Unmet Needs in the Treatment of Advanced Hepatocellular Carcinoma

Joong-Won Park

Center for Liver Cancer
National Cancer Center, Korea
“Advanced” HCC

• Definition
  - An abstract concept, Not clear, No consensus

• General meaning
  - ‘Advanced stage’ in BCLC stage
  - Vascular invasion +
    Stage II, III, IVa, IVb in modified UICC stage
    Stage II, IIIA-C, IV in AJCC stage
  - Not indicated of curative treatments
  - Candidate of systemic chemotherapy
## Modified UICC Staging of HCC

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IV-A</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IV-B</td>
<td>T1-4</td>
<td>N0-N1</td>
<td>M1</td>
</tr>
</tbody>
</table>

### Tumor Size

- **① Number 1** (3/3)
- **② Size < 2cm** (2/3)
- **③ Vascular invasion (-)** (1/3)
- **T4 (0/3)**

**Advanced HCC?**

Treatment Plan for HCC
(Korean J Hepatol 2009;15:391-423)

**Hepatocellular carcinoma**
- TNM stage (modified UICC by LCSGJ)
- Child-Pugh class
- ECOG performance

**Tumor treatable**
- Optional test
  - ICG test
  - Bone scan
  - Chest CT
  - Angiography
  - $^{18}$FDG PET-CT
  - Volume measurement
  - Gastric endoscopy

**Curative treatment**
- Hepatic resection (II)
- Liver transplantation (II)
- Radiofrequency ablation (I)
- PEIT (II-1)

**Non-curative treatment**
- TACE (I)
- Radiation therapy (II-1)
- Chemotherapy*
  - Sorafenib (I)
  - Cytotoxic agents (III)

**Clinical trial**
- Drug eluting bead-TACE
- Radioembolization
- HIFU
- Hepatic arterial infusion chemotherapy
- Cytotoxic chemotherapy
- Metastatectomy

**Tumor untreatable**
- Far advanced tumor stage
- Decompensated liver functions (Child-Pugh class C)**
- Compromised performance (ECOG >2)
- Accompanied uncontrolled systemic disease

**Best supportive care**

**considering liver transplantation (I)**
Unmet Needs in the Treatment of Advanced Hepatocellular Carcinoma

Key Reference
HCC: Consensus Recommendations of the NCI Clinical Trials Planning Meeting
The NCI Clinical Trials Planning Meeting (CTPM): the Gastointestinal Cancer Steering Committee (GISC)

- To identify the critical clinical questions and unmet needs in HCC
- To develop strategies for future clinical trials in HCC and to provide rationale for the recommendations
- To reach consensus on priority of clinical trials, both near term and longer term
- To facilitate collaboration among clinicians and scientists

The Greatest Unmet Need in HCC

Advanced HCC who will need systemic therapy

- HCC staging system to compare clinical trials
- Multistep hepatocarcinogenesis: numerous potential therapeutic target
- Optimal imaging to assess drug activity

Molecular characterization of tumor to validate stratification of Pts
- MAPK pathway
- PI3K/Akt/mTOR pathway
- Growth Factor: EGFR, VEGF
- A threshold for tumor size detection
- Assessment of tumor pathology, vascular features, and biologic change

The Greatest Unmet Need in HCC

Advanced HCC who will need systemic therapy

HCC staging system to compare clinical trials

- Multistep hepatocarcinogenesis: numerous potential therapeutic target

Optimal imaging to assess drug activity

- A threshold for tumor size detection
- Assessment of tumor pathology, vascular features, and biologic change

Molecular characterization of tumor to validate stratification of Pts

- MAPK pathway
- PI3K/Akt/mTOR pathway
- Growth Factor: EGFR, VEGF

The Greatest Unmet Need in HCC

Advanced HCC who will need systemic therapy

HCC staging system to compare clinical trials

Multistep hepatocarcinogenesis: numerous potential therapeutic target

Molecular characterization of tumor to validate stratification of Pts

- MAPK pathway
- PI3K/Akt/mTOR pathway
- Growth Factor: EGFR, VEGF

Optimal imaging to assess drug activity

- A threshold for tumor size detection
- Assessment of tumor pathology, vascular features, and biologic change

The Greatest Unmet Need in HCC

- Advanced HCC who will need systemic therapy
- HCC staging system to compare clinical trials
- Molecular characterization of tumor to validate stratification of Pts
- Multistep hepatocarcinogenesis: numerous potential therapeutic targets
- Optimal imaging to assess drug activity
- MAPK pathway
- PI3K/Akt/mTOR pathway
- Growth Factor: EGFR, VEGF
- A threshold for tumor size detection
- Assessment of tumor pathology, vascular features, and biologic change

