Sorafenib in Unresectable Hepatocellular Carcinoma from Mild to Advanced Stage Liver Cirrhosis

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Key Words. Hepatocellular carcinoma • Liver cirrhosis • Sorafenib • Multikinase inhibitors

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ABSTRACT
Background. Few data are available on the safety and efficacy of sorafenib in patients with multifocal hepatocellular carcinoma (HCC) and advanced liver cirrhosis.

Methods. Between May 2006 and December 2007, we treated 59 patients (Child-Pugh class A/B/C, 26/23/10) with unresectable HCC with sorafenib (daily target dose, 400 mg twice daily). Data were collected retrospectively. Survival curves were calculated via the Kaplan–Meier method.

Results. One patient (Child-Pugh class B) had a partial response, 14 patients (Child-Pugh class A/B/C, 5/7/2) had stable disease, and 32 patients (Child-Pugh class A/B/C, 15/11/6) had progressive disease; 12 patients were not evaluable because they had no follow-up radiologic evaluation. In the intention-to-treat group, the median time to progression and overall survival (OS) time were 2.8 months (range, 1.4–6.5 months) and 6.5 months (range, 0.4–17.4 months), respectively. Well-preserved liver function and lower Barcelona Clinic Liver Cancer stage were associated with a longer OS time on univariate analysis. There were four severe gastrointestinal bleedings (grade 4–5; Child-Pugh class B/C, 2/2). Most drug-related side effects were low grade.

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and manageable irrespective of liver function.

Conclusions. Sorafenib is effective and safe in patients with multifocal HCC and Child-Pugh class A cirrhosis. Survival in Child-Pugh class B patients is significantly less than in Child-Pugh class A patients, warranting a prospective randomized trial with a placebo group. Child-Pugh class C patients have a limited life expectancy despite sorafenib treatment because of their severe underlying disease and derive little benefit from sorafenib treatment. The Oncologist 2009;14:70–76

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death and has a very poor prognosis in advanced stages with a median survival time of 6–9 months [1, 2]. In the Western hemisphere, HCC mostly develops in patients with liver cirrhosis, which is most commonly caused by hepatitis C virus (HCV) infection, hepatitis B virus infection, or chronic alcoholism [3, 4]. The HCC incidence has increased over the last years, largely because of chronic HCV infection–related liver cirrhosis [5].

Therapeutic options are stage dependent. Potential curative therapies such as surgical resection, liver transplantation, and percutaneous techniques (ethanol injection, radiofrequency ablation) can be performed successfully in early-stage patients. Asymptomatic patients with well-preserved liver function may benefit from arterial chemoembolization [6–8]. However, as cancer-related symptoms often emerge late after a long-standing asymptomatic period, HCC is often diagnosed at an advanced stage of disease [9]. For the longest time, no effective treatment was available for these patients [8].

Sorafenib is a multikinase inhibitor that has already been approved for the treatment of metastatic renal cancer. Sorafenib targets the Raf/mitogen-activated protein kinase/extracellular signal–related kinase (ERK) kinase/ERK signaling pathway as well as other tyrosine kinases like vascular endothelial growth factor receptor, platelet-derived growth factor receptor β, KIT, FLT-3, or REarranged during Transfection, which are important for tumor cell proliferation and angiogenesis. Encouraging preclinical results in several human tumors, including HCC [10], led to a large, open-label, nonrandomized, phase II trial in patients with HCC. In that phase II trial with 137 advanced HCC patients, the investigators reported modest efficacy and manageable toxicity, qualifying sorafenib for a large, randomized, placebo-controlled, multicenter trial for this indication [11]. The phase III Sorafenib HCC Assessment Randomized Protocol (SHARP) trial finally demonstrated a significant survival benefit (placebo, 7.9 months; sorafenib, 10.7 months) and good tolerance in patients with HCC, making sorafenib the new reference standard for systemic therapy of patients with advanced HCC [12]. However, this phase III trial was restricted to patients with well-preserved liver function (Child-Pugh class A). Thus, little is known about the safety and efficacy of sorafenib in patients with multifocal HCC and Child-Pugh class B cirrhosis. For Child-Pugh class C patients, only symptomatic treatment is suggested [8]. Nevertheless, we have treated some patients with HCC and Child-Pugh class C cirrhosis with sorafenib because no data are available on the first effective drug therapy for HCC in this group of patients.

