Research Article

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Relationship between baseline hepatic status and outcome, and effect of sorafenib on liver function: SHARP trial subanalyses☆

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Background & Aims: Hepatic markers are utilized in many classification systems of patients with hepatocellular carcinoma and, by measuring organ damage and tumor stage, can influence treatment. Moreover, elevated serum concentrations of aminotransferases and alpha-fetoprotein are indicators of poor prognosis in patients with hepatocellular carcinoma. We examined the effects of sorafenib on hepatic markers by performing exploratory subset analyses of the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial in patients categorized by baseline concentrations of alanine aminotransferase/aspartate aminotransferase, alpha-fetoprotein, and bilirubin; and by evaluating the effects of sorafenib on bilirubin concentrations during treatment.

Methods: Patients (n = 602) were grouped by baseline concentrations of alanine aminotransferase/aspartate aminotransferase (not significantly elevated, mildly elevated, or moderately elevated), alpha-fetoprotein (normal or elevated), and bilirubin (normal or elevated). Bilirubin was measured at baseline and on day 1 of each cycle.

Results: Patients with elevated baseline concentrations of alanine aminotransferase/aspartate aminotransferase, alpha-fetoprotein, or bilirubin had shorter overall survival (OS) than those with normal baseline concentrations, irrespective of treatment group. No notable differences in safety profiles were observed between patients with normal *vs.* elevated alanine aminotransferase/aspartate aminotransferase, alpha-fetoprotein, or bilirubin. Median changes from baseline in bilirubin concentration at the last cycle of treatment were +0.17 and +0.19 mg/dl in the sorafenib and placebo groups, respectively.

Conclusions: These subset analyses suggest that sorafenib is safe and effective for hepatocellular carcinoma, irrespective of baseline alanine aminotransferase/aspartate aminotransferase, alpha-fetoprotein, or bilirubin concentration and that hepatic function remains stable over the course of sorafenib therapy.

Cancer

Keywords: Sorafenib; Alanine aminotransferase; Aspartate aminotransferase; Alpha-fetoprotein; Bilirubin; Hepatic markers.
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Abbreviations: HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; OS, overall survival; ALT, alanine aminotransferase; AST, aspartic aminotransferase; SHARP, Sorafenib HCC Assessment Randomized Protocol; AP, Sorafenib Asia-Pacific Trial; TTP, time to disease progression; ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal; DCR, disease control rate; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; NCI–CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events; HR, hazard ratio; CI, confidence interval; AE, adverse event; SAE, serious adverse event.

Introduction

Abnormalities in hepatic marker concentrations have been shown to be an adverse prognostic indicator in patients with hepatocellular carcinoma (HCC). For example, a large cohort study of patients with unresectable HCC found that elevated bilirubin, alkaline phosphatase, and alpha-fetoprotein (AFP) concentrations were all significantly correlated with adverse prognosis [1]. Median overall survival (OS) was shorter in patients with elevated than with normal AFP concentrations, even in the presence of portal vein thrombosis, large or bilobar tumors, or cirrhosis. In a study of 606 patients divided into quartiles by AFP level, median survival was inversely correlated with increasing concentrations of AFP [2]. Furthermore, a recent retrospective analysis of 201 patients with sorafenib-treated, metastatic HCC indicated that serum concentrations of AFP, bilirubin, and albumin were significantly associated with OS and failure-free survival [3]. In addition to elevated AFP levels, laboratory markers of cholestasis and hepatocellular injury, including alkaline phosphatase, bilirubin, alanine aminotransferase (ALT), and aspartic aminotransferase (AST) concentrations, have been shown to be independent markers of poor prognosis and have been incorporated into a variety of HCC staging and prognostic schemes [4–13].

Advances in molecular oncology and rational drug design have led to the development of targeted therapies for a variety of hematologic and solid tumors, including HCC [14–16]. Sorafenib is a potent multikinase inhibitor that targets the RAF/MEK/ERK pathway as well as growth factor receptors such as VEGF-1/2/3, PDGFR-b, KIT, FLT-3, and RET [17–19].

Two large, randomized, placebo controlled, phase III clinical trials—the Sorafenib HCC Assessment Randomized Protocol (SHARP) and the Sorafenib Asia-Pacific (AP) trial—showed that sorafenib significantly enhanced median OS in patients with advanced HCC [20,21]. Because of the impact of hepatic markers on outcomes of patients with HCC, we performed a series of exploratory subset analyses, based on baseline serum concentrations of aminotransferases, AFP, and total bilirubin, to examine the effects of sorafenib on OS and time to disease progression (TTP) in subsets of patients enrolled in the SHARP trial. We also assessed the effects of sorafenib on hepatic function, as indicated by bilirubin concentrations, during the course of treatment.

Materials and methods

SHARP study

The design of the SHARP trial, a multinational, randomized, double blind, placebo-controlled trial comparing sorafenib with placebo in patients with advanced HCC, has been described in detail [20]. Briefly, 602 patients with advanced HCC were randomized 1:1 to receive sorafenib (400 mg twice daily) or matching placebo. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status $\leqslant$2; Child-Pugh liver function class A; and adequate hematologic, hepatic, and renal function. Patients were stratified by geographic region, ECOG performance status (0 *vs.* 1 or 2), and the presence or absence of macroscopic vascular invasion (portal vein or branches or extrahepatic spread).

