Hepatocellular carcinoma: Present treatment strategy in Japan

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Disclosure

- Consulting fee or honorarium
  - Bayer, Taiho, Eli lilly, Chugai, Eisai
- Grants
  - GSK, Pfizer, Yakult, Eli lilly, Takeda, Bayer
Cancer Incidence and Mortality in Japan

**Incidence in 2002**

- Stomach
- Colorectal
- Lung
- Breast
- Liver - 40,604
- Prostate
- Uterus
- Pancreas
- Biliary tract
- Esophagus

**Mortality in 2006**

- Lung - 33,662
- Stomach
- Colorectal
- Liver
- Pancreas
- Biliary tract
- Esophagus
- Breast
- Prostate
- Uterus

Cancer Statistics in Japan 2008
Multistep carcinogenesis in hepatocellular carcinoma (HCC)

Persistent/ chronic inflammation

Etiology of HCC varies by regions

- **Japan**: 70% HCV, 10-20% HBV, 10-15% Alcohol, 5-10% Others
- **Asia/Africa**: 70% HCV, 20% HBV, 20% Alcohol, 10% Others
- **North America**: 60-70% HCV, 20% HBV, 20% Alcohol, 10% Others
- **Europe**: 70% HCV, 10-20% HBV, 10-15% Alcohol, 5-10% Others

Background of the Liver in Patients with HCC

- Cirrhosis: 60%
- Chronic hepatitis: 24%
- Normal: 16%

the Liver Cancer Study Group of Japan, 2007
Balance between liver function and tumor stage is the most important in selection of treatments for HCC.
Contents

1. Treatment strategy for HCC in Japan according to the Japanese guideline
2. Efficacy and safety of sorafenib in practice
3. Clinical trials using sorafenib in Japan, especially combination with hepatic arterial infusion chemotherapy
Algorism of HCC Treatments

Liver function

- A, B
- C

Tumor number

- Solitary
- 2, 3
- ≥4
- 1~3
- ≥4

Tumor size

- ≤3cm
- >3cm
- ≤3cm†

Treatment

- Resection
- Ablation*
- Resection Ablation
- Resection TACE
- TACE HAIC
- Liver transplantation
- BSC

* Ablation should be applied to patients with liver damage B and ≤2 cm
† In case of solitary tumor, <5 cm

Japan HCC Treatment guideline revised, 2009
Changes of treatment methods as the first line treatment for HCC in Japan

From Nationwide Survey by the Liver Cancer Study Group of Japan

The efficacy of local treatments

- Surgical resection
- Local ablation
- Transarterial chemoembolization
The efficacy of local treatments

- Surgical resection
- Local ablation
- Transarterial chemoembolization
Overall Survival of Resection and RFA

the 17th nationwide survey of the Liver Cancer Study Group of Japan

Solitary HCC smaller than 5 cm, Child-Pugh A

<table>
<thead>
<tr>
<th></th>
<th>3y</th>
<th>5y</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFA</td>
<td>91%</td>
<td>84%</td>
</tr>
<tr>
<td>Resection</td>
<td>87%</td>
<td>78%</td>
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</tbody>
</table>

Disease-free survival after surgery or ablation therapy

Recurrence rate of HCC is very high even in patients with HCC who can receive curative treatments.

Recurrence rate
1 year: 20-30%
3 year: 50-60%
5 year: 70-90%

The efficacy of local treatments

- Surgical resection
- Local ablation
- Transarterial chemoembolization
Transarterial chemoembolization (TACE): Tumor response

National Cancer Hospital East (2000-2006): N=118

<table>
<thead>
<tr>
<th>Response</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>CR</td>
<td>39 (33%)</td>
</tr>
<tr>
<td>PR</td>
<td>43 (36%)</td>
</tr>
<tr>
<td>SD</td>
<td>21 (18%)</td>
</tr>
<tr>
<td>PD</td>
<td>8 (7%)</td>
</tr>
</tbody>
</table>

