

Predictors of survival in patients with established cirrhosis and hepatocellular carcinoma treated with sorafenib

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with an established diagnosis of cirrhosis and HCC treated with sorafenib were consecutively enrolled. According to the Barcelona Clinic Liver Cancer (BCLC) classification, patients were in the advanced stage (BCLC-C) or in the intermediate stage (BCLC-B) but unfit or unresponsive to other therapeutic strategies. Treatment was evaluated performing a 4-phase computed tomography or magnetic resonance imaging scan every 2-3 mo, and analyzed according to the modified Response Evaluation Criteria in Solid Tumors. Sorafenib was administered at 800 mg/d, until radiological progression or occurrence of unacceptable adverse events (AEs). Univariate and multivariate analyses identified predictors of 16-wk clinical benefit and overall survival.

RESULTS: Forty-four patients were enrolled, 15 had intermediate HCC and 14 a Child-Pugh score of B7. AEs caused treatment interruption in 19 patients (43%), and median treatment duration was shorter in this subset (5 wk *vs* 19 wk, $P < 0.001$) and in the BCLC-C subgroup (13 wk *vs* 40 wk, $P = 0.015$). No significant differences in the reason for treatment interruption or in treatment duration were found comparing patients in Child-Pugh class A *vs* B or in patients older or younger than 70 years. After 16 wk of treatment, 18 patients (41%) had stable disease or partial response. Patients with viral infection or BCLC-C were at higher risk of disease progression. ECOG, extrahepatic spread, macrovascular invasion, alpha-fetoprotein or alkaline phosphatase levels at admission were independent predictors of overall survival.

CONCLUSION: In patients with cirrhosis and HCC treated with sorafenib, AEs are a common cause of early treatment withdrawal. Vascular invasion and extrahepatic spread condition early response to treatment and survival. Baseline biochemical parameters may be helpful to identify patients at higher risk of shorter

Abstract

AIM: To investigate in greater detail the efficacy and safety of sorafenib for the treatment of hepatocellular carcinoma (HCC) in patients with established cirrhosis.

METHODS: From October 2009 to July 2012 patients

overall survival.

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Key words: Hepatocellular carcinoma; Sorafenib; Cirrhosis; Adverse events; Barcelona Clinic Liver Cancer

Core tip: The study provides information on the clinical characteristics and laboratory findings that predict survival in patients with hepatocellular carcinoma and established cirrhosis treated with sorafenib. This group of patients is particularly fragile and difficult to treat, and therapy with systemic agents, including sorafenib, requires careful monitoring. We report that parameters related to the tumor (extrahepatic spread, vascular invasion), common laboratory tests (alpha-fetoprotein or alkaline phosphatase) and patients characteristics (performance status) are significant predictors of overall survival in this group. These data provide important clinical information for the management of this type of patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most deadly cancers worldwide, and its incidence has increased steadily over the last 20 years in Western Europe and North America^[1]. One of the hallmarks of HCC is its strict association with chronic liver disease and in particular cirrhosis, which represents the major risk factor for this type of cancer. The presence of cirrhosis makes the treatment of HCC particularly challenging, as tumor destruction must maximally preserve the amount of functioning liver tissue to prevent hepatic failure^[1].

According to the Barcelona Clinic Liver Cancer (BCLC) classification, advanced HCC is identified as an unresectable HCC associated with symptoms, and/or macrovascular invasion, and/or extrahepatic spread^[2]. While advanced HCC has long been considered untreatable, recent controlled trials have shown that sorafenib, a multi-kinase inhibitor, prolongs survival of these patients^[3,4]. However, the survival benefit afforded by this drug is limited to a median of 8-10 wk over placebo, and information indicating which patients are more likely to take advantage from treatment with sorafenib is still very limited. Better patient selection would also be associated with rationalization of health care costs, given the high reimbursement price of sorafenib treatment^[5]. Additionally, the burden of side effects associated with systemic

therapies may be particularly heavy in patients with cirrhosis, who are prone to decompensation of the underlying disorder^[6].

Although the safety of sorafenib has been the focus of some post-marketing studies, few have analyzed its effects in patients with a clear diagnosis of cirrhosis. Aim of this study was to evaluate the safety of sorafenib in patients with HCC and established cirrhosis, consecutively recruited in a single tertiary referral center, and to carefully analyze the variables that could be predictive of response to treatment or survival.