Hepatic marker subanalyses

The population for subset analyses was the intent-to-treat population, defined as all randomized patients. Patients were analyzed by baseline serum concentrations of ALT/AST (not significantly elevated [<1.8 $\times$ upper limit of normal (ULN)], mildly elevated [1.8–3.0 $\times$ ULN], or moderately elevated [>3.0 $\times$ ULN], AFP (normal [$\leqslant$ULN], moderately elevated [>ULN-400 ng/ml], or highly elevated [>400 ng/ml]); and total bilirubin (normal [$\leqslant$ULN] or elevated [>ULN]). Bilirubin was measured at baseline and on day 1 of each cycle. The population for safety analysis included all patients who received at least one dose of sorafenib or placebo. Endpoints assessed included OS; TTP, based on independent radiologic review; disease control rate (DCR); and safety. OS was measured from the date of randomization until death from any cause; and TTP was measured from the date of randomization until disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST). DCR was defined as the percentage of patients who had a best response of complete response (CR), partial response (PR), or stable disease (SD) for $\geqslant$4 weeks from the first demonstration of stabilization, based on independent radiologic review. Safety was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI–CTCAE) version 3.0.

Table 1. Baseline characteristics of patients categorized by baseline concentrations of aminotransferases (AST/ALT), α-fetoprotein (AFP), and bilirubin.

	All patients		ALT/AST levels						AFP levels						Bilirubin levels			
			Not significantly elevated		Mildly elevated		Moderately elevated		Normal		Mildly elevated		Moderately elevated		Normal		Elevated	
	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla
n	299	303	152	153	77	78	68	72	111	97	78	86	93	108	225	226	72	77
Median age, yr (range)	67 (21-89)	68 (21-86)	67 (33-87)	69 (21-82)	66 (21-89)	68 (39-86)	65 (21-81)	68 (40-82)	67 (21-87)	68 (21-80)	66 (39-84)	69 (40-82)	67 (39-89)	67 (43-86)	67 (21-89)	68 (21-86)	66 (28-82)	67 (21-82)
Male, %	87	87	88	88	86	89	87	85	85	87	86	87	89	88	85	87	92	87
Child–Pugh class A, %	95	98	98	99	95	99	88	94	93	98	96	99	99	98	97	100	88	94
EHS, %	53	50	57	52	51	41	50	54	52	49	51	49	56	50	56	51	44	46
MVI, %	36	41	34	33	40	41	38	56	28	36	49	34	37	50	36	39	39	46
ECOG PS, %																		
0	54	54	59	58	44	55	53	46	53	60	64	52	46	49	55	58	50	42
1	38	39	35	37	47	36	37	44	42	36	31	41	38	40	38	35	39	48
2	8	7	7	5	9	9	10	10	5	4	5	7	16	11	7	6	11	10
Etiology, %																		
HBV	19	18	20	20	20	13	15	21	26	25	21	24	30	29	18	19	22	17
HCV	29	27	13	20	44	32	49	38	21	20	21	19	14	18	27	27	35	26
Alcohol	26	26	34	30	20	23	16	22	26	20	31	38	31	27	28	24	22	35

EHS, extrahepatic spread; MVI, microvascular invasion; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; ALT, alanine aminotransferase; AST, aspartic aminotransferase; AFP, alpha-fetoprotein; Sor, sorafenib; Pla, placebo.

Statistical analysis

In the subgroups categorized by AST/ALT, AFP, and bilirubin concentrations, OS and TTP were estimated by Kaplan–Meier analysis. The hazard ratio (HR) and 95% confidence interval (CI), calculated from Cox regression analyses with only treatment in the model were estimated for sorafenib compared with placebo in all subgroups. DCR was calculated as a percentage. Adverse events (AEs) were summarized descriptively, and the incidence of treatment-emergent and drug-related treatment-emergent serious AEs (SAEs) and drug-related treatment-emergent AEs in the sorafenib and placebo subgroups was compared. Concentrations of total, conjugated, and unconjugated bilirubin, and changes of each of them relative to baseline concentration, were measured over time.

Results

Baseline characteristics

In patients categorized by baseline concentrations of ALT/AST, AFP, and bilirubin, the relationship between baseline characteristics of patients in the SHARP trial, including median age, gender, Child-Pugh class, extrahepatic spread, microvascular invasion, ECOG performance status, etiology (chronic hepatitis B, hepatitis C, or alcohol), and hepatic markers, is shown in Table 1. When patients were grouped by concentrations of hepatic markers (i.e. baseline ALT/AST, AFP, and bilirubin concentrations), there were no differences in baseline characteristics between the sorafenib and placebo groups. Our data confirm the prognostic value of these parameters, as shown in the placebo arm. Elevated aminotransferase concentrations were associated with a more aggressive disease, as shown by shorter TTP and OS and a lower DCR rate, as well as elevated AFP and bilirubin concentrations. It is particularly noteworthy that patients in the placebo group with AFP >400 ng/ml had very aggressive disease, with a very low DCR rate and short TTP and OS (6.0 months).