Seven Priorities for Future Studies in Advanced HCC

1. Because of limited patients resource, agents with new mechanism of action should be given priority

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib Tosylate With or Without Doxorubicin Hydrochloride in</td>
<td>CALGB-80802*</td>
<td>Actively recruiting</td>
</tr>
<tr>
<td>treating Patients With Locally Advanced or Metastatic Liver Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial of Beads Versus Doxorubicin Eluting Beads for Arterial</td>
<td>MSKCC</td>
<td>Actively recruiting</td>
</tr>
<tr>
<td>Embolization of Hepatocellular Carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Study of IMC-A12 in Combination With Sorafenib in Patients With</td>
<td>ImmunClone Systems</td>
<td></td>
</tr>
<tr>
<td>Advanced Cancer of the Liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Phase III Randomized, Double-Blind Trial of Chemoembolization With</td>
<td>ECOG E-1208*</td>
<td>Actively recruiting</td>
</tr>
<tr>
<td>or Without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>in Patients With and Without Vascular Invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of</td>
<td>Industry</td>
<td>Actively recruiting</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma (STORM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib Therapy Prior to Radiofrequency Ablation for Intermediate</td>
<td>Beth Israel Deaconess</td>
<td></td>
</tr>
<tr>
<td>Sized Hepatocellular Cancer</td>
<td>Medical Center</td>
<td></td>
</tr>
<tr>
<td>Phase 3 Study of ThermoDox With Radiofrequency Ablation (RFA) in</td>
<td>Industry</td>
<td>Actively recruiting</td>
</tr>
<tr>
<td>Treatment of Hepatocellular Carcinoma (HCC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial of Beads Versus Doxorubicin Eluting Beads for Arterial</td>
<td>MSKCC</td>
<td>Actively recruiting</td>
</tr>
<tr>
<td>Embolization of Hepatocellular Carcinoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CTPM, Clinical Trials Planning Meeting; HCC, hepatocellular carcinoma; CALGB, Cancer and Leukemia Group B; MSKCC, Memorial Sloan-Kettering Cancer Center; ECOG, Eastern Cooperative Oncology Group.

*Trial developed by the National Cancer Institute Gastrointestinal Study Group.
Multiple Cellular Signaling Pathways Implicated in Pathogenesis of HCC

VEGFR, PDGFR
FGFR, EGFR, IGF-IR
c-MET

Tyrosin Kinase Receptor

Cell membrane

Wnt/β-catenin Receptor

PI3K
Akt
BAD
Bcl-XL

PTEN
mTOR
NF-κB

PI3K
PTEN
Akt
mTOR
NF-κB
BAD
Bcl-XL

SHC
GrB2
GEF
Ras
PLCε
MEK1/2
ERK1/2

GSK3β
GBP

DSH

GSK3β
β-catenin

Hedgehog pathway

PTC
SMO

NF-κB

p53

β-catenin

Proliferation, Survival
Transcription/translation

Cell differentiation

Multiple Cellular Signaling Pathways Implicated in Hepatocarcinogenesis

Whittaker, et al. Oncogene 2010
Map of 214 studies found by search of: hepatocellular carcinoma, molecular | Phase I, II, III, IV

Click on the map below to show a more detailed map (when available) or search for studies (when map not available).

Colors indicate number of studies with locations in that region

Least

Labels give exact study count

Most
# Molecular Targeted Agents for HCC with Trials in ClinicalTrials.gov

<table>
<thead>
<tr>
<th>Agent</th>
<th>VEGF</th>
<th>VEGFR</th>
<th>PDGFR</th>
<th>FGF</th>
<th>FGFR</th>
<th>EGFR</th>
<th>Raf</th>
<th>MEK</th>
<th>mTOR</th>
<th>IGF1R</th>
<th>TRAILR1</th>
<th>Heparanase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>☑</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>☑</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brivanib</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linifanib</td>
<td>☑</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSU-68</td>
<td>☑</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZD6244</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAY86-9766</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI-88</td>
<td>☑</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mapatumumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSI-906</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Kim HY, Park JW. Dig Dis 2011
Seven Priorities for Future Studies in Advanced HCC

• 2. Clinical trial design parameters
  - Sorafenib as the control in first-line trials
  - Placebo as the control in second-line trials
  - TTP as a 1° end point in randomized ph II
  - Identification of stratification factors
  - Preclinical data for second-line therapy
  - Organ dysfunction studies during phase I/II
  - Tissue banking

Sorafenib and Beyond

✓ “A good responder” shows good results
  Who is a good responder?
  → patients selection: biomarker, clinical factors

✓ “Good response” has some limitations
  How can we overcome secondary resistance?
  → combination, adjuvant treatment, other first line trials