CT, PR include tumor necrosis of lipiodol accumulation

Furuse J, et al. ILCA 2007
Overall survival of TACE

the 17th nationwide survey of the Liver Cancer Study Group of Japan

N=8,542

Median OS: 34 months

1-y%: 82%

3-y%: 47%

5-y%: 26%

Selection of treatments according to tumor condition

- Resection or RFA
- Vascular invasion + Extrahepatic spread
- TACE
Selection of treatments according to tumor condition

- Resection or RFA
- TACE
- Resection or RFA
- Hepatic arterial infusion chemotherapy (HAIC)
- Systemic chemotherapy
- Extrahepatic spread
Indication of chemotherapy

- Extrahepatic spread
- Vascular invasion (portal vein)
- TACE refractory

- Systemic chemotherapy
  - Sorafenib
  - New agents in clinical trials

- Hepatic arterial infusion chemotherapy (HAIC)
  - Japanese guideline: recommended
  - EASL–EORTC guideline: not recommended
Overall survival in RCTs of sorafenib vs. placebo

**SHARP trial**
- **N=602**
- Median OS: Sorafenib 10.7 mo, Placebo 7.9 mo
- HR: 0.69
- P-value: <0.001

**Asia-Pacific trial**
- **N=226**
- Median OS: Sorafenib 6.5 mo, Placebo 4.2 mo
- HR: 0.68
- P-value: 0.014

Llovet JM, et al. NEJM, 2008
Phase I study of sorafenib for Japanese patients with HCC

Advanced HCC
ECOG PS 0 or 1
Child-Pugh 分類 A or B

n=27

Sorafenib
200 mg bid
7 days rest

Sorafenib
200 mg bid day 1–28

Sorafenib
400 mg bid
7 days rest

Sorafenib
400 mg bid day 1–28

1 cycle

DLT: hand-foot skin reaction in 1/12 patients of 400 mg bid
Recommended dose: 400 mg bid

## Adverse Events: all grade

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>SHARP</th>
<th>A-P</th>
<th>Jpn P-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>22%</td>
<td>20%</td>
<td>37%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>9%</td>
<td>-</td>
<td>30%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>14%</td>
<td>25%</td>
<td>29%</td>
</tr>
<tr>
<td>Dry skin</td>
<td>8%</td>
<td>-</td>
<td>11%</td>
</tr>
<tr>
<td>Hand–foot skin reaction</td>
<td>21%</td>
<td>45%</td>
<td>44%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8%</td>
<td>-</td>
<td>30%</td>
</tr>
<tr>
<td>Rash or desquamation</td>
<td>16%</td>
<td>20%</td>
<td>56%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>14%</td>
<td>13%</td>
<td>22%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39%</td>
<td>26%</td>
<td>56%</td>
</tr>
<tr>
<td>Nausea</td>
<td>11%</td>
<td>11%</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Voice changes</td>
<td>6%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5%</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>&lt;1%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal pain not specified</td>
<td>8%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bleeding</td>
<td>7%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
In 2009, sorafenib was approved to unresectable advanced HCC in Japan
Consensus-based treatment algorithm proposed by the Japan Society of Hepatology

HCC

- Extrahepatic spread
- Liver function
- Vascular invasion

Child-Pugh A/B
- No
- Yes

C-P C
- No
- Yes

C-P B/C
- No
- Yes

C-P A

Vascular invasion

Number

Size

Treatment

- Hypovascular Early HCC
- Single
- 1-3
- 4 or more
- ≤3cm
- >3cm
- Within Milan criteria and Age≤65
- Exceeding Milan criteria or Age>65

- Intensive follow-up
- Ablation
- Resection
- TACE
- TACE+
- Ablation
- Resection
- TACE
- HAIC
- Resection
- Ablation
- Sorafenib (TACE refractory, C-P A)
- Sorafenib (TACE/HAIC refractory, C-P A)
- HAIC (Vp3,4)
- Sorafenib (Vp3,4)
- TACE (Vp1,2)
- Resection (Vp1,2)
- TACE (Vp1,2)
- Resection (Vp1,2)
- Transplantation
- TACE/Ablation for C-P C pts
- HAIC (Vp3,4)
- Sorafenib (Vp3,4)
- TACE (Vp1,2)
- Resection (Vp1,2)
- TACE/Ablation for C-P C pts