Efficacy

ALT/AST: Three subsets were included in the analysis of baseline ALT/AST concentrations (Fig. 1): patients with not significantly elevated (<1.8 × ULN; n = 305), mildly elevated (1.8–3.0 × ULN; n = 155), and moderately elevated (>3.0 × ULN; n = 140) ALT/AST concentrations. In patients with not significantly elevated ALT/AST concentrations, median OS (11.6 *vs.* 8.8 months) and median TTP (5.7 *vs.* 3.9 months) were longer with sorafenib (n = 152) than with placebo (n = 153), and the DCR rate (52.6% *vs.* 38.6%) was higher (Table 2). Patients with mildly elevated ALT/AST concentrations had a longer median OS (9.5 *vs.* 8.5 months) and TTP (5.3 *vs.* 2.8 months) and a higher DCR (36.4% *vs.* 28.2%) with sorafenib (n = 77) than with placebo (n = 78). In patients with moderately elevated ALT/AST concentrations, sorafenib (n = 68) was associated with a longer median OS (6.3 *vs.* 4.6) and TTP (5.8 *vs.* 2.6 months) and a higher DCR (32.4% *vs.* 20.8%) than placebo (n = 72).

AFP: Three subsets were included in the analysis of baseline AFP concentrations (Fig. 2): patients with normal (⩽ULN; n = 208), mildly elevated (>ULN to 400 ng/ml; n = 164), and moderately elevated (>400 ng/ml; n = 201) AFP levels (Fig. 2). In patients with normal AFP concentrations, sorafenib (n = 111) enhanced median OS (12.4 *vs.* 9.5 months) and median TTP (9.6 *vs.* 4.1 months) but had little effect on DCR (47.8% *vs.* 41.2%) compared with placebo (n = 97; Table 2). In patients with mildly elevated AFP concentrations, sorafenib (n = 78) increased median OS (10.3 *vs.* 8.5 months) and TTP (6.7 *vs.* 3.9 months) but had little effect on DCR (39.7% *vs.* 36.1%) compared with placebo (n = 86). In patients with moderately elevated AFP concentrations, sorafenib (n = 93) increased median OS (7.0 *vs.* 6.0 months) and median TTP (4.9 *vs.* 2.7 months) and DCR (39.8% *vs.* 17.6%) compared with placebo (n = 108).

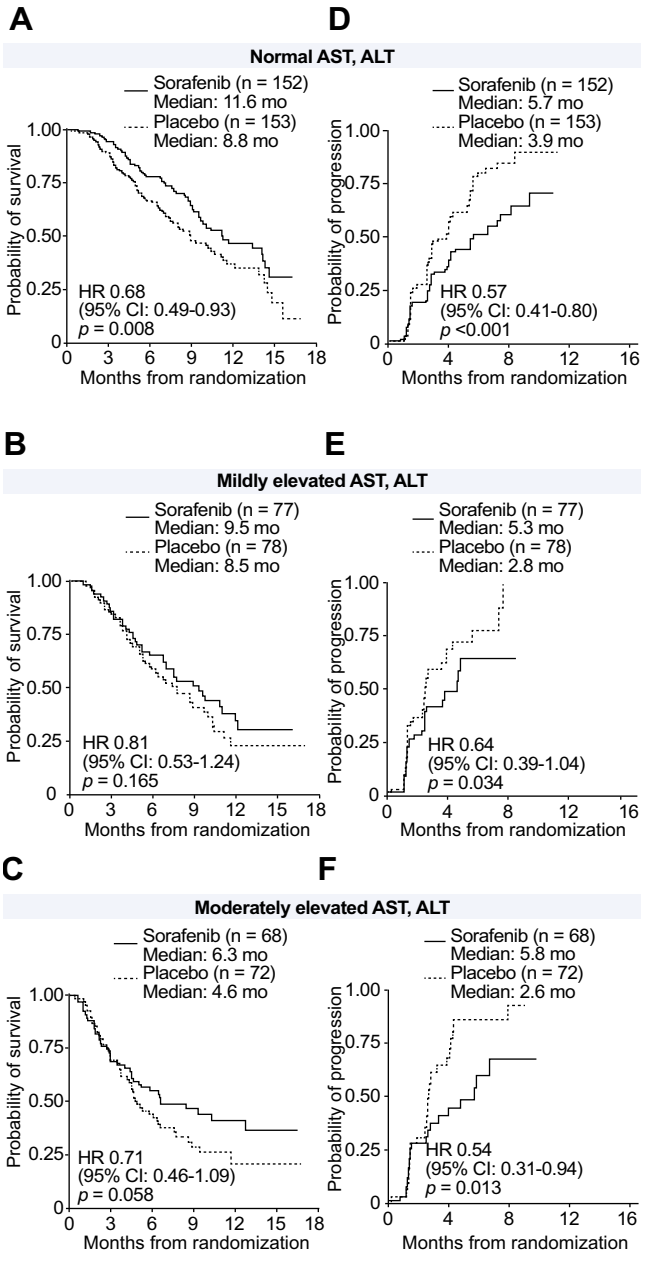

Fig. 1. Relationship between baseline alanine aminotransferase/aspartic aminotransferase (ALT/AST) concentrations and survival outcomes in patients enrolled in the SHARP trial. Overall survival (OS) in patients with (A) normal, (B) mildly elevated, and (C) moderately elevated baseline ALT/AST concentrations. Time to disease progression (TTP) in patients with (D) not significantly elevated, (E) mildly elevated, and (F) moderately elevated baseline ALT/AST concentrations.