MATERIALS AND METHODS

Patients

Between May 2006 and December 2007, 59 patients with advanced HCC without an option for any standard therapy were treated with sorafenib at five experienced institutions in Austria. HCC was diagnosed either by histology or by the combination of characteristic radiographic findings and elevated α-fetoprotein serum levels according to the European Association for the Study of the Liver criteria [13]. Relevant data from the patients’ clinical records, including history, laboratory results, radiological findings, histological results, and survival data, as well as the dosage and adverse events of sorafenib therapy, were collected retrospectively.

Sorafenib Treatment

An initial sorafenib dose of 400 mg was administered orally twice daily. Discontinuation and dose reduction were based on tolerance. Side effects of sorafenib were determined via the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 3.0.

Assessment of Tumor Response

Based on the computed tomography/magnetic resonance tomography (MRT) scans of the liver performed at baseline and every 2–4 months, tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [14]. Patients who died before their first radiographic control were judged as having progressive disease (PD).
Statistics
Patients’ basal characteristics were analyzed by descriptive statistical methods. The overall survival (OS) time was defined as the time from sorafenib initiation to the date of death or the patient’s last follow-up. The survival curves were calculated via the Kaplan–Meier method. Univariate survival curves were compared using the log-rank test. A p-value < .05 was considered statistically significant. All analyses were performed using the statistical software package SPSS (version 15.0; SPSS Inc., Chicago, IL).

RESULTS

Patient Characteristics
There were 46 male patients (78%) and 13 female patients (22%) with a mean age of 64 years (range, 27–85). The predominant etiology of cirrhosis was alcohol (n = 22; 37%). Twenty-six (44%) patients had Child-Pugh class A, 23 (39%) patients had Child-Pugh class B, and 10 (17%) patients had Child-Pugh class C liver cirrhosis. Forty-six (78%) individuals had portal vein thrombosis (PVT) or extrahepatic metastases. The Eastern Cooperative Oncology Group performance status scores were 0 (n = 31; 53%), 1 (n = 26; 44%), and 3 (n = 2; 3%). Tumor stage was classified according to the Barcelona Clinic Liver Cancer (BCLC) staging classification [7] and also according to the tumor–node–metastasis stage [15]. Thirty-one (53%) patients had been treated prior to sorafenib therapy with surgical, locoregional, or pharmacologic therapies (Table 1).

Overall Response and Efficacy
The median time of follow-up was 5.4 months (range, 0.4 – 17.4 months). Thirty-three patients (56%) died during the observation period whereas 26 patients (44%) were still alive at the end of the follow-up time. The median OS duration of the intention-to-treat (ITT) group (n = 51) was 6.5 months (range, 0.4 – 17.4 months), with a 1-year survival rate of 8%. One patient (2%) had a partial response (PR), 14 patients (24%) had stable disease (SD), and 32 patients (54%) had PD at the first radiologic control; 12 patients (20%) were not evaluable because they had no follow-up radiologic evaluation (Child-Pugh class A/B/C, n = 6/4/2; 23%/17%/20%). The median time to progression (TTP) of the ITT group was 2.8 months (range, 1.4 – 6.5 months).

Response and Efficacy According to Severity of Underlying Liver Disease (Child-Pugh Class)
Efficacy results according to Child-Pugh class are given in Table 2. Five of the 26 Child-Pugh class A patients (19%) had SD, with a median TTP of 2.2 months (range, 1.4 – 6.5 months). Of the 23 Child-Pugh class B patients, one (4%)
had a PR and seven (30%) had SD; the median TTP was 2.9 months (range, 1.6–6.0 months). Two of the 10 (20%) Child-Pugh class C patients had SD for 2.8 months and 5.2 months; the median TTP in Child-Pugh class C patients was 4.0 months. TTP was not statistically different among patients with different severities of liver disease (log-rank p = .866).