✓ There are many “poor responders”
  How can we overcome prim resistance and toxicities?
  → Second line, combination treatment
Who is a good responder?
:clinical variables predicting response


Seven Priorities for Future Studies in Advanced HCC

3. Studies to identify circulating biomarkers to complement analysis of HCC tissues

### Table 4. Analysis of correlation between change in circulating inflammatory cells and blood plasma/progenitor cell biomarkers at day 14 after sunitinib treatment. (Significant correlations are shown in bold font)

<table>
<thead>
<tr>
<th>Kendall’s $\tau_b$</th>
<th>WBCs</th>
<th>Lymphocytes</th>
<th>Monocytes</th>
<th>Platelets</th>
<th>Neutrophils</th>
</tr>
</thead>
<tbody>
<tr>
<td>sVEGFR1</td>
<td>-0.09 (-0.37 to 0.18)</td>
<td>-0.34 (-0.55 to -0.13)</td>
<td>-0.13 (-0.45 to 0.18)</td>
<td>-0.03 (-0.28 to 0.21)</td>
<td>-0.07 (-0.31 to 0.18)</td>
</tr>
<tr>
<td>$P$</td>
<td>0.48</td>
<td>0.0075</td>
<td>0.32</td>
<td>0.8</td>
<td>0.62</td>
</tr>
<tr>
<td>sVEGFR2</td>
<td>-0.32 (-0.54 to -0.10)</td>
<td>-0.12 (-0.37 to 0.14)</td>
<td>-0.26 (-0.57 to 0.04)</td>
<td>0.04 (-0.30 to 0.38)</td>
<td>-0.43 (-0.62 to -0.24)</td>
</tr>
<tr>
<td>$P$</td>
<td>0.02</td>
<td>0.41</td>
<td>0.055</td>
<td>0.8</td>
<td>0.0013</td>
</tr>
<tr>
<td>IL-1β</td>
<td>-0.31 (-0.53 to -0.09)</td>
<td>-0.11 (-0.34 to 0.11)</td>
<td>-0.07 (-0.31 to 0.18)</td>
<td>0.05 (-0.20 to 0.31)</td>
<td>-0.23 (-0.42 to -0.04)</td>
</tr>
<tr>
<td>$P$</td>
<td>0.022</td>
<td>0.43</td>
<td>0.65</td>
<td>0.71</td>
<td>0.096</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.07 (-0.15 to 0.30)</td>
<td>-0.08 (-0.40 to 0.25)</td>
<td>0.23 (-0.02 to 0.48)</td>
<td>0.05 (-0.26 to 0.37)</td>
<td>0.21 (-0.04 to 0.47)</td>
</tr>
<tr>
<td>$P$</td>
<td>0.59</td>
<td>0.59</td>
<td>0.096</td>
<td>0.71</td>
<td>0.12</td>
</tr>
<tr>
<td>IL-8</td>
<td>-0.27 (-0.51 to 0.02)</td>
<td>0.05 (-0.22 to 0.32)</td>
<td>-0.07 (-0.33 to 0.19)</td>
<td>0.01 (-0.31 to 0.33)</td>
<td>-0.30 (-0.55 to -0.05)</td>
</tr>
<tr>
<td>$P$</td>
<td>0.058</td>
<td>0.73</td>
<td>0.63</td>
<td>0.97</td>
<td>0.033</td>
</tr>
<tr>
<td>TNF-α</td>
<td>-0.41 (-0.64 to -0.18)</td>
<td>-0.24 (-0.52 to 0.03)</td>
<td>-0.08 (-0.35 to 0.19)</td>
<td>-0.03 (-0.28 to 0.22)</td>
<td>-0.34 (-0.60 to -0.08)</td>
</tr>
<tr>
<td>$P$</td>
<td>0.0027</td>
<td>0.08</td>
<td>0.56</td>
<td>0.84</td>
<td>0.013</td>
</tr>
<tr>
<td>sVEGFR3</td>
<td>-0.08 (-0.41 to 0.24)</td>
<td>-0.30 (-0.57 to -0.04)</td>
<td>-0.05 (-0.27 to 0.17)</td>
<td>-0.32 (-0.59 to -0.06)</td>
<td>0.13 (-0.20 to 0.47)</td>
</tr>
<tr>
<td>$P$</td>
<td>0.61</td>
<td>0.056</td>
<td>0.77</td>
<td>0.042</td>
<td>0.42</td>
</tr>
<tr>
<td>VEGF-C</td>
<td>-0.17 (-0.42 to 0.08)</td>
<td>0.00 (-0.26 to 0.26)</td>
<td>-0.02 (-0.26 to 0.24)</td>
<td>0.30 (0.08 to 0.52)</td>
<td>-0.24 (-0.49 to 0.00)</td>
</tr>
<tr>
<td>$P$</td>
<td>0.2</td>
<td>1</td>
<td>0.89</td>
<td>0.025</td>
<td>0.069</td>
</tr>
</tbody>
</table>