Table 2. Efficacy of sorafenib for the treatment of HCC in patients categorized by baseline concentrations of aminotransferases (AST/ALT), α-fetoprotein (AFP), and bilirubin.

Subgroup domain	Group evaluated	n		OS (mo)			TTP (mo)			DCR (%)	
		Sor	Pla	Sor	Pla	HR (95% CI)	Sor	Pla	HR (95% CI)	Sor	Pla
Subgroup	All patients	299	303	10.7	7.9	0.69 (0.55-0.87)	5.5	2.8	0.58 (0.45-0.74)	43.5	31.7
ALT/AST levels	Not significantly elevated	152	153	11.6	8.8	0.68 (0.49-0.93)	5.7	3.9	0.57 (0.41-0.80)	52.6	38.6
	Mildly elevated	77	78	9.5	8.5	0.81 (0.53-1.24)	5.3	2.8	0.64 (0.39-1.04)	36.4	28.2
	Moderately elevated	68	72	6.3	4.6	0.71 (0.46-1.09)	5.8	2.6	0.54 (0.31-0.94)	32.4	20.8
AFP levels	Normal	111	97	12.4	9.5	0.76 (0.51-1.13)	9.6	4.1	0.72 (0.46-1.11)	47.8	41.2
	Mildly elevated	78	86	10.3	8.5	0.67 (0.43-1.04)	6.7	3.9	0.51 (0.31-0.84)	39.7	36.1
	Moderately elevated	93	108	7.0	6.0	0.77 (0.54-1.08)	4.9	2.7	0.57 (0.38-0.85)	39.8	17.6
Bilirubin levels	Normal	225	226	11.1	9.1	0.70 (0.54-0.91)	5.8	3.0	0.52 (0.39-0.69)	48.9	34.1
	Elevated	72	77	6.2	5.0	0.77 (0.51-1.15)	2.9	2.7	0.76 (0.46-1.26)	27.8	24.7

ALT, alanine aminotransferase; AST, aspartic aminotransferase; AFP, alpha-fetoprotein; OS, overall survival; TTP, time to progression; DCR, disease control rate; HR, hazard ratio; CI, confidence interval; Sor, sorafenib; Pla, placebo.

Bilirubin: Two subsets were included in the analysis of baseline total bilirubin concentrations (Fig. 3): patients with normal (⩽ULN; n = 451) and elevated (>ULN; n = 149) bilirubin levels. In patients with normal bilirubin concentrations, sorafenib (n = 225) enhanced median OS (11.1 *vs.* 9.1 months), TTP (5.8 *vs.* 3.0 months), and DCR (49.8% *vs.* 34.1%) compared with placebo (n = 226; Table 2). In patients with elevated bilirubin concentrations, sorafenib (n = 72) increased median OS (6.2 *vs.* 5.0 months) but had little effect on median TTP (2.9 *vs.* 2.7 months) and DCR (27.8% *vs.* 24.7%) compared with placebo (n = 77). Best responses relative to baseline concentrations of AST/ALT, AFP, and bilirubin are shown in Table 3.

Liver function during treatment

Baseline AFP and total bilirubin concentrations in the sorafenib and placebo groups were similar across cohorts. During the course of treatment, sorafenib did not significantly alter total bilirubin levels compared with placebo (Fig. 4). In the sorafenib group, however, there was a transient increase in total bilirubin, due primarily to an increase in conjugated bilirubin, during cycle 2 of treatment.

Safety

No notable differences in sorafenib safety profiles were observed in patients with normal and elevated AST/ALT, AFP, and bilirubin concentrations (Table 4). Drug-related AEs reported by patients receiving sorafenib were predominantly grade 1 or 2. Grade 3 or greater AEs were reported in 35% of patients in the sorafenib group and in 15% of patients in the placebo group. The most frequently reported AEs for patients in the sorafenib *vs.* the placebo group were hand-foot skin reactions (8% *vs.* <1%; p <0.001) and diarrhea (8% *vs.* 2%; p <0.001).

Discussion

These exploratory subset analyses of patients in the randomized, double blind, placebo-controlled, phase III SHARP trial showed that sorafenib was safe and effective for patients with advanced HCC, irrespective of baseline concentrations of hepatic markers. Although patients with elevated baseline concentrations of ALT/AST, AFP, and total bilirubin had shorter OS and TTP and lower DCR than those with normal baseline concentrations of these enzymes, regardless of treatment arm, within each subcategory, OS and TTP remained longer and DCR remained higher in patients who received sorafenib than in those who received placebo. This suggests that sorafenib has benefits for these patients, regardless of the degree of abnormality. These subset analyses also suggest that sorafenib remained safe and tolerable, irrespective of baseline hepatic marker concentration. Nevertheless, the results of these exploratory unplanned subset analyses are limited by the small numbers of patients in each subset, precluding definitive statistical analysis.