MATERIALS AND METHODS

Patients

From October 2009 to July 2012 all patients with hepatocellular carcinoma and an established diagnosis of cirrhosis undergoing treatment with sorafenib at one of the prescribing Centers at the Careggi Hospital, Florence, were enrolled. These included patients with advanced (stage C) HCC, according to BCLC classification^[7] or with intermediate stage (BCLC-B) who were unfit or failed to respond to other approved therapeutic strategies. Patients were either referred to a group of gastroenterologists and hepatologists specifically dealing with the management of HCC (collectively defined as "Hepatology Unit") or to the Medical Oncology Unit of Careggi Hospital.

HCC was diagnosed by radiologic criteria according to American Association for the Study of Liver Diseases^[8] or EASL guidelines^[2] and/or by biopsy when required. In this study only patients with an established diagnosis of cirrhosis were included. Cirrhosis was diagnosed on the basis of a history of chronic liver disease, and clinical (presence of signs of portal hypertension, previous episodes of decompensation), imaging (liver nodular surface or splenomegaly), elastographic (stiffness ≥ 18 kPa) and/or hematological and biochemical findings (thrombocytopenia, hyperbilirubinemia, high International Normalized Ratio). Patients were sub-classified according to the Child-Pugh score^[9]. All patients in whom a score of 7, but not higher, was calculated at least once in the two months preceding enrollment were considered as Child-Pugh class B, regardless of the actual score at the time of sorafenib initiation. Concomitant antiviral therapy for hepatitis B was allowed. Performance status was evaluated according to the Eastern Cooperative Oncology Group (ECOG)^[10].

Treatment schedule and interruption, and dose modification

Sorafenib was administered at 800 mg/d. Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0^[11]. Elevation of aminotransferases and/or bilirubin were collectively considered as "hepatic" AEs and graded according to CTCAE of the individual component. Appearance of AEs with a grade ≥ 2 resulted in dose re-

Table 1 Clinical characteristics of the patients with cirrhosis and hepatocellular carcinoma enrolled in the study *n* (%)

Characteristics	<i>n</i> = 44
Age (yr)	
mean (SD)	67.7 (10.1)
median (min-max)	70 (44-83)
Males	38 (86.4)
Recruiting unit	
Hepatology	29 (65.9)
Medical Oncology	15 (34.1)
Etiology of cirrhosis	
HCV	19 (43.2)
HBV	9 (20.5)
Alcohol	7 (15.9)
Multifactorial	4 (9.1)
Cryptogenic	4 (9.1)
Primary biliary cirrhosis	1 (2.3)
ECOG performance status	
0	24 (54.5)
1	18 (40.9)
2	2 (4.5)
BCLC	
B	15 (34.1)
C	29 (65.9)
Child-Pugh class	
A	29 (65.9)
B	15 (34.1)
Extrahepatic spread	9 (20.5)
Portal vein thrombosis	8 (18.2)
Varices	15 (34.1)
Macroscopic category	
Extrahepatic only	1 (2.3)
Uninodular	3 (6.8)
≤ 3 nodules	34 (77.3)
> 3 nodules	6 (13.6)
Previous therapies	
TACE ¹	20 (45.5)
Locoregional ablation	3 (6.8)
Surgical resection	2 (4.5)
None	19 (43.2)

¹Includes 7 patients in whom trans arterial chemo-embolization (TACE) was performed in combination with other treatment modalities, and 2 patients treated with ⁹⁰Y radio-embolization. HCV: Hepatitis C virus; HBV: Hepatitis B virus; ECOG: Eastern Cooperative Oncology Group; BCLC: Barcelona clinic liver cancer.

duction, temporary withdrawal or permanent interruption according to the physician's decision. Dose reduction or temporary interruption were maintained until AE resolution or grade regression, and was based on the physician's judgment. Therapy was continued until progression, death, or appearance of unacceptable AEs. Treatment was also stopped upon withdrawal of patient's consent.

Patient follow-up

Patients underwent evaluation at baseline and at weekly to monthly intervals, according to the physician's judgment. Blood tests were obtained at intervals not greater than 4 wk and included a complete blood count and serum chemistries. Treatment was evaluated performing a 4-phase computed tomography (CT) or magnetic resonance (MR) scan, and analyzed according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST)^[12]. Radiologic evaluation was repeated every 2-3

mo until progression or treatment interruption for AEs. Patients were followed after treatment suspension and overall survival was evaluated.

Statistical analysis

In descriptive statistics χ^2 test and Fisher's exact test were used for testing differences for categorical variables and Mann-Whitney *U* test for continuous variables between patient groups. A *P* value < 0.05 was considered statistically significant. Further analyses were targeted on: (1) 16-wk clinical benefit (*i.e.*, presence/absence of partial response or stable disease at imaging) using logistic regression; and (2) overall survival (end-point was death during follow-up, other patients were censored up to the date of the last contact) using Kaplan-Meier method, log-rank test and Cox PH modeling.

