Sorafenib in patients with Child-Pugh class A and B advanced hepatocellular carcinoma: a prospective feasibility analysis

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Background: Sorafenib has shown survival benefits in patients with advanced hepatocellular carcinoma (HCC) and Child-Pugh (CP) class A liver function. There are few prospective data on sorafenib in patients with HCC and CP class B.

Patients and methods: A consecutive prospective series of 300 patients with CP class A or B HCC were enrolled in a dual-phase trial to determine survival and safety data according to liver function (class A or B) in patients receiving oral sorafenib 800 mg daily. [Results of this study were presented in part at the ASCO 2012 Gastrointestinal Cancers Symposium, 19–21 January 2012. J Clin Oncol 2012; 30 (Suppl 4): abstract 306.]

Results: Overall progression-free survival (PFS), time to progression (TTP) and overall survival (OS) were 3.9, 4.1 and 9.1 months, respectively. For patients with CP class A versus B status, PFS was 4.3 versus 2.1 months, TTP was 4.2 versus 3.8 months and OS was 10.0 versus 3.8 months. Extrahepatic spread was associated with worse outcomes but taken together with CP class, liver function played a greater role in reducing survival. Adverse events for the two CP groups were similar.

Conclusion: Although patients with HCC and CP class B liver function have poorer outcomes than those with CP class A function, data suggest that patients with CP class B liver function can tolerate treatment and may still benefit from sorafenib.

Key words: carcinoma, Child-Pugh class, cirrhosis, hepatocellular, sorafenib

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and its incidence is rising in western countries [1]. In ~50% of cases, HCC is diagnosed at an advanced stage when unsuitable for loco-regional treatment, with few systemic therapies available, and a median survival <1 year [1–4]. The introduction of therapies targeting signalling pathways involved in cell proliferation and angiogenesis has improved the management of advanced HCC [5].

Sorafenib, a small molecule multikinase inhibitor [6], was the first systemic agent to prolong survival in patients with advanced HCC, as demonstrated in two phase III trials [4, 7] and it is now the reference standard for systemic treatment of these patients [3, 5, 8]. Both trials enrolled only patients with Child-Pugh (CP) class A liver function at baseline to limit the confounding effect of deaths due to advanced cirrhosis [4, 7].

Two recent retrospective analyses and a case–control study evaluated sorafenib in patients with advanced HCC to assess differences in safety and efficacy based on CP status. They showed that the clinical outcome was poorer in CP class B
patients, even if treatment maintained an acceptable safety profile [9–11]. A review of data from 267 patients with advanced HCC treated with sorafenib showed that CP class B patients had worse clinical outcomes. Although some patients with a score of 8–9 discontinued sorafenib due to cirrhosis-related complications, this was still considered beneficial for CP class B patients [10]. Other investigations supported the feasibility of sorafenib in subjects with CP class B status, but were retrospective and/or conducted in a limited number of patients [11–13]. The recent results of an interim analysis of the GIDEON real-life study suggested that the safety profile of sorafenib is similar for CP class B and A patients. However, a shorter median overall survival (OS) was observed in CP class B patients, likely due to the poorer prognosis of liver cirrhosis [14]. A recent observational study of sorafenib in patients with intermediate (if ablative therapies failed in patients) or advanced HCC reported survival outcomes in line with those already published and, notwithstanding an increased rate of dose reduction/interruption in patients with more compromised liver function, CP class B patients still experienced survival benefits [15]. However, the conclusions of this study have been strongly questioned [16].

The question whether or not to use sorafenib in CP class B patients is of major relevance as a large number of patients with advanced HCC present with suboptimal liver function. There is an urgent need to evaluate the safety of sorafenib in this population to identify which patients are eligible for treatment and at what dosage given the inconsistency of data from phase I and II trials on pharmacokinetics and recommended dose [9–11, 17, 18]. Additional studies are ongoing, the results of which are eagerly awaited.