Our findings are consistent with those of a retrospective, multicenter study of sorafenib in 59 patients with advanced, unresectable HCC, mild-to-advanced-stage cirrhosis and Child-Pugh class A (n = 26), B (n = 23), or C (n = 10) liver function [22]. The median OS in the 51 intention-to-treat patients was 6.5 months (range, 0.4–17.4 months) and the median TTP was 2.8 months (range, 1.4–6.5 months). Univariate analysis showed that improved hepatic marker concentration was associated with longer OS. In addition, most of the drug-related AEs were grades 1–2 and were

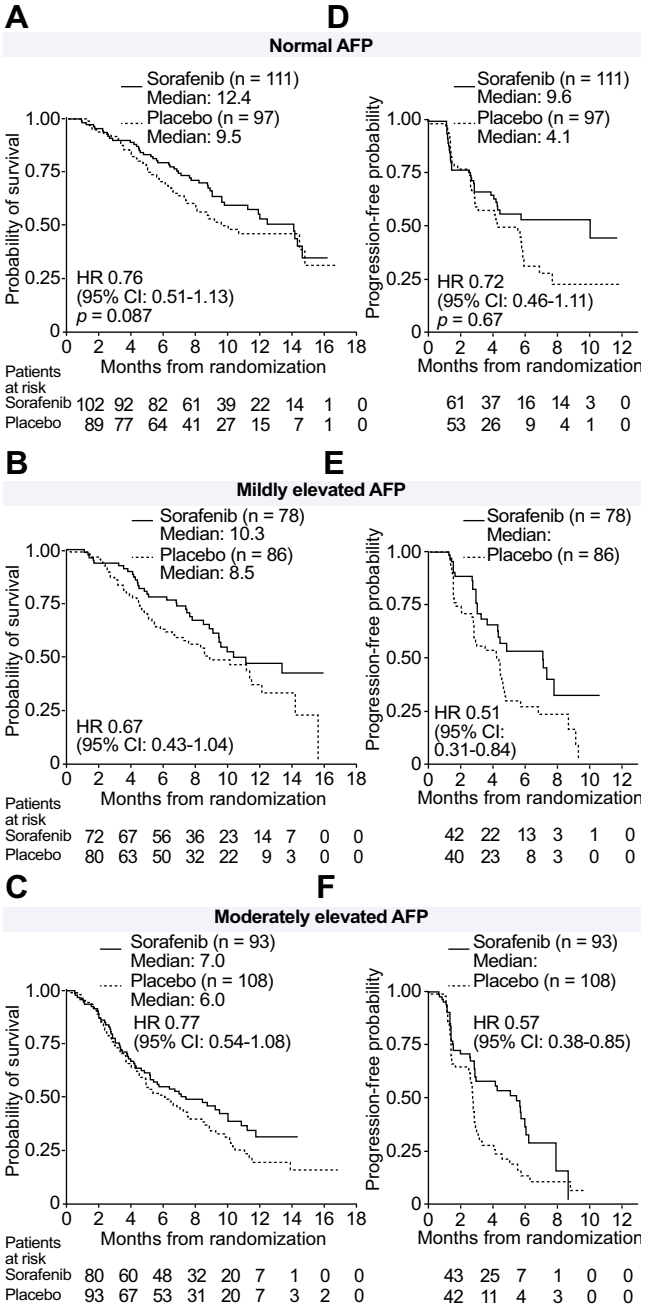

Fig. 2. Relationship between baseline alpha-fetoprotein (AFP) concentrations and survival outcomes in patients enrolled in the SHARP trial. Overall survival (OS) in patients with (A) normal, (B) mildly elevated, and (C) moderately elevated baseline AFP concentrations. Progression-free survival (PFS) in patients with (D) normal, (E) mildly elevated, and (F) moderately elevated baseline AFP concentrations.

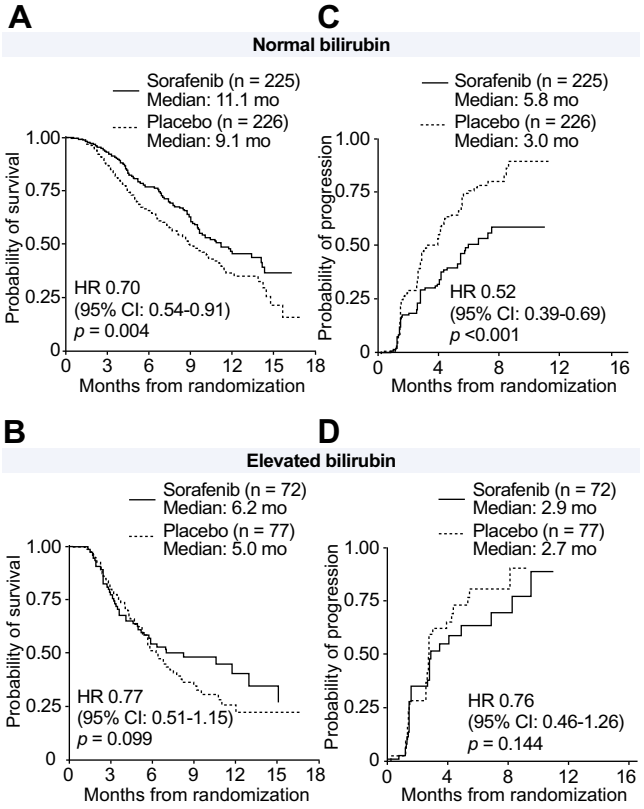

Fig. 3. Relationship between baseline bilirubin concentrations and survival outcomes in patients enrolled in the SHARP trial. Overall survival (OS) in patients with (A) normal and (B) elevated baseline bilirubin concentrations. Time to disease progression (TTP) in patients with (C) normal and (D) elevated baseline bilirubin concentrations.

manageable. These results, in which >50% of patients had Child-Pugh classes B and C liver function, as well as our subset analyses, indicate that, although enrollment in the SHARP trial was restricted to patients with well-preserved liver function (Child-Pugh class A), sorafenib was of benefit in patients with impaired hepatic function.

