Research Article

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Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib

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Background & Aims: There are no clinical data/markers to predict improved survival in patients with hepatocellular carcinoma treated with sorafenib. Majority of sorafenib adverse events appear within the first 60 days of treatment and studies correlating them with outcome are needed.

Methods: We prospectively studied 147 hepatocellular carcinoma patients (97% cirrhotic, 82% Child-Pugh A, BCLC-B 77, BCLC-C 69) treated with sorafenib. Follow-up included monthly clinical and laboratory monitoring and tumor staging at week 4 and every 8 weeks.

Results: After a median follow up of 11.6 months (treatment duration 6.7 months), time to progression and overall survival were 5.1 and 12.7 months. All but one patient presented at least one adverse event (median time to appearance 56 days). Time dependent covariate analysis (HR [95% CI]) identified baseline performance status (2.86 [1.75 to 4.55], p <0.001), BCLC (1.69 [1.18 to 2.50], p = 0.005), and dermatologic adverse event requiring dose adjustment within the first 60 days (0.58 [0.36 to 0.92], p = 0.022) as independent predictors of better outcome. Other early adverse events did not have an impact in outcome. The predictive value of dermatologic adverse events for survival was confirmed by the landmark analysis (p = 0.0270).

Conclusions: Development of dermatologic adverse events within 60 days of sorafenib initiation is associated with better survival. Therefore, this should not to be taken as a negative event and discourage treatment maintenance. Likewise, second line clinical trials should be designed and/or evaluated considering this information to avoid significant bias.

Keywords: Hepatocellular carcinoma; Sorafenib; Early adverse events; Clinical marker; Overall survival.

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Abbreviations: OS, Overall survival; HCC, Hepatocellular carcinoma; AE, adverse events; PS, Performance status; BCLC, Barcelona Clinic Liver Cancer classification; TTP, Time to progression; AASLD, American Association for the Study of Liver Disease; AE60, AE with in the first 60 days; HCV, Hepatitis virus C; HBV, Hepatitis virus B; DAE60, Dermatologic AE60; AHT, Arterial hypertension; P25, P33, P66, P75, 25th, 33th, 66th, and 75th percentiles, respectively.

Introduction

Sorafenib improves the overall survival (OS) of patients with advanced hepatocellular carcinoma (HCC) with a good safety profile and it is the first molecular target treatment approved for HCC therapy [1]. It decreases the risk of death by 31% (Hazard Ratio 0.69) and its impact in the OS of patients with HCC is maintained regardless of race, etiology, and the baseline characteristics of patients [1,2].

Despite the analysis of different biomarkers [3] and/or functional radiologic evaluation in this population, it has been unfeasible to identify those patients that benefit most from this treatment. Thus, there is no baseline or early marker (clinical, radiologic, and/or biochemical) within the first 30–60 days after starting sorafenib that would inform patients and physicians about the higher or lower impact of treatment.

Previous retrospective studies have suggested a correlation between dermatologic AE (adverse events) and TTP (time to progression)/OS [4–6]. These dermatologic AEs have been proposed as a marker of enhanced efficacy of sorafenib treatment. However, this possibility has not yet been demonstrated in a prospective study using time dependent covariate analysis and taking into account all other factors related to the prognosis of HCC patients. Thus, our goal was to prospectively evaluate the impact of the recognition of a dermatologic adverse event within the first 60 days in the outcome of patients.

In that regard it is worth recalling that none of the phase III head to head trials challenging sorafenib in HCC patients has been positive [7,8]. Interestingly enough, the frequency of hand foot skin reaction grade III in sorafenib arm of these trials was more prevalent than in the sunitinib [7] (21% *vs.* 13%) or brivanib arm [8] (15% *vs.* 2%). Hence, putting together the data from the phases III trials in first line [7,8] and the retrospective studies

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[4–6], the potential link between dermatologic adverse events and improved outcome could be reinforced. Confirmation of this association in a large cohort study would prove important to understand the prognosis of patients under molecular targeted therapies and modify the current design of treatment trials. Ultimately, the investigation of the mechanisms responsible for the emergence of dermatologic adverse events as a predictor of improved therapeutic response would permit a personalized treatment approach.

Patients and methods

This prospective study considered all patients referred to our center between March 2008 and July 2011 for sorafenib treatment according to the BCLC strategy [9,10].

Inclusion criteria were: (1) HCC diagnosed according to AASLD guidelines [9,11] (2) presence of a naïve target lesion; (3) adequate liver function (albumin >2.8 g/dl; total bilirubin <3 mg/dl; and alanine and aspartate aminotransferases <5 times the upper limit of the normal range), and Child-Pugh score $\leqslant$7 points; (4) performance status (PS) 0–1; (5) controlled arterial hypertension and stable peripheral vascular disease; (6) adequate hematologic profile (platelet count >60 $\times$ 10^9/L; haemoglobin >8.5 g/dl; and prothrombin time >50%); (7) adequate renal function (serum creatinine <1.5 times the upper limit of the normal range).