In both types of analyses all clinical variables collected at enrolling were considered. The frequency of missing values ranged from 0% to 13.6%, mostly present in laboratory parameters. Due to the small number of patients in the sample, missing values were handled by single imputation technique. The results coming from univariate analyses before and after data imputation were compared. Parameters resulting statistically significant with *P* < 0.20 in univariate analyses were further included into multivariate analyses. Then, starting from the full model with all variables included, the models were built applying backwards stepwise selection procedure with *P* > 0.10 as remove and *P* < 0.10 re-entry criteria. As a strength of association between each predictor and outcome the OR and 95%CI for logistic regression and HR, and 95%CI for survival analysis were calculated. Statistical analysis was performed with SAS 9.2 software (SAS Institute Inc., Cary, NC, United States).

RESULTS

The clinical characteristics of the 44 patients enrolled in the study are shown in Table 1. Patients were mostly males and their age concentrated in the 7th-8th decade. Viral etiology, alone or in combination with other factors, was present in more than two-thirds of patients. Nine patients had extrahepatic spread (4 lungs, 3 lymph nodes and 2 skeleton). The majority of patients (84%) had a tumor burden ≤ 3 nodules. Approximately half of the patients (56.8%) had been previously treated with other modalities, chemoembolization being the most frequent. No patient had undergone liver transplantation. No patient was lost to follow up during treatment, while 2 patients were lost to follow up after sorafenib withdrawal.

Median treatment duration was 15 wk (range 1-81). At the time of analysis no patients were still under treatment. The reason for stopping treatment was disease progression in 25 patients (56.8%) and unacceptable AEs in 19 (43.2%). Median treatment duration was significantly shorter in patients who stopped treatment because of AEs [5 (range 1-57) *vs* 19 (5-81) wk, *P* < 0.001]. No significant differences in the reason for treatment interruption or in treatment duration were found comparing patients

Table 2 Incidence of adverse events in 44 patients with cirrhosis and hepatocellular carcinoma undergoing treatment with sorafenib *n* (%)

Adverse events	Statistics
Fatigue	29 (65.9)
Grade 1	11 (25.0)
Grade 2	11 (25.0)
Grade 3	7 (15.9)
Bleeding	7 (15.9)
Grade 1	3 (6.8)
Grade 2	1 (2.3)
Grade 3	3 (6.8)
Hand-foot syndrome	14 (31.8)
Grade 1	7 (15.9)
Grade 2	7 (15.9)
Grade 3	0 (0.0)
Diarrhea	15 (34.1)
Grade 1	6 (13.6)
Grade 2	8 (18.2)
Grade 3	1 (2.3)
Hepatic grade 3 ¹ AEs	8 (18.2)
Other AEs ²	20 (45.5)

¹An increase in aminotransferase and bilirubin after starting sorafenib was observed in all patients; ²Including rash, hypertension, alopecia, diabetes, mucositis, abdominal pain, voice changes. All grades were evaluated according to Common Terminology Criteria for Adverse Event version 3.0. AEs: Adverse events.

in Child Pugh A *vs* B class or patients older or younger than 70 years. Patients in the BCLC-C stage had a significantly shorter median duration of treatment compared to BCLC-B patients [13 (2-73) *vs* 40 (1-81) wk, $P = 0.015$]. However, these two latter groups did not differ considering the causes of treatment interruption. Interestingly, patients enrolled in the Oncology Unit were more likely to interrupt treatment due to AEs than patients enrolled in the Hepatology Unit (73.3% *vs* 27.6%, $P = 0.01$).

The overall incidence of AEs during the treatment period was 93.2%. As shown in Table 2, fatigue was the most frequently observed AE, and occurred in 2 out of 3 patients. Twenty-eight patients (63.7%) presented 2 or more AEs during treatment, irrespective of the grade. Remarkably, 25% and 11% of the whole series presented 3 or 4 AEs, respectively, and in one case (2.3%) 5 AEs were recorded. Grade 3 AEs were observed in 19/44 patients (43.2%), but no more than one grade 3 AE was observed in the same patient. In the 19 patients who stopped treatment because of AEs, grade 3 fatigue (7 patients) or hepatic AEs (8 patients) were those most frequently involved. Twenty-one patients (47.7%) required dose reduction or temporary interruption of sorafenib treatment. Considering the whole series, 28 patients (63.6%) received a mean daily dose of sorafenib greater than 400 mg. After excluding those patients whose treatment duration was lower than 4 wk, 24 out of 37 patients (64.9%) received more than 400 mg/d sorafenib. No significant differences in the overall occurrence of AEs was found comparing patients in Child A *vs* B classes. Grade 3 hepatic AEs tended to be more common in Child B patients, although this difference did not reach

statistical significance (33.3% *vs* 10.3%, $P = 0.099$). AEs occurred at a similar frequency comparing patients older or younger than 70 years or those in BCLC-C *vs* B stage. Biochemical parameters at the start and at the end of sorafenib therapy are shown in Table 3, subdivided according to the reason for interruption.