Various staging systems are used for the prognosis of patients with HCC, with several utilizing the results of liver function testing and AFP concentrations [23]. Although aminotransferases are sensitive indicators of hepatocellular injury, they are not components of any of the common HCC prognostic and staging schemes [24]. The release of ALT and AST into the blood has been shown to increase as the cell membranes of injured or dying hepatocytes lose their integrity. Thus, elevated concentrations of these enzymes reflect ongoing liver damage. Elevated concentrations of these aminotransferases in patients with HCC may result from ischemic necrosis of hepatocytes immediately adjacent to one or more tumor masses, HCC-associated steatohepatitis, or ongoing chronic hepatitis B or C infection [25]. The absence of aminotransferase concentrations from current staging systems may be due to the inability of conventional assays to measure total ALT, only the fraction that is enzymatically active [26]. Alternatively, elevated aminotransferase levels may reflect tumor-induced liver damage or the ability of a patient's liver to withstand the rigors of chemotherapy rather than locoregional treatment. For example, we found that median OS rates in sorafenib-treated patients with mild and moderately elevated ALT/AST concentrations were 2.1 and 5.3 months shorter, respectively, than those in patients with normal ALT/AST concentrations.

AFP is a glycoprotein that is normally released by the fetal liver and yolk sac [27]. Elevated concentrations of this protein have been reported in patients with HCC, gonadal tumors, and

Table 3. Summary of best response by baseline concentrations of aminotransferases (AST/ALT), α-fetoprotein (AFP), and bilirubin.

	All patients		ALT/AST levels						AFP levels						Bilirubin levels			
			Not significantly elevated		Mildly elevated		Moderately elevated		Normal		Mildly elevated		Moderately elevated		Normal		Elevated	
	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla
n	299	303	152	153	77	78	68	72	111	97	78	86	93	108	225	226	72	77
Complete response, %	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Partial response,%	2.3	0.7	4.6	0.7	0	1.3	0	0	2.7	1.0	1.3	0	3.2	0.9	3.1	0.9	0	0
Stable disease, %	70.6	67.3	75.0	71.9	68.8	62.8	64.7	62.5	71.2	74.2	82.1	73.3	60.2	58.3	74.7	69.0	59.7	62.3
Progressive disease, %	18.1	24.1	16.5	23.5	20.8	28.2	19.1	20.8	18.9	17.5	10.3	24.4	23.7	28.7	16.4	24.8	23.6	22.1
Disease control rate*, %	43.5	31.7	52.6	38.6	36.4	28.2	32.4	20.8	47.8	41.2	39.7	36.0	39.8	17.6	48.9	34.1	27.8	24.7

*Proportion of patients with a best response rating of complete response, partial response, or stable disease, according to RECIST criteria maintained for ⩾28 days from first demonstration of that rating. ALT, alanine aminotransferase; AST, aspartic aminotransferase; AFP, alpha-fetoprotein; Sor, sorafenib; Pla, placebo.

gastrointestinal malignancies (e.g. gastric cancer), and mildly elevated concentrations of AFP have been observed in patients with hepatitis. Although AFP concentration has not been directly correlated with the size or stage of HCC, it offers prognostic information and is a component of several HCC staging systems [7–9,28,29]. Indeed, we found that median OS rates in sorafenib-treated patients with mild or moderately elevated AFP concentration were 2.1 and 5.4 months shorter, respectively, than in patients with normal AFP concentration. In comparison, a recent trial in patients with HCC and baseline serum AFP concentration >20 ng/ml reported that a >20% decrease in baseline AFP concentration after 6 weeks of treatment with sorafenib in patients with HCC was a significant predictor of clinical benefit, defined as a best response of complete response, partial response, or stable disease; and significantly better progression-free survival (PFS), but not OS, than patients without a drop in AFP [30].

Elevated total bilirubin levels in patients with HCC usually reflect elevated levels of conjugated bilirubin, which accompany parenchymal liver disease and biliary tract obstruction [31]. Bilirubin concentrations are components of several HCC scoring systems [5,6,10–12,28,29]. We found that bilirubin concentrations were associated with OS in sorafenib-treated patients, being a median 4.9 months shorter in patients with elevated levels than in those with normal bilirubin levels. We also observed a transient increase in total bilirubin concentration during the second cycle of treatment with sorafenib, but not with placebo, an increase due primarily to a transient increase in conjugated bilirubin concentration.

Several hypotheses may explain the transient elevation in bilirubin concentration observed during cycle 2 of sorafenib treatment. For example, this transient elevation may be due to direct toxicities of sorafenib or indirect toxicities caused by agents used to treat sorafenib-associated AEs. Alternatively, this sorafenib-associated transient elevation in bilirubin concentration may be unrelated to liver

Table 4. Grade ⩾3 drug-related adverse events relative to baseline concentrations of aminotransferases (AST/ALT), α-fetoprotein (AFP), and bilirubin occurring in ⩾5% of patients of any population.