Exclusion criteria were: (1) myocardial infarction in the past year or active ischemic heart disease; (2) acute variceal bleeding in the past month; (3) severe peripheral arterial disease; (4) cardiac arrhythmia under treatment with drugs other than beta-blockers or digoxin; (5) uncontrolled ascites; (6) encephalopathy; (7) unfeasibility to fulfil the follow-up schedule.

All the patients provided written informed consent before enrolment. The study was approved by the institutional review board and complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki.

Outcomes and assessments

Time to progression was defined as the time from the date of starting sorafenib to disease progression. Radiologic evaluation of response during follow-up was done by CT-scan according to the RECISTv1.1 [12] with the amendments that were implemented in the pivotal SHARP trial [1] that ultimately was reflected in the mRECIST proposal [13,14]. Radiology assessment was blinded to the evolution and outcome of the patients. Those patients who died before the first imaging assessment were classified as progressors.

Overall survival was measured from the date of starting sorafenib until the date of death and survival post-definitive interruption was defined as the time from definitive sorafenib interruption until death occurred.

Treatment

Sorafenib was initiated at full dose (400 bid), which was modified upon development of adverse events according to manufacturer's recommendations. Treatment was continued until symptomatic progression, unacceptable adverse events or death occurred.

Follow-up

Clinical and laboratory assessments were done monthly and radiology tumour evaluation at week 4 and afterwards every 8 weeks. Unscheduled visits due to adverse events occurred according to patients' needs.

Adverse events (AE) were graded according to version 3.0 of the CTCAE of the National Cancer Institute, during treatment and 30 days after the last dose. Despite the cause of the AE, we focused on the AE within the first 60 days (AE60) of treatment, which determined dose modification. Thus, the following results will be especially focused on those kinds of patients: patients who developed AE60 (between day zero and day 60) and needed dose modification.

We divided the AE60 in 5 groups: dermatologic (*hand-foot reaction/rash/edema-erythema/foliculitis*) cardiovascular (arterial hypertension/rhythm alteration/ischemic events), gastrointestinal, bleeding, infection, and others.

Statistical analysis

Categorical variables are described as frequencies and percentages, and continuous variables as median and percentiles 25 and 75 (P25-P75), or as otherwise specified. Time to event data for survival are estimated by Kaplan-Meier for death or using the cumulative incidence curves of progression in a competing risks framework, with death without progression as competing event [15,16]. The landmark approach [17] was used to rule-out time-dependent bias of dermatologic adverse events as a predictor for survival and to reinforce the findings by excluding patients with early events (i.e., before 60 days). To define the predictors of overall survival we used a time-dependent covariates survival approach including statistically significant clinical variables (p <0.05) from the univariate Cox analysis [18].

The Fisher's exact test was used to compare categorical variables and the Mann-Whitney method was used to compare ordinal and continuous variables.

The analysis was performed using SAS version 9.2 software (SAS Institute Inc., Cary, NC, USA), SPSS v18 (SPSS, Inc., Chicago IL) and significance was established at the 0.05 level (two-sided).

Results

Between March 2008 and July 2011, 229 patients were assessed for sorafenib treatment. Of the 229, 82 patients were excluded per study criteria and 147 were eventually enrolled in the study. The majority of exclusions were due to impaired PS and deteriorated liver function at screening.

At the time of database lock (May 2012), their median follow-up was 11.6 months (range: 0.4–51.8): 111 died, 28 out of 147 patients were still alive (with 7 continuing sorafenib) and 8 were lost to follow-up.

Baseline characteristics

Clinical and laboratory baseline characteristics are summarized in Table 1. All but 4 patients were cirrhotic. The most frequent etiology of cirrhosis was HCV (57.1%), followed by alcohol abuse (25.2%) and HBV (11.6%). The majority of the patients were asymptomatic (PS-0 83.6%) and 77 (52.3%) were BCLC B who failed or presented contraindication to loco-regional treatment. Fifty-one patients (34.7%) presented vascular invasion, 121 patients (82.3%) were Child–Pugh A class. Sixty-five patients had not received previous therapies and 82 (55.8%), had received prior locoregional therapy. None of the patients had received systemic therapy.

Overall survival and radiologic evaluation

The median OS was 12.7 months [(95% CI; 10.3 to 15.2), (percentiles 33th-66th, P33-P66: 8.2–16.1 months)] (Supplementary Fig. 1A). The response rate was: stable disease (SD) in 36 patients (24.5%), partial response in 2 patients and complete response in 1 patient. Tumor progression occurred in 108 patients (73.5%). Median TTP was 5.1 months (95% CI; 3.7 to 6.4) (Supplementary Fig. 1B).

Treatment, adverse events, and dose modification

The median duration of treatment was 6.7 months (range: 0.26–35) (P33: 3.6, P66: 10.2 months)]. The median (percentile 25th–75th) cumulative dose was 70,400 mg (29,200–154,400) and the median daily dose was 546 mg (343–795).

All but one patient presented at least one adverse event (median time to appearance 56 days; this primed the use of 60 days as the cut-off to define early *vs.* late AE), and all but 4 out of 147