**NOTE:** Data are shown as Kendall’s $\tau_b$ (95% CI) between ratios of day 14 to baseline ratios of biomarkers levels, with $P$ value from Kendall’s test.
Alpha-fetoprotein and human telomerase reverse transcriptase mRNA levels in peripheral blood of patients with hepatocellular carcinoma

Sun-Young Kong · Joong-Won Park · Jin Oak Kim · Nam Oak Lee · Jung An Lee · Kyung Woo Park · Eun Kyung Hong · Chang-Min Kim

Received: 10 November 2008 / Accepted: 13 January 2009 / Published online: 31 January 2009 © Springer-Verlag 2009

Abstract

Purpose Tumor-associated gene expression in peripheral blood reflects the presence of circulating hepatocellular carcinoma (HCC) cells and might be associated with aggressive features of HCC. We assessed the prognostic significance of alpha-fetoprotein (AFP) and human telomerase reverse transcriptase protein (hTERT) mRNA expression in the peripheral blood of HCC patients.

Methods About 343 HCC patients, treated at the National Cancer Center, Korea, were included in this study. We measured AFP and hTERT mRNA levels in peripheral blood using quantitative real-time reverse transcription polymerase chain reaction. The association between the expression of each gene and survival was analyzed.

Results AFP and hTERT mRNA were detected in 204 (59.5%) and 48 (14.0%) patients with HCC, respectively. The mean AFP copy number was 203 copies/μL (range 0–19992 copies/μL) and that of hTERT was 26 copies/μL (0–1711 copies/μL). AFP mRNA expression was correlated with the number of tumors (P = 0.05), but there were no significant association between hTERT expression and clinical features. There was also no relationship between overall survival and AFP (P = 0.08) or hTERT (P = 0.67) mRNA expression.

Conclusions This is the first report to evaluate the association between peripheral blood hTERT mRNA expression, and survival of HCC patients. The results indicate that AFP and hTERT mRNA expression in peripheral blood may not be useful HCC prognostic markers.

Keywords Alpha-fetoprotein (AFP) · Human telomerase reverse transcriptase (hTERT) · Circulating tumor cells · Hepatocellular carcinoma (HCC) · Survival · Prognosis

Introduction
Seven Priorities for Future Studies in Advanced HCC

4. Novel imaging correlative end points should be defined for HCC since RECIST is a suboptimal tool for HCC MTA study

mWHO, RECIST, and mRECIST Response Criteria in HCC: Imaging Diagnosis

<table>
<thead>
<tr>
<th>Method</th>
<th>RECIST/mWHO</th>
<th>mRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>RFA</td>
<td>CR</td>
<td>PR</td>
</tr>
<tr>
<td>MTT</td>
<td>SD</td>
<td>CR</td>
</tr>
<tr>
<td>TACE</td>
<td>SD</td>
<td></td>
</tr>
</tbody>
</table>
Example Case That Changed From PR by mWHO to CR by mRECIST in Brivanib Phase II Study

This patient was initially assessed as having PR by mWHO criteria. Upon scan reassessment by mRECIST, PR changed to CR.

Seven Priorities for Future Studies in Advanced HCC

- 5. Novel imaging methods **should be prospectively** studied

- 6. Phase zero studies of imaging modalities

  Phase 0
  - Human *microdosing* studies
  - To speed up the development of promising drugs or *imaging agents* by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies.
  - Administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's *pharmacodynamics* and *pharmacokinetics*.

A Prospective Evaluation of 18F-FDG and 11C-Acetate PET/CT for Detection of Primary and Metastatic Hepatocellular Carcinoma

Joong-Won Park1, Ji Hoon Kim1, Seok Ki Kim2, Keon Wook Kang3, Kyung Wook Park3, Jun-II Choi1, Woo Jin Lee1, Chang-Min Kim1, and Byung Ho Nam4

1Center for Liver Cancer, National Cancer Center, Goyang, Gyeonggi-do, Republic of Korea; 2Department of Nuclear Medicine, National Cancer Center, Goyang, Gyeonggi-do, Republic of Korea; 3Center for Cancer Prevention and Detection, National Cancer Center, Goyang, Gyeonggi-do, Republic of Korea; and 4Cancer Registration and Biostatistics Branch, National Cancer Center, Goyang, Gyeonggi-do, Republic of Korea

