Role of Biopsy in the Era of Targeted Therapy

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✔ Introduction
✔ Substitutions for LB
✔ LB is still needed!
✔ What will we get from LB?
✔ Problems to be solved
✔ Conclusion
Introduction

• First liver aspiration in 1883
• First percutaneous biopsy in 1923
• Since then LB has been the gold standard in the diagnosis of diffuse and focal liver diseases
Drawbacks of LB

- Invasive procedure (morbidity ~3%)
- Sampling Error
- Interobserver variability
- Not suitable for repeated examination
Substitution for LB

• Inflammation
  – AST, ALT, GGT, etc...

• Fibrosis
  – platelet count
  – serum markers: hyaluronic acid, type IV collagen
  – Transient Elastography (FibroScan®)

• Focal liver lesions
  – Imaging modalities
  – tumor markers
FibroScan® can stratify HCC risk

Chronic Hepatitis C without IFN Tx

<table>
<thead>
<tr>
<th>Elasticity Range</th>
<th>Percentage</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7 kPa</td>
<td>0.5%</td>
<td>269</td>
</tr>
<tr>
<td>7-10 kPa</td>
<td>1.3%</td>
<td>113</td>
</tr>
<tr>
<td>10-15 kPa</td>
<td>4.4%</td>
<td>106</td>
</tr>
<tr>
<td>15-25 kPa</td>
<td>8.9%</td>
<td>96</td>
</tr>
<tr>
<td>&gt;25 kPa</td>
<td>14.4%</td>
<td>69</td>
</tr>
</tbody>
</table>

EOB-MRI facilitate early diagnosis

Slow growing tumor in non-viral cirrhosis
Defect in hepatobiliary phase of EOB-Gd-DTPA MRI
Stromal invasion
Number of Liver Biopsy @ UTH

The University of Tokyo Hospital 2002-2012
Liver Biopsy is still needed
What can we get from LB?

- Some chronic liver diseases still need LB for final diagnosis
  - non-alcoholic steatohepatitis (NASH)
  - AMA-negative PBC
- LB is needed to evaluate
  - minimal fibrosis/inflammation in CLD
- To differentiate small cholangioma and atypical HCC by imaging is difficult
Differentiate NASH from Simple Steatosis

Simple Steatosis

NASH

- Mallory-Denk Body
- ballooning
- acidophilic body
To detect minimal fibrosis

Sandrin et al. Ultrasound Med 2003
Atypical HCC vs. CCC

poorly diff. HCC

Cholangioma
What will we get from LB?
The era of targeted therapy

• Imatinib opened a door into the era of targeted therapy.
Rationale of molecular targeted agents

- The reversal of only one or few genetic abnormalities sometimes can profoundly inhibit the growth of cancer cells.

<table>
<thead>
<tr>
<th>Target</th>
<th>Disease</th>
<th>Agent</th>
<th>Regimen</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER-2</td>
<td>Breast</td>
<td>Trastuzumab</td>
<td>Combination</td>
<td>Slamon et al. (2001)(^{28,b}), Piccart-Gebhart et al. (2005)(^{29,b})</td>
</tr>
<tr>
<td>EGFR</td>
<td>Head and neck, colorectum(^a)</td>
<td>Cetuximab</td>
<td>Combination</td>
<td>Baselga et al. (2005)(^{32}), Cunningham et al. (2004)(^{40})</td>
</tr>
<tr>
<td>EGFR</td>
<td>Pancreas(^a)</td>
<td>Erlotinib</td>
<td>Combination</td>
<td>Moore (2005)(^{34})</td>
</tr>
<tr>
<td>VEGF</td>
<td>Breast, colorectum(^a), kidney</td>
<td>Bevacizumab</td>
<td>Combination</td>
<td>Miller et al. (2005)(^{41}), Hurwitz et al. (2004)(^{42,b}), Yang et al. (2003)(^{43})</td>
</tr>
<tr>
<td>VEGFR, B-Raf</td>
<td>Kidney(^b)</td>
<td>Sorafenib</td>
<td>Monotherapy</td>
<td>Stadler (2005)(^{55})</td>
</tr>
</tbody>
</table>

Treatment regimen indicates agent alone (monotherapy) or in combination with cytotoxic agents (combination). \(^a\)FDA-approved; \(^b\)Phase III evidence demonstrates improved disease-free or overall survival rates. Abbreviations: NSCLC, non-small-cell lung cancer; VEGFR, vascular endothelial growth factor receptor.