Palliative care

Sorafenib

Consensus-based treatment algorithm proposed by the Japan Society of Hepatology

- **Extrahepatic spread**
- **Liver function**
  - Child-Pugh A/B
  - **Yes**
    - **C-P C**
    - **Exceeding Milan criteria or Age > 65**
      - Transplantation
      - TACE/Ablation for C-P C pts
    - **Yes**
      - Palliative care
  - **No**
    - **C-P B/C**
    - **C-P A**
      - **Sorafenib**
      - HAIC (Vp3-4)
      - TACE (Vp1-2)
      - Resection (Vp1-2)
  - **C-P A**

- **Vascular invasion**
  - **Yes**
    - **Sorafenib**
    - HAIC (Vp3-4)
    - TACE (Vp1-2)
    - Resection (Vp1-2)
  - **No**
    - **C-P C**
    - **Within Milan criteria and Age ≤ 65**
      - TACE
      - HAIC
      - Resection
    - **Yes**
      - **C-P A**

- **Number**
  - Single
  - 1-3
  - 4 or more
- **Size**
  - Hypovascular Early HCC
  - Hypovascular Early HCC

- **Treatment**
  - Intensive follow-up
  - Ablation
  - Resection
  - TACE
  - HAIC
  - Resection
  - Ablation

Efficacy and safety of sorafenib in practice

The Study Group on New Liver Cancer Therapies

264 patients who received sorafenib were enrolled between June 2009 and December 2010

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Median</th>
<th>Range</th>
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<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>21%</td>
</tr>
<tr>
<td>Child-Pugh class</td>
<td>A</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>19%</td>
</tr>
<tr>
<td>HBs antigen (+)</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>HCV antibody (+)</td>
<td></td>
<td>62%</td>
</tr>
<tr>
<td>Vascular invasion (+)</td>
<td></td>
<td>18%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>I</th>
<th>1%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>II</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>IV a</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>IV b</td>
<td>43%</td>
</tr>
<tr>
<td>Prior treatment (+)</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>Resection</td>
<td></td>
<td>31%</td>
</tr>
<tr>
<td>Local ablation</td>
<td></td>
<td>47%</td>
</tr>
<tr>
<td>TACE</td>
<td></td>
<td>78%</td>
</tr>
<tr>
<td>Hepatic arterial infusion</td>
<td></td>
<td>29%</td>
</tr>
</tbody>
</table>

# Drug-related adverse events of sorafenib

**The Study Group on New Liver Cancer Therapies in Japan**

N=264

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand-foot skin reaction</td>
<td>44%</td>
<td>10%</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>31%</td>
<td>5%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32%</td>
<td>5%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>27%</td>
<td>4%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26%</td>
<td>8%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24%</td>
<td>2%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Elevated AST or ALT</strong></td>
<td>70%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Elevated T-Bil</strong></td>
<td>53%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Elevated lipase</strong></td>
<td>78%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Efficacy data of sorafenib in practice

N=264
Response rate: 4%
Tumor control rate: 49%

Median OS: 11.0 months
Median PFS: 2.1 months

Clinical trials for HCC in Japan
Targets of clinical trials of systemic chemotherapy

**Advanced**
- 1st line
- 2nd line
- Combination with TACE
- Extrahepatic spread

**Multiple**
- 1st line
- 2nd line
- Combination with TACE

**Solitary or a few tumors**
- 1st line
- 2nd line
- Adjuvant therapy
- Resection or RFA

TACE
Targets of clinical trials of systemic chemotherapy

**Advanced**
- Extrahepatic spread
- 1st line: Sunitinib, Brivanib, Linifanib
- 2nd line: Brivanib, Everolimus, S-1, Ramucirumab, Axitinib, GC33, etc.