Because 18F-FDG PET has insufficient sensitivity for the detection of hepatocellular carcinoma (HCC), 11C-acetate PET has been proposed as another technique for this use. We prospectively evaluated the value of PET/CT using these 2 tracers for the detection of primary and metastatic HCC. Methods: One hundred twelve patients (69 with HCC, 13 with cholangiocellular carcinoma) underwent biopsy and 18F-FDG and 11C-acetate PET/CT. Results: The overall sensitivities of 18F-FDG, 11C-acetate, and dual-tracer PET/CT in the detection of 110 lesions in 90 patients with primary HCC were 60.9%, 75.4%, and 82.7%, respectively. Elevated serum α-fetoprotein levels, an advanced tumor stage, portal vein tumor thrombosis, large tumors, and multiple tumors were significantly associated with positive 18F-FDG PET/CT results. Uptake of 11C-acetate was associated with large and multiple tumors. For 18F-FDG, the sensitivities according to tumor size (1-2, 2-3, and ≥3 cm) were 27.2%, 47.8%, and 92.8%, respectively, for 11C-acetate, these respective values were 31.8%, 78.2%, and 100%. 18F-FDG was more sensitive in the detection of poorly differentiated HCC. Overall survival was lower in patients with 18F-FDG PET/CT positive for all indexed lesions than in those with FDG negative or partially positive through the entire follow-up period. In analysis based on biopsied lesions, the sensitivity of 18F-FDG PET/CT was 64.4% for primary HCC and 84.4% for 11C-acetate PET/CT. The overall sensitivities of 18F-FDG, 11C-acetate, and dual-tracer PET/CT for 35 metastatic HCCs were 85.7%, 77.0%, and 85.7%, respectively. There was no significant difference in the sensitivity of tracers according to metastatic tumor size, location, or differentiation. Conclusion: The addition of 11C-acetate to 18F-FDG PET/CT increases the overall sensitivity for the detection of primary HCC but not for the detection of extrahepatic metastases. 18F-FDG, 11C-acetate, and dual-tracer PET/CT have a low sensitivity for the detection of small primary HCC, but 18F-FDG/PET/CT has a relatively high sensitivity for the detection of extrahepatic metastases of HCC.

Key Words: hepatocellular carcinoma; oncology; PET/CT; FDG; acetate; sensitivity

DOI: 10.2967/jnumed.108.055087

The prognosis of patients with hepatocellular carcinoma (HCC) is related to tumor stage at presentation and underlying liver function. Reliable staging of HCC is a fundamental precondition for deciding on the treatment modality, and the Barcelona Clinic Liver Cancer (BCLC) staging system links tumor stage with treatment modality (1). In particular, accurate characterization of primary and metastatic HCC, showing the tendency toward early vascular invasion of the tumor (2), is critical for proper treatment (3). Imaging studies by dynamic CT and contrast-enhanced MRI are important in the diagnosis and staging of HCC (1,3,4), but there is no consensus on which imaging tests are proper for detecting extrahepatic metastases. Whole-body PET has been used in a portion of HCC patients, but its usefulness has not yet been established. Because whole-body combined PET/CT using 18F-FDG effectively detects numerous cancerous lesions (5), this method was expected to improve the accuracy of HCC staging. However, the high level of glucose-6-phosphatase in liver tissue leads to the release of FDG-6-phosphate, resulting in reduced accumulation in differentiated HCCs (6). Thus, 18F-FDG PET has an average false-negative rate of 40%-50% for the detection of HCC (7), and data on the role of PET/CT in the detection of HCC metastasis are limited (7-9).

11C-labeled acetate PET effectively detects urologic malignancies (10). This tracer enters the Krebs cycle as a substrate for β-oxidation in fatty acid synthesis and cholesterol synthesis. Fatty acid synthesis is believed to be the major reason for uptake of 11C-acetate by liver tumors. Recently, a Chinese study reported that 11C-acetate PET...
## TABLE 4