To identify possible predictors of the clinical response to sorafenib, we analyzed our series of patients after 16 wk of sorafenib treatment, defining a group with “clinical benefit”, as the composite of stable disease or partial response by CT/MR dynamic imaging. This group was compared to patients who showed progressive disease at this or earlier time points, or who interrupted treatment because of AEs. At the time of this evaluation, no complete responses were recorded, and no patients had died. Eighteen out of 44 patients (40.9%) had a clinical benefit at week 16, with 14 (31.8%) showing stable disease and 4 (9.1%) a partial response. Eleven patients (25%) had stopped because of a radiological progression and 15 (34.1%) due to the appearance of unacceptable AEs. Univariate analysis of the parameters associated with clinical benefit demonstrated that ECOG performance status 0, cirrhosis of non-viral etiology and BCLC-B stage of disease were significantly associated with a clinical benefit at week 16 (Table 4). In a multivariate model, only BCLC-B and the presence of non-viral cirrhosis emerged as independent predictors of clinical benefit after 16 wk of treatment (Table 4). When a sub-analysis comparing patients infected with Hepatitis C virus (HCV) or Hepatitis B virus (HBV) was performed, no significant differences in survival were observed.

Median overall survival was 11.4 mo (range 7.1-15.7) (Figure 1A). At the time of analysis, 8 patients were still alive, none of them continuing sorafenib. In univariate analysis we found that ECOG performance status ≥ 1 , presence of metastases or macrovascular invasion, BCLC-C stage, and elevated baseline levels of alpha-fetoprotein (AFP) or alkaline phosphatase (ALP) were significantly related to a shorter overall survival (Table 5). The multivariate model (Table 6) indicated that the presence of symptoms (ECOG performance status ≥ 1), macrovascular invasion, high levels of ALP or AFP at admission were independent predictors of mortality. Figure 1B and C show Kaplan-Meier curves for the series of patients stratified according to AFP or ALP levels, respectively.

DISCUSSION

Sorafenib is the only systemic therapy approved for HCC in its advanced stage and has also been proposed for patients with otherwise untreatable, intermediate stage HCC^[13]. In this study, we report data from a group of patients with HCC and a definite diagnosis of cirrhosis, consecutively recruited in single, tertiary referral center. Tolerability of sorafenib treatment was slightly lower than the one reported in the registration studies, in particular the SHARP trial (93% *vs* 80% incidence of AEs)^[3], and

Table 3 Changes in laboratory parameters at the beginning and the end of sorafenib treatment according to the reason of treatment interruption

			Bilirubin (mg/dL)	gGT (U/L)	ALP (U/L)	Platelets/mm ³	INR	AST (U/L)	AFP (ng/mL)
Patients with treatment suspension due to progressive disease (<i>n</i> = 25; median treatment duration 19 wk)	Baseline	mean (SD)	1.3 (0.8)	192.5 (187.5)	173.8 (92.5)	143160 (83075.6)	1.18 (0.25)	66.5 (35.7)	3668.6 (8533.3)
		med (min-max)	1.2 (0.2-3.5)	114 (41-648)	142 (64-436)	125000 (50000-337000)	1.10 (0.9-2.2)	66 (3.6-191)	18.8 (2.7-28136)
	End of treatment	mean (SD)	2.3 (1.7)	256.4 (276.8)	225.4 (196.3)	151360 (93196.4)	1.17 (0.26)	106.4 (97.8)	11060.4 (21903)
		median (min-max)	1.6 (0.3-6.4)	165 (20-1249)	182 (75-1048)	114000 (42000-426000)	1.1 (0.9-2.2)	71 (2-472)	83.4 (3.0-73434.5)
	Mann-Whitney test	<i>P</i> value	0.003	0.008	0.163	0.391	0.724	0.012	0.013
Patients with treatment suspension due to AEs (<i>n</i> = 19; median treatment duration 5 wk)	Baseline	mean (SD)	1.6 (0.7)	144.4 (107.4)	170 (83)	122125 (67280.4)	1.14 (0.92)	76.0 (38.6)	1739.0 (2841.1)
		med (min-max)	1.4 (0.6-3.1)	123 (40-416)	159.5 (65-345)	102000 (35000-254000)	1.1 (1.0-1.3)	66.5 (27-188)	70.6 (1.6-6836.9)
	End of treatment	mean (SD)	2.9 (2.8)	168.3 (147.1)	218.8 (142.8)	135500 (75371.1)	1.14 (0.17)	91.1 (41.5)	2204.4 (4406.1)
		median (min-max)	2.3 (0.7-12.2)	121.5 (40-525)	183 (75-515)	123000 (37000-277000)	1.05 (1.0-1.4)	83.5 (27-153)	124.1 (2.1-14000)
	Mann-Whitney test	<i>P</i> value	0.029	0.441	0.051	0.147	0.891	0.125	0.333

