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Response criteria</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spira et al</strong>¹</td>
<td>25</td>
<td>RECIST v1.1</td>
<td>4</td>
<td>0</td>
<td>72</td>
<td>24</td>
</tr>
<tr>
<td>Retrospective analysis</td>
<td></td>
<td>EASL</td>
<td>4</td>
<td>24</td>
<td>52</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mRECIST</td>
<td>4</td>
<td>44</td>
<td>36</td>
<td>16</td>
</tr>
<tr>
<td><strong>Iavarone et al</strong>²</td>
<td>26</td>
<td>RECIST</td>
<td>0</td>
<td>12</td>
<td>61</td>
<td>27</td>
</tr>
<tr>
<td>Prospective study</td>
<td></td>
<td>mRECIST</td>
<td>0</td>
<td>38</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td><strong>Kuzuya et al</strong>³</td>
<td>43</td>
<td>RECIST</td>
<td>0</td>
<td>3</td>
<td>70</td>
<td>28</td>
</tr>
<tr>
<td>Prospective study</td>
<td></td>
<td>mRECIST</td>
<td>0</td>
<td>35</td>
<td>41</td>
<td>24</td>
</tr>
<tr>
<td><strong>Edeline et al</strong>⁴</td>
<td>53</td>
<td>RECIST v1.1</td>
<td>0</td>
<td>2</td>
<td>79</td>
<td>19</td>
</tr>
<tr>
<td>Retrospective study</td>
<td></td>
<td>mRECIST</td>
<td>4</td>
<td>19</td>
<td>57</td>
<td>21</td>
</tr>
</tbody>
</table>

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Patient Case 2

- Male, 71 yrs old
- Chronic Hepatitis C since 1991
- Alpha-interferon for one year (1991-1992)
- Diabetes treated with metformin since 2005
- High blood pressure
- October 2010: diagnosis of HCC (multiple lesions in the right lobe) treated with TACE. Disease controlled with repeated TACE sessions until...
- October 2012: multiple liver lesions in both hepatic lobes; AFP = 412. Child-Pugh A6; ECOG PS = 0.
Patient Case 2
What will you do?

- Start sorafenib
- Start radioembolization
- Start chemotherapy
SHARP subgroup analysis suggests sorafenib has survival benefits in intermediate HCC

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval.
### Previous treatment for HCC<sup>a</sup>

<table>
<thead>
<tr>
<th>% of n&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Total (N=1571)</th>
<th>Japan (n=161)</th>
<th>AP (n=450)</th>
<th>Europe (n=588)</th>
<th>US (n=313)</th>
<th>Latin America (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior surgery</td>
<td>19</td>
<td>40</td>
<td>24</td>
<td>14</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Prior LRT&lt;sup&gt;c&lt;/sup&gt;</td>
<td>55</td>
<td>84</td>
<td>69</td>
<td>44</td>
<td>49</td>
<td>29</td>
</tr>
<tr>
<td>TACE</td>
<td>46</td>
<td>76</td>
<td>64</td>
<td>31</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>RFA</td>
<td>15</td>
<td>38</td>
<td>12</td>
<td>15</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of TACE treatments, % of n&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Total (N=722)</th>
<th>Japan (n=122)</th>
<th>AP (n=289)</th>
<th>Europe (n=186)</th>
<th>US (n=116)</th>
<th>Latin America (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>19</td>
<td>36</td>
<td>47</td>
<td>59</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>15</td>
<td>20</td>
<td>23</td>
<td>27</td>
<td>11</td>
</tr>
<tr>
<td>3-5</td>
<td>27</td>
<td>43</td>
<td>27</td>
<td>25</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>≥6</td>
<td>12</td>
<td>23</td>
<td>17</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Patients may have received >1 prior treatment; <sup>b</sup>Missing / not evaluable patients not tabulated; <sup>c</sup>Other LRT received included percutaneous ethanol injection (4%), hepatic artery infusion (5%), other (9%)

Kudo M et al. ILCA 2011; abstract 0-030
Patient Case 1

- Patient started sorafenib 400 mg p.o. b.i.d.
- No significant side effects (grade 1 nausea, fatigue and HFSR)
- January 2011: Admitted to the hospital because of melena. Hb = 5.5 g/dl. Received four packs of red blood cells. Upper GI endoscopy showed a bleeding gastric polyp. Bleeding was stopped endoscopically. AFP = 78.
What will you do?

- Restart sorafenib at full dosage
- Restart sorafenib at reduced dosage
- Start radioembolization
- Start chemotherapy
- Best supportive care
- Clinical trial
Patient case 2

- After discussing the options with the patient, he decided not to continue sorafenib and accepted to be enrolled in a clinical trial with the c-MET inhibitor tivantinib.
Tivantinib (ARQ 197) in MET-High Pretreated Hepatocellular Carcinoma

**Design:** International, multicenter, randomized, placebo-controlled, double-blind, Phase 2 study. Patients randomized 2:1 to tivantinib (360 mg twice daily [bid], amended to 240 mg bid for emergent Grade 23 neutropenia) or placebo until disease progression. Crossover after radiographic progression. Patients stratified by ECOG PS and vascular invasion.

**Primary Endpoint:** TTP in ITT population at central radiology review by RECIST 1.1.

**Secondary Endpoints:** PFS, OS, ORR, DCR, crossover ORR, safety, PK; efficacy analysis in subgroups by: MET Diagnostic status, Viral status, duration of prior systemic therapy.

**Key eligibility:** Advanced-stage, second line HCC; Child-Pugh A; PS 0-1.

![Graph showing TTP in ITT Population](image)

<table>
<thead>
<tr>
<th></th>
<th>Median TTP</th>
<th>Patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tivantinib</td>
<td>6.9 wks</td>
<td>71</td>
<td>46</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.0 wks</td>
<td>36</td>
<td>30</td>
</tr>
</tbody>
</table>

HR: 0.64 (90% CI: 0.43-0.94) Log Rank: P=0.04

ESMO 2012. Vienna, Austria
**Tivantinib (ARQ 197)**

**Efficacy in MET-High Pretreated HCC**

- **Median OS**
  - **Tivantinib**: 7.2 mos (Patients: 22, Events: 17)
  - **Placebo**: 3.8 mos (Patients: 15, Events: 15)

**HR**: 0.38 (95% CI: 0.18-0.81) Log Rank: P=0.01

*8 MET High patients crossed-over, 5 remained on open-label tivantinib for at least 6 weeks (1 non-evaluable at cut-off date)*

- **OS slightly better at 240mg BID** (median not achieved, HR: 0.30 [95% CI: 0.11-0.84] P=0.02)
- **TTP**: 11.7 wks on tivantinib, 6.1 wks on placebo. HR: 0.43 (95% CI: 0.19-0.97) Log Rank: P=0.03
- **DCR**: 50% (28-72), on tivantinib, 20% (4-48) on placebo
- **OS in MET Low patients**: no statistical difference observed with crossing curves: HR: 1.33 (95% CI: 0.58-3.04) P=0.50

ESMO 2012. Vienna, Austria