Sensitivity of $^{18}$F-FDG and $^{11}$C-Acetate PET/CT in 90 Patients with Primary HCC: Lesion-Based Analysis of 110 Lesions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of index lesion ($n = 110$)</th>
<th>$^{18}$F-FDG Lesions positive ($n$)</th>
<th>$P$</th>
<th>$^{11}$C-acetate Lesions positive ($n$)</th>
<th>$P$</th>
<th>$P^*$ between 2 PET/CT types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq 1$, $&lt; 2$</td>
<td>22</td>
<td>6 (27.2)</td>
<td>$&lt;0.001$</td>
<td>7 (31.8)</td>
<td>$&lt;0.001$</td>
<td>NS</td>
</tr>
<tr>
<td>$\geq 2$, $&lt; 5$</td>
<td>46</td>
<td>22 (47.8)</td>
<td></td>
<td>36 (78.2)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>$\geq 5$</td>
<td>42</td>
<td>39 (92.8)</td>
<td>$&lt;0.001^\dagger$</td>
<td>40 (95.2)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Tumor number</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>46</td>
<td>27 (58.7)</td>
<td>0.021</td>
<td>37 (80.4)</td>
<td>0.027</td>
<td>0.006</td>
</tr>
<tr>
<td>2–3</td>
<td>31</td>
<td>14 (45.2)</td>
<td></td>
<td>18 (58.0)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>26 (78.8)</td>
<td>NS†</td>
<td>28 (84.8)</td>
<td>NS†</td>
<td></td>
</tr>
<tr>
<td>Tumor differentiation†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I and II</td>
<td>70</td>
<td>35 (50.0)</td>
<td>$&lt;0.001$</td>
<td>50 (71.4)</td>
<td>NS</td>
<td>0.006</td>
</tr>
<tr>
<td>III and IV</td>
<td>31</td>
<td>27 (87.0)</td>
<td>$&lt;0.001^\dagger$</td>
<td>27 (90.0)</td>
<td>NS†</td>
<td></td>
</tr>
</tbody>
</table>

*Comparison of sensitivity between $^{18}$F-FDG and $^{11}$C-acetate PET/CT according to tumor characteristics using McNemar $\chi^2$ test.
†Score test for trend.
‡Edmonson–Steiner grade: 7 of 90 patients with primary HCC had inappropriate biopsy specimen for evaluation of pathologic grade, and 101 index lesions of 83 patients were finally evaluated.
NS = not significant.
Data in parentheses are sensitivity (%).
Seven Priorities for Future Studies in Advanced HCC

- 7. Tumor markers screening at-risk populations and assessing treatment response

Study of PIVKA-II and AFP Measurement in Surveillance Program for Early Detection of Hepatocellular Carcinoma

Verified by: Yonsei University, September 2009
First Received: January 14, 2011 | Last Updated: January 14, 2011 | Phase: N/A | Start Date: June 2007
Overall Status: Recruiting | Estimated Enrollment: 1000

There is no prospective study on the test intervals of alpha-fetoprotein (AFP) or on the role of prothrombin induced vitamin K absence or antagonist-II (PIVKA-II) in surveillance program for early detection of hepatocellular carcinoma (HCC). The goal of this study is to compare if the testing of AFP + PIVKA-II in intervals of 3 months is more effective in diagnosing early stages of HCC than the 6...

**Brief Summary**

**Official Title:** “Prospective, Randomized Study of PIVKA-II and AFP Measurement Every 3 Months Compared to AFP Every 6 Months in Surveillance Program for Early Detection of Hepatocellular Carcinoma”
Seven Priorities for Clinical Evaluation of Regional Therapy: TACE, HAIC, DEB, $^{90}$Y

- 1. Prospective phase II, III trials of TACE+ablation, TACE+ systemic therapy

Combination Treatment of TACE and Sorafenib in *ClinicalTrials.gov*

<table>
<thead>
<tr>
<th>Local therapy</th>
<th>MTT Agents</th>
<th>Study design</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACE (doxorubicin)</td>
<td>Sorafenib</td>
<td>II, randomized placebo-controlled</td>
<td>International</td>
</tr>
<tr>
<td>TACE (doxorubicin)</td>
<td>Sorafenib</td>
<td>II, single arm</td>
<td>Korea (NCC)</td>
</tr>
<tr>
<td>TACE (doxorubicin)</td>
<td>Sorafenib</td>
<td>II, single arm</td>
<td>USA (John Hopkins)</td>
</tr>
<tr>
<td>TACE (cisplatin)</td>
<td>Sorafenib</td>
<td>II, single arm</td>
<td>USA (Pittsburgh)</td>
</tr>
<tr>
<td>TACE (doxorubicin+MMC)</td>
<td>Sorafenib</td>
<td>II, single arm</td>
<td>USA (New Jersey)</td>
</tr>
<tr>
<td>TACE (doxorubicin)</td>
<td>Sorafenib (2 wks before TACE)</td>
<td>II, single arm</td>
<td>Germany (Heinrich Heine)</td>
</tr>
<tr>
<td>TACE (doxorubicin)</td>
<td>Sorafenib (2 wks before TACE)</td>
<td>I/II</td>
<td>Italy</td>
</tr>
<tr>
<td>TACE (doxorubicin)</td>
<td>Sorafenib</td>
<td>I</td>
<td>Switzerland (Bern)</td>
</tr>
<tr>
<td>SIR-Spheres (yttrium-90)</td>
<td>Sorafenib</td>
<td>I/II</td>
<td>Singapore</td>
</tr>
</tbody>
</table>
Interim Analysis of a Phase II Study of the Combination of TACE and Sorafenib in Patients with Unresectable HCC in National Cancer Center, Korea (COTSUN Korea Trial, NCT00919009)