gGT: Gamma-glutamyltranspeptidase; ALP: Alkaline phosphatase; AST: Aspartate transaminase; AFP: Alpha-fetoprotein; INR: International normalized ratio.

Table 4 Univariate and multivariate analysis of the factors associated with a 16-week “clinical benefit” as defined by the presence of partial response or stable disease at imaging, according to modified Response Evaluation Criteria in Solid Tumors criteria

Variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	<i>P</i> value	OR (95%CI)	<i>P</i> value
ECOG				
0	1 (ref.)	0.013	²	²
1-2	0.18 (0.05-0.70)			
Cirrhosis etiology				
Non-viral	1 (ref.)	0.040	1 (ref.)	0.043
HCV or HBV ¹	0.23 (0.06-0.94)		0.21 (0.05-0.95)	
HCV infection				
Absent	1 (ref.)	0.032	²	²
Present	0.24 (0.07-0.88)			
BCLC class				
B	1 (ref.)	0.003	1 (ref.)	0.004
C	0.12 (0.03-0.48)		0.10 (0.02-0.49)	
Previous therapy				
No	1 (ref.)	0.172	²	²
Yes	0.42 (0.12-1.45)			
AFP (ng/mL)				
≤ 400	1 (ref.)	0.069	²	²
> 400	0.28 (0.07-1.10)			

¹Including patients with other concurrent etiologies; ²Removed during the stepwise variable selection, not included in the final multivariate model. AFP: Alpha-fetoprotein; HCV: Hepatitis C virus; HBV: Hepatitis B virus; ECOG: Eastern Cooperative Oncology Group; BCLC: Barcelona clinic liver cancer.

was similar to other field practice studies^[13]. It should be kept in mind that sorafenib is a non-curative treatment, and therefore maintenance of the best possible quality of life should always be considered as an essential target in these patients^[15,14]. We found that the impact of AEs was more marked than in the SHARP trial, because fatigue was complained by two thirds of our patients, and in one fourth of these it reached grade 3 severity. In all patients

who complained of fatigue, this symptom had a major influence on the quality of life, and was the cause of dose reduction in several cases. We also observed a higher incidence of grade 3 hepatic AEs, which are particularly worrisome in patients with cirrhosis such as the ones investigated in this study. It is important to emphasize that almost half of the whole group of patients (19/44) could not continue therapy due to intolerable AEs, and in 15 out of these 19 patients (78.9%) treatment interruption was related to grade 3 fatigue or hepatic AEs. Of note, we observed a significantly shorter median duration of treatment in patients who interrupted treatment due to AEs. This may reflect on patient management, as close follow-up with office visits together with early and aggressive symptomatic therapy may maximize the possibility to drive the patient through this initial critical phase of the therapy. On the other hand, a prompt recognition of initial signs of hepatic AEs may avoid an eventual and possibly fatal deterioration of liver function.

A somehow surprising finding of this study is the lack of difference in terms of AEs incidence or AE-related treatment interruption comparing Child A *vs* Child B patients. These results may be at least partially dependent on the low number of patients and on the fact that all Child-Pugh B patients were extremely well compensated. Nonetheless, Child-Pugh B patients may still have a higher propensity to deteriorate hepatic function, as a trend towards a higher frequency of severe hepatic AEs was observed. Together with data available in the literature^[15-20], the results of the present study indicate that sorafenib therapy could be reasonably proposed to ‘borderline’ Child Pugh B patients, such as the ones described herein. However, close monitoring by a multidisciplinary group involving a Hepatologist is critical, as suggested by the observation that cirrhotic patients enrolled in an Oncology Unit were more likely to interrupt treatment due to AEs, although this did not translate into any differ-