The median follow-up time for Child-Pugh class A patients (alive, 17 of 26) was 8.3 months; the median survival times for Child-Pugh class B patients (alive, 8 of 23) and Child-Pugh class C patients (alive, 1 of 10) were 4.3 months and 1.5 months, respectively (Fig. 1A), which was statistically significantly different (log-rank p = .0001). The median OS time for BCLC stage B–C patients (alive, 23 of 43) was 10.2 months and it was 1.5 months for BCLC stage D patients (alive, 3 of 16; Fig. 1B), with a statistically significant difference between these groups (log-rank p = .0001).

### Safety and Dose Adjustment

Diarrhea was the most troublesome side effect in our series, occurring in 21 (36%) patients. Other frequent toxicities were anorexia (n = 12; 20%), hand–foot reaction (n = 12; 20%), and fatigue (n = 10; 17%). Grade 3–4 toxicities included gastrointestinal (GI) bleeding (n = 3; 5%), fatigue (n = 3; 5%), diarrhea (n = 2; 3%), hand–foot reaction (n = 2; 3%), nausea (n = 1; 2%), and leukopenia (n = 1; 2%).

Table 3 shows the adverse events of sorafenib according to Child-Pugh class. GI bleeding, nausea, emesis, and epistaxis were observed only in Child-Pugh class B and class C patients and not in Child-Pugh class A patients. Four of the 26 Child-Pugh class A patients (15%), six of the 23 Child-Pugh class B patients (26%), and two of 10 Child-Pugh class C patients (20%) experienced grade 3–4 toxicities; one Child-Pugh class C patient died as a result of GI bleeding (10%; grade 5). There was no trend toward greater toxicity with more advanced liver dysfunction, but hand–foot skin reaction was more frequent in Child-Pugh class A patients than more advanced liver disease.

![Figure 1](http://theoncologist.alphamedpress.org.org)
Dose reduction or discontinuation as a result of side effects or tumor progression was necessary in 46 of 59 subjects (78%). Twelve of the 26 Child-Pugh class A patients (46%), 11 of the 23 Child-Pugh class B patients (48%), and 2 of the 10 Child-Pugh class C patients (20%) had to reduce their daily sorafenib dose. Discontinuation occurred in 11 of the 26 Child-Pugh class A patients (42%), 10 of the 23 Child-Pugh class B patients (43%), and 2 of the 10 Child-Pugh class C patients (20%).

**Table 3. Adverse events according to Child-Pugh class**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Child-Pugh class A (n = 26)</th>
<th>Child-Pugh class B (n = 23)</th>
<th>Child-Pugh class C (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grade 3–4</td>
<td>All Grade 3–4</td>
<td>All Grade 3–4/5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (31) 2 (8)</td>
<td>10 (43) –</td>
<td>3 (30) –</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (12) –</td>
<td>7 (30) –</td>
<td>2 (20) –</td>
</tr>
<tr>
<td>Hand–foot reaction</td>
<td>8 (31) 1 (4)</td>
<td>3 (13) 1 (4)</td>
<td>1 (10) –</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (12) 1 (4)</td>
<td>5 (22) 2 (9)</td>
<td>2 (20) –</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>– –</td>
<td>2 (9) 2 (9)</td>
<td>2 (20) 1 (10)</td>
</tr>
<tr>
<td>Skin</td>
<td>1 (4) –</td>
<td>1 (4) –</td>
<td>2 (20) –</td>
</tr>
<tr>
<td>Nausea</td>
<td>– –</td>
<td>1 (4) –</td>
<td>2 (20) 1 (10)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>– –</td>
<td>2 (9) –</td>
<td>1 (10) –</td>
</tr>
<tr>
<td>Emesis</td>
<td>– –</td>
<td>1 (4) –</td>
<td>1 (10) –</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1 (4) –</td>
<td>1 (4) 1 (4)</td>
<td>– –</td>
</tr>
<tr>
<td>Overall</td>
<td>14 (54) 4 (15)</td>
<td>17 (74) 7 (30)</td>
<td>4 (40) 3 (30)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The multikinase inhibitor sorafenib demonstrated a significant survival benefit and good tolerance in patients with HCC in a phase III randomized controlled trial (SHARP) [12]. However, this phase III trial was restricted to patients with well-preserved liver function (Child Pugh class A). We analyzed the safety and efficacy of sorafenib in patients with unresectable HCC in the Austrian extended access program of sorafenib, including >50% of patients with advanced-stage liver cirrhosis (Child-Pugh class B and also class C). Nevertheless, the retrospective nature of our study was a limiting factor, which should be considered if outcome results are compared with the referenced prospective trials [11, 12, 16].