	All patients		ALT/AST levels						AFP levels						Bilirubin levels			
			Not significantly elevated		Mildly elevated		Moderately elevated		Normal		Mildly elevated		Moderately elevated		Normal		Elevated	
	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla	Sor	Pla
n	297	302	151	153	77	77	67	72	109	97	78	86	93	107	223	225	72	77
All categories, %	35	15	37	13	34	18	31	15	43	21	28	12	33	14	36	16	32	13
Hand-foot skin reaction, %	8	<1	9	1	5	0	8	0	12	0	5	0	7	1	7	<1	11	0
Diarrhea, %	8	2	10	1	4	4	10	0	11	3	6	0	7	2	9	2	8	0
Hyperbilirubinemia, %	2	<1	0	1	4	0	3	0	2	0	3	1	1	0	1	0	3	1
Elevated ALT, %	1	<1	0	0	1	1	2	0	1	0	1	1	0	0	1	<1	1	0
Anemia, %	1	1	1	0	4	1	0	1	4	0	0	1	0	1	1	<1	1	1
Nausea, %	<1	1	1	1	0	0	0	1	0	2	1	0	0	1	<1	1	0	0
Vomiting, %	1	1	1	1	0	1	3	0	1	2	3	0	0	0	1	<1	0	1
CNS ischemia, %	0	1	0	0	0	1	0	0	0	1	0	0	0	1	0	<1	0	0
Hypophosphatemia, %	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fatigue, %	4	4	4	3	5	5	2	3	6	6	1	1	4	4	3	3	6	7

ALT, alanine aminotransferase; AST, aspartic aminotransferase; AFP, alpha-fetoprotein; Sor, sorafenib, Pla, placebo, CNS, central nervous system.

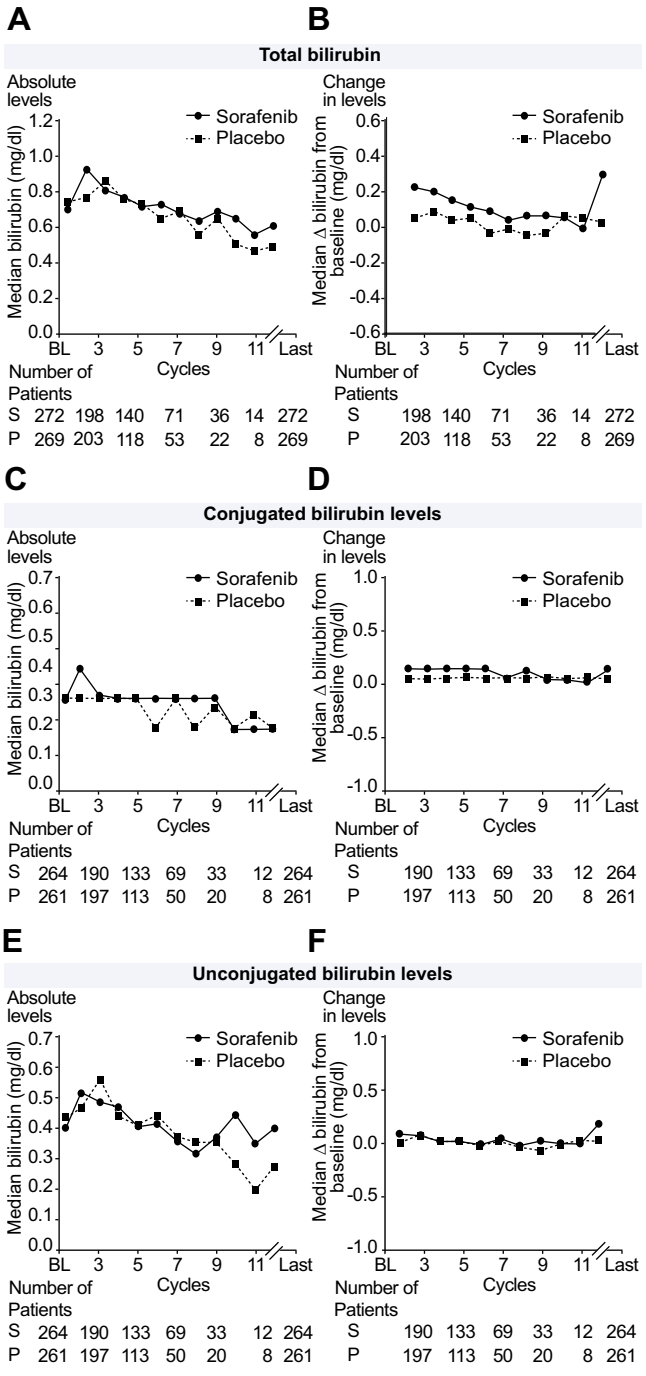

Fig. 4. Median absolute concentrations of (A) total, (C) conjugated, and (E) unconjugated bilirubin and changes in (B) total, (D) conjugated, and (F) unconjugated bilirubin concentrations during treatment.

dysfunction. Sorafenib has been shown to strongly inhibit the enzyme UGT1A1, an enzyme involved in the metabolism of bilirubin [32]. In addition, Gilbert's syndrome, a hereditary, chronic, mild unconjugated hyperbilirubinemia resulting from impaired hepatic bilirubin clearance but with otherwise normal liver function, is fairly common in Western patients, with about 30% being heterozygous for mutations and 5% being homozygous [33]. Thus, treatment with sorafenib of patients with HCC and Gilbert's syndrome may result in a transient increase in bilirubin concentration. Furthermore, sorafenib treatment of patients with cirrhosis may further increase the risk of hyperbilirubinemia by inhibiting the activity of UGT1A1, an enzyme that usually decreases in cirrhotic patients [34].