We report the results of a descriptive analysis conducted in patients included in the first phase of a dual-phase clinical trial of sorafenib in advanced HCC (results of the second phase were described elsewhere [19]). The aim of this study was to prospectively investigate the feasibility of sorafenib treatment in patients with poorer (CP class B) compared with better (CP class A) liver function.

patients and methods

patient selection

Patients were eligible for this multicentre, phase II, open-label trial if they had cyto-histologically confirmed advanced HCC unsuitable for resection or loco-regional therapy, Barcelona Clinic Liver Cancer (BCLC) stage B or C, CP liver function class A or B, Eastern Cooperative Oncology Group (ECOG) performance status (PS) score ≤2, adequate haematological, hepatic (according to CP status) and renal function and a life expectancy of ≥12 weeks. Patients must be untreated with targeted therapies and have at least one measurable target lesion according to the Response Evaluation Criteria in Solid Tumours (RECIST) v.1.0.

All patients provided written informed consent before enrolment in the study. The study was approved by the institutional review board or ethics committee at each centre and complied with the provisions of the Good Clinical Practice guidelines, the Declaration of Helsinki and Italian national laws.

study design

The study consisted of two consecutive phases. During the first phase, all patients received continuous oral treatment with sorafenib 400 mg twice daily until radiological progression (as defined by RECIST), symptomatic progression or deterioration of PS, unacceptable toxic effects or patient withdrawal. Treatment interruptions and dose reductions were permitted for drug-related adverse events (AEs).

The second phase of the trial was initiated on radiological disease progression. Patients were randomized to sorafenib dose escalation (600 mg twice daily) or best supportive care. The randomization was conducted according to the study protocol and patients were allowed to decline inclusion in the second phase of the trial.

outcomes and assessments

We report here the results of a non pre-specified descriptive analysis of data from all patients included in the study.

The present analysis assessed progression-free survival (PFS), defined as time from enrolment to clinical or radiological disease progression or death. Tumour measurements were carried out at screening, every 8 weeks during treatment, and at the end of treatment by computed tomography (CT) or magnetic resonance imaging. Time to last observation was used if a patient had not progressed or was lost to follow-up and PFS was censored. Additionally, this analysis included an evaluation of the OS, defined as time from enrolment to death from any cause. Time to last observation was used if, by study end, the patient was still alive, and OS was censored. Time to progression (TTP) was calculated from enrolment until radiological progression or until last CT evaluation for progression-free patients, censoring patients who died. Safety was assessed in all patients receiving at least one dose of sorafenib.

We reviewed patients every 4 weeks and at the end of treatment to assess compliance, based on tablets accountability, and safety, based on AEs, clinical laboratory tests, physical examination and measurement of vital signs.

statistical analysis

All data were analysed by descriptive statistics. Demographic and clinical characteristics were compared by the χ² test (Yates’ corrected) or Fisher’s exact test, as appropriate. The Wilcoxon–Mann–Whitney test was used to investigate differences among medians. Survival curves for PFS and OS were computed by means of the Kaplan–Meier analyses. Patients were stratified according to gender, age (median age <68 or ≥68 years), tumour histotype, extrahepatic spread and CP status. Differences among subgroups were evaluated by the log-rank test. Statistically significant variables in the univariate analysis were tested using multivariate Cox proportional hazards regression models and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. A P-value of <0.05 was considered statistically significant. All statistical analyses were carried out using R-package v. 2.0.