**Multiple**
- Combination with TACE
  - 1st line: Sor. + erolinib, Sor. + HAIC
  - 2nd line: Sorafenib, Brivanib, Orantinib

**Solitary or a few tumors**
- 1st line: TACE
- 2nd line: Resection or RFA
  - Adjuvant therapy: Peretinoin, Sorafenib
Targets of clinical trials of systemic chemotherapy

**Advanced**
- Extrahepatic spread +
- Sunitinib
- Brivanib
- Linifanib
- Sor.++erolinib
- Sor.++HAIC

**Multiple**
- Combination with TACE
- TACE
- Sorafenib
- Brivanib
- Orantinib

**Solitary or a few tumors**
- Resection or RFA
- TACE
- Sorafenib
- Brivanib
- Peretinoine

**1st line**
- Sunitinib
- Brivanib
- Linifanib
- Sor.++erolinib
- Sor.++HAIC

**2nd line**
- Brivanib
- Everolimus
- S-1
- Ramucirumab
- Axitinib, GC33, etc.

**Adjuvant therapy**
- Peretinoine
- Sorafenib
Targets of clinical trials of systemic chemotherapy

Advanced

1st line

Sunitinib
Brivanib
Linifanib

Sor.+erolinib
Sor.+HAIC

2nd line

Brivanib
Everolimus
S-1
Ramucirumab
Axitinib, GC33, etc.

Multiple

Combination with TACE

Solitary or a few tumors

1st line

Sunitinib
Brivanib
Linifanib

Sor.+erolinib
Sor.+HAIC

2nd line

Brivanib
Everolimus
S-1
Ramucirumab
Axitinib, GC33, etc.

Adjuvant therapy

Peretinoin
Sorafenib
Hepatic arterial infusion chemotherapy

- Indication: highly extended portal invasion and/or unresectable huge tumor
- Various regimens of HAIC are used
- No evidence of the survival benefits

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>RR (%)</th>
<th>mTTP (mo)</th>
<th>mOS (mo)</th>
<th>Author</th>
<th>Year</th>
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</thead>
<tbody>
<tr>
<td>5-FU/cisplatin</td>
<td>48</td>
<td>48</td>
<td>NA</td>
<td>10.2</td>
<td>Ando</td>
<td>2002</td>
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<td>5-FU/IFN</td>
<td>55</td>
<td>43.6</td>
<td>5.2</td>
<td>11.8</td>
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<td>2005</td>
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<tr>
<td></td>
<td>116</td>
<td>52.6</td>
<td>NA</td>
<td>6.9</td>
<td>Obi</td>
<td>2006</td>
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<tr>
<td>Cisplatin</td>
<td>25</td>
<td>28</td>
<td>3.6</td>
<td>7.1</td>
<td>Okusaka</td>
<td>2008</td>
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</tbody>
</table>
Comparison studies between sorafenib vs. sorafenib+HAIC to confirm the survival benefits of HAIC

Randomized phase II study of sorafenib + CDDP HAIC
Phase III study of sorafenib + 5-FU/CDDP HAIC
Randomized phase II study 
Sorafenib+CDDP HAIC vs. sorafenib

- Cisplatin arterial infusion is promising anti-tumor effect; response rate is 28%
- Simple methods
  - One shot infusion repeated every 4-6 months
  - Port system replacement is not necessary
- Primary endpoint: overall survival
- Assumption
  - Median OS: 7 mo in Sor → 9.5 mo in Sor+CDDP HAIC
  - HR 0.74; go to phase III study
  - Patient number: 105

http://www.umin.ac.jp/ctr/index-j.htm: UMIN000005703
Summary

- 90% patients with HCC undergo local treatments, hepatectomy, RFA and TACE as the first line treatment.
- Sorafenib is indicated in patients with advanced HCC who are not suitable candidates for local treatments.
- Safety and efficacy of sorafenib in practice are comparable with the SHARP trial.
- Many new agents are developing in every stage of treatment for HCC.
- Hepatic arterial infusion chemotherapy (HAIC) shows high response rate, but no survival benefits has been confirmed. RCTs of sorafenib+HAIC are currently ongoing in Japan.
Thank you for your kind attention.