The availability of a drug that targets proliferative and angiogenic pathways of HCC without adversely affecting other cellular pathways represents a significant advance in the treatment of patients with liver cancer. We found that treatment with sorafenib was effective, safe, and tolerable, irrespective of baseline hepatic marker concentration status, and did not induce any new or unrecognized toxicity. Our findings provide further support for the use of sorafenib as first-line therapy for patients with advanced HCC who are not candidates for locoregional treatment. Its role as adjuvant therapy and in combination with surgical interventions and transcatheter arterial embolization/transarterial chemoembolization remains to be determined.

Conclusions

These exploratory subset analyses of patients enrolled in the SHARP trial showed that patients with elevated baseline concentrations of aminotransferases, AFP, or bilirubin had shorter OS than those with baseline non-elevated concentrations of these markers, irrespective of treatment group. We also found that sorafenib was effective, safe, and tolerable in patients with advanced HCC in Child-Pugh A patients, irrespective of their baseline concentrations of AST/ALT, AFP, and bilirubin. Overall, sorafenib did not have any clinically relevant effects on bilirubin concentration, although a transient and minimal increase in bilirubin concentration was observed during the second cycle of treatment with sorafenib. Thus, concentrations of aminotransferases, AFP and bilirubin had a prognostic but not a predictive value in patients with advanced HCC treated with sorafenib.

Conflict of interest

J.L.R. has received consulting fees from Bayer HealthCare Pharmaceuticals and Biocompatibles and lecture fees from Bayer HealthCare Pharmaceuticals. J.B. has received honoraria and research funding from Bayer HealthCare Pharmaceuticals and consulting fees from Bayer HealthCare Pharmaceuticals, Onyx Pharmaceuticals, Biocompatibles, Bristol-Myers Squibb, Glaxo, Kowa, Novartis, and ArQule. T.F.G. has received consulting fees and lecture fees from Bayer HealthCare Pharmaceuticals and lecture fees from Roche and Pfizer. V.M. has received consulting fees from Bayer HealthCare Pharmaceuticals. P.H. has received lecture fees from Bayer HealthCare Pharmaceuticals and MDS Nordion. A.N. is an employee of Bayer HealthCare Pharmaceuticals. M.M. and D.V. are employees of Bayer Schering Pharma. J.M.L. has received consulting fees from Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals and honoraria and research funding from Bayer HealthCare Pharmaceuticals.

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Appendix A

The following principal investigators (listed alphabetically by country) enrolled patients in the SHARP trial:

Argentina: M.G. Pallota, J.J. Zarba; Australia: M. Boyer, S. Riordan, A. Strickland, N. Tebbutt, B. Thomson; Belgium: I. Borbath, J. De Greve, J.-L. Van Laethem, W. Van Steenbergen, H. Van Vlierberghe; Brazil: C. Barrios, A. Cosme de Oliveira; Bulgaria: I. Kotzev, D. Takov, K. Tchernev; Canada: K. Burak, M. Ma, P. Metrakos, C. Olweny, M. Sherman; Chile: C. Gamargo Garate, J. Martinez-Castillo; France: M. Beaugrand, J. Bennouna, J.-F. Blanc, J.-P. Bronowicki, F. Degos, S. Dominguez, J.-D. Grange, P. Hillon, J.-L. Raoul, J.-F. Seitz; Germany: H. Blum, P. Buggisch, W. Caspary, M. Dollinger, P.R. Galle, G. Gerken, B. Göke, M. Gregor, T. Greten, D. Häussinger, P. Hilgard, H. Scherübl, M. Scheulen, R. Schmid, U. Spengler, R. Wiest, S. Zeuzem; Greece: C. Arvanitakis, G. Germanidis, I. Katsos; Israel: A. Figer, S. Stemmer; Italy: D. Amadori, L. Bolondi, F. Cognetti, A. Craxi, F. Farinati, C. Gridelli, A. Martoni, V. Mazzaferro, C. Porta, S. Ricci, A. Sangiovanni, A. Santoro, F. Trevisani; Mexico: L.E. Cisnero Garza; New Zealand: E. Gane, A. O'Donnell; Peru: J. Leon, A. Lozano; Poland: J. Jassem, G. Rydzewska, A. Szawlowski, P. Tomczak; Romania: F. Badulescu, L. Miron; Russia: V. Kubyshkin; Spain: J. Bruix, A. Forner, J. Bustamante Schneider, M. Diago, J.L. Montero Alvarez, S. Pascual, L. Ruíz del Arbol, B. Sangro, R. Solá, J. Tabernero; Switzerland: B. Muellhaupt, A. Roth; United Kingdom: T.R. Jeffry Evans, S. Falk, T. Meyer, H. Reeves, P. Ross; United States: A. Befeler, T. Boyer, C. Britten, T. Byrne, G. Garcia-Tsao, P. Gold, A. Goldenberg, D. Heuman, P. Kennedy, A. Koch, J.M. Llovet, J. Marrero, M. Schilsky, J. Schwartz, M. Schwartz.

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