results

Between April 2007 and July 2008, 300 patients were enrolled in the study. Three patients never received sorafenib and data relevant to 297 patients are presented. The distribution of patients across centres (supplementary Table S1, available at Annals of Oncology online) and a patient flow chart (supplementary Figure S1, available at Annals of Oncology online) are available online. Baseline characteristics for all patients, and according to CP status, are summarized in Table 1. The two CP class A or B subgroups were homogeneous, except for baseline aspartate aminotransferase (AST) elevation and vascular invasion, both more frequent in CP class B patients. The median follow-up was 41.6 (0.4–49.1) months during which 272 patients (91.6%) died. The median
The median PFS for the total patient population was 3.9 (0.1–35.3) months. CP class and age showed statistically significant differences and maintained their effect in multivariate analysis. PFS for patients with CP class A or B was 4.3 (0.1–35.3) and 2.1 (0.3–27.3) months, respectively (log-rank, \( P < 0.001 \)); Table 2. In the multivariate analysis, CP class B patients had a greater risk of disease progression or death (HR 1.87, 95% CI: 1.41–2.48, \( P < 0.001 \)), corresponding to a 47% risk reduction in PFS in the CP class B compared with the class A subgroup (Figure 1). Patients <68 years compared with those \( \geq 68 \) years presented a reduced risk in PFS (HR 1.55, 95% CI: 1.15–2.08, \( P = 0.026 \)).

Data on TTP were available in 240 patients (80.8%; 206 CP class A and 34 CP class B), 57 patients did not present a radiological evaluation post-enrolment due to death (15.8%), AEs (36.8%) and other reasons (47.4%). Reasons for exclusion from this analysis are shown in the patients’ flow chart (supplementary Figure S1, available at Annals of Oncology online). The median TTP was 4.1 (0.03–16.0) months for the total patient population and was not statistically different according to CP status. TTP for CP class A patients was 4.2 (0.03–19.44) and for CP class B patients was 3.8 (range 1.3–16.0) months (log-rank, \( P = 0.102 \)). The median OS was 9.1 (0.4–49.1) months for the total patient population (Table 2). As for PFS, CP class B patients had a statistically significant greater risk of death than those with CP class A status (HR 3.23, 95% CI: 2.38–4.39, \( P < 0.001 \)). The median OS was 10.0 (0.5–49.1) for CP class A patients and 3.8 (0.4–27.3) months for CP class B patients (log-rank, \( P < 0.001 \)) (Table 2, Figure 2); the risk reduction for CP class A patients compared with those with CP class B was 69%. In the overall patient population, there were also statistically significant differences in OS according to AST baseline values (log-rank, \( P = 0.008 \)), vascular invasion (log-rank, \( P = 0.049 \)) and HCC disease extent (log-rank, \( P = 0.025 \)); the latter was confirmed in the multivariate evaluation (Table 2). Patients with extrahepatic spread had a greater risk of death than those with intrahepatic disease (HR 1.55, 95% CI: 1.15–2.08, \( P = 0.026 \)). Patients with CP class B had a higher risk of death than those with CP class A status, irrespective of the extent of disease (\( P < 0.001 \)), emphasizing the prognostic role of CP classification over disease extent (Figure 3). A subgroup analysis according to CP

Table 1. Baseline characteristics of patients included in the study

<table>
<thead>
<tr>
<th>Total patient population [n (%)]</th>
<th>Child-Pugh status [n (%)]</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A</td>
<td>Class B7</td>
<td>Class B8</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Total</td>
<td>297 (100)</td>
<td>234 (78.8)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>232 (76.1)</td>
<td>180 (76.9)</td>
</tr>
<tr>
<td>Female</td>
<td>65 (21.9)</td>
<td>54 (23.1)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;68</td>
<td>147 (49.5)</td>
<td>114 (48.7)</td>
</tr>
<tr>
<td>( \geq 68 )</td>
<td>150 (50.5)</td>
<td>120 (51.3)</td>
</tr>
<tr>
<td>Histological subtype</td>
<td></td>
<td></td>
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<tr>
<td>Trabecular</td>
<td>217 (73.1)</td>
<td>168 (92.8)</td>
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<tr>
<td>Mixed fibrolamellar</td>
<td>15 (5.0)</td>
<td>13 (7.2)</td>
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<td>Missing data</td>
<td>65 (21.9)</td>
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<tr>
<td>Vascular invasion</td>
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<td></td>
</tr>
<tr>
<td>Absent</td>
<td>193 (65.0)</td>
<td>162 (69.2)</td>
</tr>
<tr>
<td>Present</td>
<td>104 (35.0)</td>
<td>72 (30.8)</td>
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<tr>
<td>Extrahepatic spread</td>
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<tr>
<td>Absent</td>
<td>217 (73.1)</td>
<td>171 (77.7)</td>
</tr>
<tr>
<td>Present</td>
<td>62 (20.9)</td>
<td>49 (22.3)</td>
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<td>18 (6.0)</td>
<td>14</td>
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<td>AST (IU/L)</td>
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<tr>
<td>( \leq \text{ULN} )</td>
<td>76 (25.6)</td>
<td>72 (31.0)</td>
</tr>
<tr>
<td>( &gt;\text{ULN} )</td>
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<td>160 (69.0)</td>
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</tr>
</tbody>
</table>