In our ITT group, the OS time was 6.5 months. A subgroup analysis with respect to Child-Pugh class revealed a strong dependency of patient survival on the severity of the underlying cirrhosis (Table 4). For Child-Pugh class A patients, we can only report the median time of follow-up (8.3 months) up until now, but not OS, because 17 of the 26 patients (65%) were still alive at the end of follow-up. The real OS time of Child-Pugh class A patients in this study is at least 8.3 months, and most likely even longer. We are expecting a similar median OS time to that in the sorafenib group of the SHARP trial (10.7 months) [12], or even better. Hence, we confirmed the favorable efficacy of sorafenib in Child-Pugh class A patients with advanced HCC in a “real-life” patient population outside a prospective clinical trial.

Of note, the disease control rate of Child-Pugh class A patients (19%) was worse than that of Child-Pugh class B patients (35%) in this analysis. This could only partially be explained by the incomplete radiologic follow-up, which was 23% in Child-Pugh class A patients and not different in Child-Pugh class B and class C patients. Still, the OS time in Child-Pugh class A patients was better than that in Child-Pugh class B patients in this study. These observations suggest that radiologic tumor response according to the RECIST seems to be only a modest predictor of survival in patients with multifocal HCC. Thus, like the Choi response criteria [17] for GI stromal tumors, the investigation of HCC-specific radiographic changes during targeted therapy is needed to improve the predictive power of radiological tumor response evaluation in patients with advanced HCC.

Also with sorafenib treatment, patient survival is strongly dependent on the severity of liver disease. Not unexpectedly, it was significantly worse in Child-Pugh

...
class B and class C patients in our analysis. We observed an OS duration of 4.3 months for Child-Pugh class B patients, which is lower than the OS time reported in all Child-Pugh class A patients so far. It could be questioned whether tumor-related factors or the severity of underlying liver cirrhosis were responsible for this poor outcome. The lower rate of extrahepatic metastases in Child-Pugh class B patients (48%) than in Child-Pugh class A patients (58%) does not point to an influence of extrahepatic involvement on the inferior outcome of the Child-Pugh class B patients in our observation. In contrast, 52% of the Child-Pugh class B patients but only 39% of the Child-Pugh class A patients had PVT. Thus, portal vein involvement could, at least partly, be responsible for the poor survival of the Child-Pugh class B patients. TTP was not worse in Child-Pugh class B or class C patients than in Child-Pugh class A patients, indicating that the antitumor activity of sorafenib is preserved in advanced cirrhosis and not dependent on the severity of liver disease. Whether the potential gain in OS in Child-Pugh class B patients results in a clinically meaningful survival benefit can only be evaluated in a prospective, randomized, placebo-controlled trial of sorafenib in Child-Pugh class B patients with advanced HCC.

This is the very first study reporting the efficacy of sorafenib in Child-Pugh class C patients and patients should instead be treated with best supportive care, as suggested by all current guidelines [8].