Table 5 Univariate analysis of factors associated with overall survival in 44 patients with hepatocellular carcinoma and cirrhosis treated with sorafenib

Variable	n	Overall survival	
		HR (95%CI)	P value
Gender			
Male	38	1 (ref.)	0.437
Female	6	1.52(0.53-4.38)	
ECOG			
0	24	1 (ref.)	0.049
1-2	20	2.01(1.01-4.05)	
Age, yr			
< 70	22	1 (ref.)	0.297
≥ 70	22	1.43 (0.73-2.78)	
Cirrhosis etiology			
Non-viral	12	1 (ref.)	0.832
HCV or HBV ¹	32	1.09 (0.51-2.34)	
Extrahepatic spread			
Absent	35	1 (ref.)	0.049
Present	9	2.26 (1.01-5.10)	
Portal thrombosis			
Absent	36	1 (ref.)	0.043
Present	8	2.52 (1.03-6.16)	
HBV infection			
Absent	32	1 (ref.)	0.279
Present	12	0.64 (0.29-1.43)	
HCV infection			
Absent	23	1 (ref.)	0.423
Present	21	1.32 (0.67-2.57)	
Esophageal varices			
Absent	28	1 (ref.)	0.883
Present	16	1.06 (0.52-2.14)	
Child Pugh score			
A	29	1 (ref.)	0.085
B	15	1.98 (0.91-4.29)	
BCLC class			
B	15	1 (ref.)	0.007
C	29	2.89 (1.34-6.25)	
Previous therapy			
No	19	1 (ref.)	0.526
Yes	25	1.25 (0.63-2.49)	
Bilirubin (mg/dL)			
≤ 1.5	27	1 (ref.)	0.124
>1.5	17	1.76 (0.86-3.60)	
gGT (U/L)			
≤ 48	5	1 (ref.)	0.483
> 48	39	1.54 (0.46-5.14)	
ALP (U/L)			
≤ 120	13	1 (ref.)	0.013
>120	31	3.20 (1.28-7.98)	
Platelets/mm ³			
≤ 150000	28	1 (ref.)	0.317
> 150000	16	0.69 (0.33-1.43)	
AST (U/L)			
≤ 40	9	1 (ref.)	0.388
> 40	35	1.52 (0.59-3.94)	
AFP (ng/mL)			
≤ 40	22	1 (ref.)	0.016
> 40	22	2.38 (1.18-4.80)	
AFP (ng/mL)			
≤ 400	27	1 (ref.)	0.017
> 400	17	2.38 (1.17-4.86)	
Interruption due to disease progression			
No	19	1 (ref.)	0.238
Yes	25	0.67 (0.34 - 1.31)	

¹Including patients with other concurrent etiologies. gGT: Gamma-glutamyl-transpeptidase; ALP: Alkaline phosphatase; AST: Aspartate transaminase; AFP: Alpha-fetoprotein; HCV: Hepatitis C virus; HBV: Hepatitis B virus; ECOG: Eastern Cooperative Oncology Group; BCLC: Barcelona clinic liver cancer.