Joong-Won Park, Hwi Young Kim, Ju Hyun Shim, Sang Myung Woo, Joon-Il Choi, Hyun Beom Kim and Byung-Ho Nam

Center for Liver Cancer and Center for Clinical Trials, National Cancer Center, Korea
Seven Priorities for Clinical Evaluation of Regional Therapy: TACE, HAIC, DEB, $^{90}\text{Y}$

2. Evaluate the outcome of regional therapy versus systemic therapy in patients with N1 or M1 disease

Comparison of Survival in Patients with BCLC Stage C Advanced HCC: Sorafenib Vs. Other Treatments

Hwi Young Kim, Joong-Won Park*, Byung-Ho Nam†, Hyun Keun Kim, Joon-Il Choi, Tae Hyun Kim, Hyun Beom Kim and Chang-Min Kim

Center for Liver Cancer, National Cancer Center, Korea
† Cancer Biostatistics Branch, National Cancer Center Research Institute, Korea

Publication in process
## Subgroup Analyses

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AFP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200 ng/mL</td>
<td>1.699 (1.058–2.731)</td>
<td><strong>0.028</strong></td>
</tr>
<tr>
<td>≥200 ng/mL</td>
<td>0.832 (0.592–1.170)</td>
<td></td>
</tr>
<tr>
<td><strong>Intrahepatic tumor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodular</td>
<td>1.665 (1.115–2.485)</td>
<td><strong>0.013</strong></td>
</tr>
<tr>
<td>Massive/infiltrative</td>
<td>0.798 (0.543–1.172)</td>
<td></td>
</tr>
<tr>
<td><strong>Macrovascular invasion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1.854 (1.083–3.175)</td>
<td><strong>0.025</strong></td>
</tr>
<tr>
<td>Present</td>
<td>0.960 (0.691–1.335)</td>
<td></td>
</tr>
<tr>
<td><strong>Extrahepatic spread</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1.359 (0.946–1.951)</td>
<td><strong>0.007</strong></td>
</tr>
<tr>
<td>Present</td>
<td>0.557 (0.362–0.858)</td>
<td></td>
</tr>
<tr>
<td><strong>Modified UICC stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–III</td>
<td>2.276 (1.308–3.960)</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>IVA, IVB</td>
<td>0.798 (0.581–1.097)</td>
<td></td>
</tr>
</tbody>
</table>

*Kim HW, Park JW, et al. J Gastroenterol Hepatol 2011 Apr epub*
Seven Priorities for Clinical Evaluation of Regional Therapy: TACE, HAIC, DEB, $^{90}$Y

3. Design clinical trials approaches to clearly identify the patients population being studied.

<table>
<thead>
<tr>
<th>Baseline Characteristics (n=50)</th>
<th>No. (%) or median(range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (84.0)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>61.5 (29–76)</td>
</tr>
<tr>
<td><strong>Etiology of liver disease</strong></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>28 (65.1)</td>
</tr>
<tr>
<td>HCV</td>
<td>8 (18.6)</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>22 (44.0)</td>
</tr>
<tr>
<td><strong>Child-Pugh class</strong></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>47 (94.0)</td>
</tr>
<tr>
<td><strong>α-FP (ng/mL)</strong></td>
<td>43.7 (2.1–1069940)</td>
</tr>
<tr>
<td><strong>BCLC stage</strong></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>39 (78.0)</td>
</tr>
<tr>
<td>C</td>
<td>11 (22.0)</td>
</tr>
<tr>
<td><strong>Modified UICC stage</strong></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>15 (30.0)</td>
</tr>
<tr>
<td>III</td>
<td>24 (48.0)</td>
</tr>
<tr>
<td>IVA</td>
<td>11 (22.0)</td>
</tr>
<tr>
<td><strong>Portal vein invasion</strong></td>
<td>11 (22.0)</td>
</tr>
<tr>
<td><strong>Lymph node involvement</strong></td>
<td>1 (2.0)</td>
</tr>
<tr>
<td><strong>Previous treatment(s)</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>15 (30.0)</td>
</tr>
<tr>
<td>Surgery</td>
<td>8 (16.0)</td>
</tr>
<tr>
<td>RFA/PEI</td>
<td>12 (24.0)</td>
</tr>
<tr>
<td>TACE</td>
<td>24 (48.0)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>3 (6.0)</td>
</tr>
</tbody>
</table>
Seven Priorities for Clinical Evaluation of Regional Therapy: TACE, HAIC, DEB, Y\textsuperscript{90}

- 4. Conduct comparison trials of TACE, DEB, and Y\textsuperscript{90} to assess safety, efficacy, and cost-effectiveness end points

Drug Eluting Beads (DEB) vs Conventional TACE

- International, multicentre, randomised phase II study to assess the safety and efficacy of DC Bead uploaded with doxorubicin versus conventional TACE with doxorubicin-in-lipiodol emulsion followed by embolisation.