Side effects in this cohort of patients were, overall, low grade and manageable. Diarrhea (n = 21; 36%) was the most troublesome side effect, similar to the phase II study [11, 16] and the phase III randomized, controlled trial [12]. GI bleeding, nausea, emesis, and epistaxis were observed only in Child-Pugh class B and class C patients and not in Child-Pugh class A patients. The risk for high-grade toxicities could be increased in individuals with advanced liver dysfunction (Table 3). The lower discontinuation rate in Child-Pugh class C patients (20%) than in Child-Pugh class A patients (42%) and class B patients (43%) could be a result of the very short median survival time of the Child-Pugh class C patients (1.5 months). Notably, hand–foot skin reactions were more common in patients with well-preserved liver function (Child-Pugh class A patients) than in patients with more advanced disease stages. The rate of hand–foot skin reaction in Child-Pugh class A patients was similar to the rate in renal cancer patients [18]. This suggests that sorafenib metabolism by the normal liver might play a role in this toxicity, which would explain the surprisingly low rate of hand–foot skin reaction in more advanced liver disease patients.

The most severe complication in our study was GI bleeding (n = 4; 7%). We observed one episode of melaena (Child-Pugh class B, BCLC stage D), one variceal bleed (Child-Pugh class C, BCLC stage D), one bleeding of unknown origin (Child-Pugh class C, BCLC stage D), and one gastric ulcer bleeding (Child-Pugh class B, BCLC stage B).

### Table 4. Comparison with other published data of sorafenib for HCC in Child-Pugh class A, B, and C patients

<table>
<thead>
<tr>
<th>Study</th>
<th>CP</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Median TTP</th>
<th>Median OS</th>
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<tr>
<td>Prospective trials of sorafenib for HCC</td>
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<td></td>
</tr>
<tr>
<td>Abou-Alfa et al. [16]</td>
<td>A</td>
<td>–</td>
<td>2</td>
<td>49</td>
<td>NR</td>
<td>4.9</td>
<td>9.4</td>
</tr>
<tr>
<td>Abou-Alfa et al. [16]</td>
<td>B</td>
<td>–</td>
<td>–</td>
<td>26</td>
<td>74</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Llovet et al. [12], sorafenib</td>
<td>A</td>
<td>–</td>
<td>2</td>
<td>71</td>
<td>18</td>
<td>5.5</td>
<td>10.7</td>
</tr>
<tr>
<td>Llovet et al. [12], placebo</td>
<td>A</td>
<td>–</td>
<td>0.7</td>
<td>67</td>
<td>24</td>
<td>2.8</td>
<td>7.9</td>
</tr>
<tr>
<td>Retrospective trial of sorafenib for HCC</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>This study</td>
<td>A</td>
<td>–</td>
<td>–</td>
<td>19</td>
<td>58</td>
<td>2.2</td>
<td>8.3a</td>
</tr>
<tr>
<td>This study</td>
<td>B</td>
<td>–</td>
<td>4</td>
<td>30</td>
<td>48</td>
<td>2.9</td>
<td>4.3</td>
</tr>
<tr>
<td>This study</td>
<td>C</td>
<td>–</td>
<td>–</td>
<td>20</td>
<td>60</td>
<td>2.8/5.2b</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*Median time of follow-up, because 17 of 26 patients were still alive at the end of follow-up.

**TTP for each of the two Child-Pugh class C patients with SD.**

Abbreviations: CP, Child-Pugh; CR, complete response; HCC, hepatocellular carcinoma; NR, not reported; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; TTP, time to progression.
One patient (variceal bleeding) had to discontinue sorafenib treatment and another patient (bleeding of unknown origin) died as a result of the GI bleed. No direct causal relationship to sorafenib treatment could be established in any case. GI bleeding is a common complication of chronic liver disease and bleedings are a known side effect of multikinase inhibitors [19], but the rate of bleeding was not greater than that seen with placebo in the prospective phase III trials reported so far. Still, caution is warranted before starting sorafenib therapy in patients with advanced liver dysfunction. Prophylactic endoscopic evaluation with prophylactic variceal band ligation in patients with high-risk varices could be considered in this group of patients.

CONCLUSION
Sorafenib is effective and safe in patients with multifocal HCC and Child-Pugh class A cirrhosis, as shown by several large prospective trials [12, 20]. The efficacy and safety of sorafenib in Child-Pugh class B patients require further evaluation in a prospective, placebo-controlled trial. Child-Pugh class C patients have a limited life expectancy because of their severe underlying disease, which cannot be substantially improved by sorafenib treatment.

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