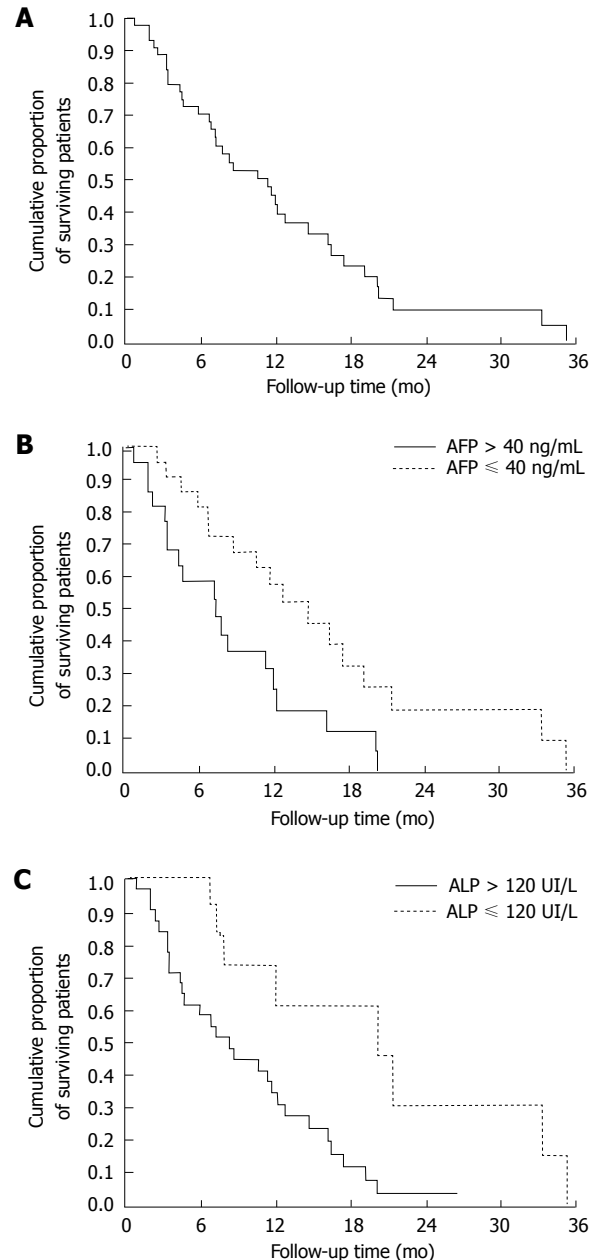


Figure 1 Kaplan-Meier survival curves of patients enrolled in this study. Forty-four patients with hepatocellular carcinoma and established cirrhosis were enrolled and treated with sorafenib. A: Overall survival; B: Survival of patients stratified according to their baseline alpha-fetoprotein (AFP) levels ($P = 0.021$); C: Survival of patients stratified according to their baseline alkaline phosphatase (ALP) levels ($P = 0.017$).

ences in survival. Interestingly, we did not find any differences in the overall appearance of AEs in a sub-analysis performed according to the age of the patients (below or above 70 years), in agreement with data from a Korean study^[21]. This is particularly relevant, as in Western countries HCC is increasingly observed in the elderly^[22].

A common clinical problem is the need to inform patients on the possible outcomes of sorafenib therapy in the medium term. For this reason, we analyzed the “clinical benefit” afforded by sorafenib treatment at 16 wk as a composite of radiological stable disease or partial response, versus treatment interruption regardless of its

Table 6 Multivariate analysis of overall survival in 44 patients with hepatocellular carcinoma and cirrhosis treated with sorafenib

Variable	OS		
	HR (95%CI)	Median OS in weeks (range)	P value
ECOG			
0	1 (ref.)	50.2 (9.3-153.1)	0.031
1-2	2.36 (1.08-5.16)	29.0 (2.9-92.6)	
Extrahepatic spread			
Absent	1 (ref.)	45.9 (8.1-153.1)	0.059
Present	2.41 (0.97-6.01)	19.1 (2.9-83)	
Portal thrombosis			
Absent	1 (ref.)	45.8 (2.9-153.1)	0.015
Present	3.33 (1.27-8.72)	29.9 (8.1-50)	
ALP (U/L)			
≤ 120	1 (ref.)	45.9 (16.6-153.1)	0.017
> 120	3.13 (1.23-8.00)	33.2 (2.9-115.4)	
AFP (ng/mL)			
≤ 40	1 (ref.)	52.5 (10.7-153.1)	0.021
> 40	2.33 (1.13-4.78)	31.0 (2.9-87.4)	

OS: Overall survival; ECOG: Eastern Cooperative Oncology Group; ALP: Alkaline phosphatase; AFP: Alpha-fetoprotein.

reason. This provides an indication of sorafenib efficacy at a time when the impact of early withdrawal due to AEs could be outbalanced by benefit in the subsequent weeks. Intermediate stage, and non-viral etiology of cirrhosis were independent predictors of clinical benefit at week 16 of treatment. These data support the potential usefulness of sorafenib in selected BCLC-B patients, in line with recent evidence reported in a sub-analysis of the SHARP trial or in field-practice studies^[13,23]. The possible significance of the predictive role of a non-viral etiology remains speculative, although in another, larger study the time to progression in HBV infected patients was not affected by sorafenib treatment^[23]. Both HBV and HCV have been shown to interact with the Raf pathway and/or to modulate angiogenesis^[24-27]. As these biologic actions are two of the major targets of sorafenib, viral infection may translate in a lower sensitivity to treatment. Although cirrhosis caused by HBV or HCV has generally different outcomes and prognosis, we found no significant differences in clinical benefit and overall survival comparing these two groups of patients. This result could be related to the small number of patients enrolled, although at this time no clear associations between the type of viral infection and the outcome of HCC patients treated with sorafenib have been reported.