Cetuximab, a monoclonal antibody to EGFR, is only effective in those without K-ras mutation.

Christos S, et al. NEJM 2008
## KRAS exam is included in daily practice

**NCCN Guidelines Version 3.2013**

### Colon Cancer

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>ADJUVANT THERAPY</th>
<th>SURVEILLANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable synchronous liver and/or lung metastases only</td>
<td>FOLFOX/CapeOx preferred</td>
<td>If patient stage IV, NED:</td>
</tr>
<tr>
<td>Colectomy, with synchronous or staged liver or lung resection</td>
<td></td>
<td>- History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y</td>
</tr>
<tr>
<td>Neoadjuvant therapy (for 2-3 months)</td>
<td></td>
<td>- CEA every 3-6 mo x 2 y, then every 6 mo x 3-5 y</td>
</tr>
<tr>
<td>FOLFIRI or FOLFOX or CapeOx ± bevacizumab&lt;sup&gt;cc&lt;/sup&gt; or FOLFIRI or FOLFOX ± panitumumab or FOLFIRI ± cetuximab (KRAS wild-type [WT] gene only)&lt;sup&gt;de,dd&lt;/sup&gt; followed by synchronous or staged colectomy&lt;sup&gt;aa&lt;/sup&gt; and resection of metastatic disease</td>
<td></td>
<td>- Chest/abdominal/pelvic CT&lt;sup&gt;h&lt;/sup&gt; scan every 3-6 mo x 2 y, then every 6-12 mo up to a total of 5 y</td>
</tr>
<tr>
<td>Colectomy, followed by chemotherapy (for 2-3 months)</td>
<td>Consider observation or shortened course of chemotherapy</td>
<td></td>
</tr>
<tr>
<td>FOLFIRI or FOLFOX or CapeOx± bevacizumab&lt;sup&gt;cc&lt;/sup&gt; or FOLFIRI or FOLFOX ± panitumumab or FOLFIRI ± cetuximab (KRAS WT gene only)&lt;sup&gt;de,dd&lt;/sup&gt; and staged resection of metastatic disease</td>
<td></td>
<td>- If advanced adenoma, repeat in 1 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If no advanced adenoma, repeat in 3 y, then every 5 y&lt;sup&gt;y&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Development of test kit in parallel with anti-cancer agents

Crizotinib (ALK inhibitor) kills ALK-positive lung cancer

Molecular biomarker-informed personalized treatment

By courtesy of Dr. Hoshida
Biopsy is critical especially during development of therapeutic strategy
Genome-based personalized HCC surveillance

- Cirrhosis no HCC
- Gene signature test
- Signature-based schedule
- Ultrasound x2/yr
- Poor (HCC: 5.8%/yr)
- Intermediate (2.2%)
- Good (1.5%)

Medical care cost ↓  Life expectancy ↑

Problems to be solved
Seven years after imatinib, sorafenib, a multikinase inhibitor, was first (and still only) approved as a molecular targeted drug for HCC.
No established predictive biomarkers for sorafenib response

Plasma protein

Blood cell RNA

Tissue staining

Gene Symbol

\[
\begin{array}{l}
\text{KIAA0102} \\
\text{EIF2C1} \\
\text{CAP350} \\
\text{LOC144363} \\
\text{DNM1L} \\
\text{ARP5} \\
\text{TNFAIP2} \\
\text{FLJ34443} \\
\text{PTP4A1} \\
\text{NAT1} \\
\text{DSCR2} \\
\text{CL640} \\
\text{S100A8} \\
\text{MIC1} \\
\text{C20orf16}
\end{array}
\]

Abou Alfa, JCO 2006, Llovet, CCR 2012
No major mutations found in HCC

Table 1: Significantly mutated genes and their mutation frequency in the validation set