Patients randomised 1:1 (n=212)

**TACE with DC Bead**
Doxorubicin dose = 150mg

- TACE repeated at 2 and 4 months

**Conventional TACE**
Doxorubicin dose = 50–75mg/m² (maximum 150mg)

- TACE repeated at 2 and 4 months

- Primary endpoint: tumor response at 6 months (EASL criteria by blinded independent review of MR images)

- Secondary endpoints: safety (toxicity according to SWOG), TTP
PRECISION V: DC Bead\textsuperscript{®} did not improve overall TTP compared with cTACE

Lencioni R, et al. CIRSE 2008, Copenhagen, Denmark
Seven Priorities for Clinical Evaluation of Regional Therapy: TACE, HAIC, DEB, Y^{90}

5. Define the role of TACE in liver transplantation:
   - TACE response have an impact on the outcome in LT?
   - What is the efficacy of TACE as a bridge to LT?
   - Pre-LT TACE: survival gain?, downstaging feasibility?

Seven Priorities for Clinical Evaluation of Regional Therapy: TACE, HAIC, DEB, Y\textsuperscript{90}

- 6. Conduct prospective trials of regional therapy options: there would be numerous challenges, including standardization of technique.

Seven Priorities for Clinical Evaluation of Regional Therapy: TACE, HAIC, DEB, Y\textsuperscript{90}

- 7. ECOG 1208 trial, A phase III randomized, double-blind trial of chemoembolization with or without sorafenib in unresectable HCC in patients with and without vascular invasion, is a priority study

## ECOG 1208

**For Patients with Unresectable Hepatocellular Carcinoma**

E1208 is Now Available Through the CTSU
A Phase III Randomized, Double-Blind Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion

### Patient Population

See Section 3 for Complete Eligibility Details

- Patients must have a diagnosis of HCC according to at least one of the following: a) histologic confirmation, b) MRI or CT consistent with cirrhosis and at least one solid liver lesion > 2 cm regardless of AFP levels, or c) AFP > 400 ng/mL and at least one solid liver lesion > 2 cm regardless of specific imaging characteristics.
- Patients must have HCC limited to the liver.
- Patients with HBV or HCV are allowed to have portal lymphadenopathy.
- Patients must have measurable disease constituting > 50% of liver parenchyma ≤ 4 weeks of registration.
- Patients must not have ascites detectable on PE.
- Patients must not be candidates for curative resection, orthotopic liver transplantation, or RFA.
- Patients may have been treated with RFA in the past, but not within 4 weeks of registration.
- Patients may have undergone previously attempted curative liver resection.
- Patients may not have been previously treated with brachytherapy such as Yttrium-90 microsphere.
- Patients must not have been treated previously with sorafenib, chemoembolization, or systemic chemotherapy including cytotoxic agents or molecularly targeted agents.
- Patients must not have main portal vein invasion by tumor (branch portal vein invasion is permitted).
- Patients must have Child-Pugh score A or B ≤ 4 weeks of registration.

### Treatment Summary

See Section 5 for Complete Treatment Details

**Blinded Randomization**

#### Arm A

- Sorafenib 400 mg (2 × 200 mg tablets) PO BID until progression

**PLUS**

- Chemoembolization
  - Up to 4 chemoembolizations to be completed within 6 months of first chemoembolization

#### Arm B

- Placebo 2 tablets PO BID until progression

**PLUS**

- Chemoembolization
  - Up to 4 chemoembolizations to be completed within 6 months of first chemoembolization

---

### Number of Participants: 400

### Patient Enrollment

Non-ECOG Members: CTSU Patient Registrar 1-888-462-3009

### Protocol Information

CTSU Help Desk: 1-888-823-5923, CTSUcontact@westat.com, www.ctsu.org

Please Enroll Your Eligible Patients!
Three Priorities for Clinical Evaluation of Local Therapy: Resection, Ablation, EB Radiotherapy

1. Evaluate the outcome of adjuvant systemic therapy following resection or ablation: STORM trial
2. Conduct a phase II trial of adjuvant chemotherapy following regional therapy
3. Compare modalities, such as hepatic resection versus ablation
Two Priorities for Clinical Evaluation of Liver Transplantation

1. Downstaging therapy
   - can pts outside UNOS benefit? Which pts?
   - ph II, single arm, treated with TACE

2. Adjuvant therapy
   - can decrease post-LT recurrence in high risk pts?
   - randomized ph II, III trials with sorafenib

경청해주셔서 감사합니다