Median overall survival of the patients included in the present study was comparable to the one of the SHARP study and of the largest field-practice studies published so far^[3,13,15], indicating that selection of the patients was similar to what reported by other groups treating patients with advanced HCC. Macrovascular invasion and extrahepatic spread were strong predictors of survival, as reported in other studies^[13,17,28], confirming the prognostic significance of the BCLC classification, where these parameters characterize transition from stage B to

C. Moreover, a performance status greater than 0 was associated with a 2-fold greater risk of shorter overall survival, in agreement with data reported by the SOFIA group^[13]. However, when evaluating the significance of performance status in HCC, the presence of cirrhosis should be considered, which by itself has an impact on the quality of life of the patient^[29].

Increased AFP baseline levels were found to confer a risk of mortality 2.33 times higher than patients below that limit. A possible role of AFP as a predictor of mortality in HCC has been reported in other field practice studies^[3,15,18,21], but the observed cut-off values were usually in a higher range. AFP levels have been shown to be associated with activation of the progenitor cell compartment and to correlate with a 'hepatoblastoma' signature in transcriptomic studies^[30]. Similar considerations may be made for the role of ALP, because patients with abnormal levels had a more than three times higher risk of shorter survival at multivariate analysis. ALP levels have been reported to predict survival in patients treated with different modalities^[31-33], although its role during systemic therapy has not been completely established. The pathophysiological significance of this parameter remains uncertain, although it may be related to invasion of the smaller bile ducts as expression of the tendency of HCC to infiltrate adjoining structures. Taken together, data related to AFP and ALP indicate that simple baseline biochemical parameters may help to frame the patient in the most appropriate prognostic group.

Several limitations of the present study should be acknowledged, particularly the relatively small number of patients enrolled. On the other hand, although other studies have been published since sorafenib approval in 2008, in few cases a detailed analysis of patients with established cirrhosis associated with HCC has been conducted. Another limitation is related to the lack of histologic biomarkers to be possibly correlated with clinical outcomes. The fact that in cirrhotic patients imaging studies are usually sufficient to make a diagnosis of HCC^[2] has considerably limited the use of biopsy, an invasive procedure, but has hindered the discovery of molecular factors associated with prognosis. Although no molecular predictors of the response to sorafenib have yet been identified, additional investigation is warranted to try to select those patients who are more likely to benefit from a therapy which is expensive and sometimes difficult to tolerate.

In conclusion, in patients with cirrhosis and HCC treated with sorafenib, early management of AEs is critical, as they present in the large majority of patients and are a common cause of early withdrawal of the treatment. Tumor vascular invasion and extrahepatic spread are the most relevant factors conditioning early response to treatment and survival. Moreover, tumor burden rather than parameters of liver function is critically relevant in the prognosis of these patients. Finally, common baseline biochemical parameters, such as AFP and ALP allow to identify patients at higher risk of a shorter overall survival.

COMMENTS

Background

Sorafenib has been recently approved for the treatment of hepatocellular carcinoma, but only limited information is available on its effects in conditions of everyday practice. This is particularly true when patients with a clear diagnosis of cirrhosis are considered. Due to the high costs of sorafenib therapy and the burden of side effects, it is very important to obtain information on the predictors of survival and of clinical response in patients treated with this drug, especially in the presence of established cirrhosis.

Research frontiers

The registration studies showing the efficacy of sorafenib in prolonging survival of patients with advanced hepatocellular carcinoma have given a great impulse to further research trying to better define which patients have a higher likelihood to benefit from treatment with this drug. This topic has a high clinical relevance and generates major efforts.

Innovations and breakthroughs

Identification of the predictive parameters of the response to sorafenib has been the focus of several studies after approval of this drug. Cirrhotic patients are extremely fragile and difficult to treat, and therapy with systemic agents should be conducted with great care. The authors found that parameters related to the tumor (extrahepatic spread, vascular invasion), and the patient (e.g., laboratory tests including alpha-fetoprotein or alkaline phosphatase, or the patient's performance status) are predictors of overall survival in this group.

Applications

Data presented in this study provide useful clinical information for the management of cirrhotic patients with advanced hepatocellular carcinoma.

Terminology

Hepatocellular carcinoma is the most prevalent primary liver tumor and is notoriously difficult to treat. It is associated in the great majority of cases with chronic liver injury or cirrhosis. Sorafenib is a multi-kinase inhibitor approved for the treatment of advanced hepatocellular carcinoma. It acts both limiting tumor-associated angiogenesis and tumor cell proliferation.

Peer review

In this manuscript, the Authors reported the efficacy and safety of sorafenib for hepatocellular carcinoma in patients with cirrhosis, and analyzed biomarker as predictors of outcomes. The results obtained seem to be reasonable and have some new information. The paper is well written, although there are some drawbacks, particularly the fact that the size of study is small.

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