*\( P \) value compares Child–Pugh class A versus class B. AST, aspartate aminotransferase; ULN, upper limit of normal.
score B7 versus B8 + B9 showed a statistically significant difference in terms of OS (4.6 versus 2.9 months; \( P = 0.048 \)), whereas non-statistically significant differences were observed in PFS and TTP. Due to the small number of CP class B patients, we did not perform further subgroup analyses.

Finally, a statistically significant correlation between drug exposure and outcome in terms of TTP and OS was observed in the overall patient population \( (P < 0.001) \), whereas no outcome differences were documented between high- and low-volume centres.

### safety

The type and the incidence of AEs were similar in the overall patient population and in patients with CP class A and B.
cancer severity [10, 14, 22]. PFS also differed with the age of patients: younger patients (<68 years) had a longer median PFS, with a HR for progression of 0.77 compared with patients ≥68 years. While liver function and disease spread (intra-versus extrahepatic disease), as observed in the multivariate analysis, independently influenced OS, survival appears to be affected by liver function more than by disease spread. CP class B patients, regardless of disease spread, had a higher risk of death than those with CP class A function and extrahepatic disease. Moreover, CP class B patients with a B8 + B9 score did worse in terms of OS compared with those with a B7 score. These results confirm that CP liver function status affects the clinical outcomes in patients with advanced HCC treated with sorafenib.

A further finding of our study was the statistically significant correlation between drug exposure and outcome in terms of TTP and OS (P < 0.001), emphasizing the importance of maintaining the highest dose intensity acceptable for each patient. Importantly, despite the multicentre nature of this study, no differences in terms of drug exposure or outcome were documented between high- and low-volume centres.

In conclusion, although limited by the statistical design of our study, tolerability data suggest that CP class B patients might be safely treated with sorafenib. However, its activity in this patient population remains to be defined, bearing in mind that it is not a homogeneous group. Further prospective trials specifically designed to investigate the efficacy and safety of sorafenib in CP class B subgroups,
particularly in those patients with less compromised liver function (CP score 7), are warranted. While waiting for the results of these studies, the administration of sorafenib in CP class B patients with advanced HCC remains open to discussion and in our opinion could be feasible in carefully selected patient groups.

**Acknowledgements**

The corresponding author (LR) confirms that she had full access to all the data in the study and had final responsibility for the decision to submit this manuscript for publication. Editorial assistance for the preparation of this manuscript was provided by Laura Brogelli of Content Ed Net; this assistance was funded by Bayer Italy. All the investigators were responsible for the decision to publish the results of the study, had unrestricted access to the final data and vouch for the completeness and accuracy of the data and data analyses.

**Funding**

This work was supported in part by Bayer Italy. The study was designed by the lead investigator (AS, Humanitas Cancer Center). Bayer Italy, the manufacturer of sorafenib, provided the investigational drug and supported the study with a grant, but had no role in data analysis or in the decision to publish the results.

**Disclosures**

CP received research grants from Bayer-Schering Pharma and acted as consultant and speaker for the same company. CB participated in a board for Sanofi. SF conducted a trial sponsored by Bayer. AS was a consultant for Bayer. The remaining authors have declared no conflicts of interest.

**References**