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chr.</th>
<th>Start</th>
<th>End</th>
<th>CDS length (bp)</th>
<th>Coding indel</th>
<th>Missense</th>
<th>Nonsense</th>
<th>Splice site</th>
<th>Total</th>
<th>P value</th>
<th>q value</th>
<th>Frequency in validation set</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>17</td>
<td>7,572,927</td>
<td>7,579,912</td>
<td>1,218</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>3</td>
<td>14</td>
<td>0.00020</td>
<td>0.0034</td>
<td>3.1% (2/65)</td>
</tr>
<tr>
<td>ERRFI1</td>
<td>1</td>
<td>8,073,270</td>
<td>8,075,679</td>
<td>1,397</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>0.00050</td>
<td>0.0041</td>
<td>3.3% (4/120)</td>
</tr>
<tr>
<td>ZIC3</td>
<td>X</td>
<td>136,648,851</td>
<td>136,652,229</td>
<td>1,412</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0.0015</td>
<td>0.0071</td>
<td>NA</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>3</td>
<td>41,265,560</td>
<td>41,280,833</td>
<td>2,398</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0.0013</td>
<td>0.0071</td>
<td>0.8% (1/120)</td>
</tr>
<tr>
<td>GXYLT1</td>
<td>12</td>
<td>42,481,588</td>
<td>42,538,448</td>
<td>1,351</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0.0015</td>
<td>0.0071</td>
<td>0.8% (1/120)</td>
</tr>
<tr>
<td>OTOPI1</td>
<td>4</td>
<td>4,190,530</td>
<td>4,228,591</td>
<td>1,859</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0.0022</td>
<td>0.0089</td>
<td>3.3% (4/120)</td>
</tr>
<tr>
<td>ALB</td>
<td>4</td>
<td>74,270,045</td>
<td>74,286,015</td>
<td>1,882</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0.0037</td>
<td>0.013</td>
<td>5.0% (6/120)</td>
</tr>
<tr>
<td>ATM</td>
<td>11</td>
<td>108,098,352</td>
<td>108,236,235</td>
<td>9,415</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0.0043</td>
<td>0.014</td>
<td>3.3% (4/120)</td>
</tr>
<tr>
<td>ZNF226</td>
<td>19</td>
<td>44,674,234</td>
<td>44,681,827</td>
<td>2,424</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0.0051</td>
<td>0.015</td>
<td>0% (0/120)</td>
</tr>
<tr>
<td>USP25</td>
<td>21</td>
<td>17,102,713</td>
<td>17,250,794</td>
<td>1,260</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0.0060</td>
<td>0.016</td>
<td>7.7% (5/65)</td>
</tr>
<tr>
<td>WWP1</td>
<td>8</td>
<td>87,386,280</td>
<td>87,479,122</td>
<td>2,857</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0.0091</td>
<td>0.023</td>
<td>3.3% (4/120)</td>
</tr>
<tr>
<td>IGSF10</td>
<td>3</td>
<td>151,154,477</td>
<td>151,176,497</td>
<td>2,892</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0.011</td>
<td>0.026</td>
<td>10% (12/120)</td>
</tr>
<tr>
<td>ARID1A</td>
<td>1</td>
<td>27,022,895</td>
<td>27,107,247</td>
<td>6,934</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0.018</td>
<td>0.041</td>
<td>0.8% (1/120)</td>
</tr>
<tr>
<td>UBR3</td>
<td>2</td>
<td>170,684,018</td>
<td>170,938,353</td>
<td>5,819</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0.024</td>
<td>0.050</td>
<td>1.6% (2/120)</td>
</tr>
<tr>
<td>BAZ2B</td>
<td>2</td>
<td>160,176,776</td>
<td>160,335,230</td>
<td>5,643</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Significantly mutated genes with more than two mutations are shown. Chr., chromosome.
Tivantinib as second-line

- Survival could be divided by MET expression

Santoro et al. Lancet Oncol 2013
Conclusion

• The understanding of molecular mechanism of cancer sheds a new light on liver biopsy
• However “tailored medicine” is still far from clinical practice in HCC
• Further studies are needed for the development in this field
Thank you for your attention!