Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

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

Jean-Luc Raoul[1,2,*,†], Jordi Bruix[3,†], Tim F. Greten[4,†], Morris Sherman[5,†], Vincenzo Mazzaferro[6,†], Philip Hilgard[7,†], Hans Scherubl[8,†], Max E. Scheulen[9,†], Georgios Germanidis[10,†], Sophie Dominguez[11,†], Sergio Ricci[12,†], Andrea Nadel[13,†], Marius Moscovici[14,†], Dimitris Voliotis[14,†], Josep M. Llovet[3,15,16,†]

[1]*Institut Paoli-Calmettes, Marseille, France;* [2]*Institut National de la Santé et de la Recherche Médicale (INSERM) U991, Rennes, France;* [3]*Barcelona Clínic Liver Cancer (BCLC) Group, Liver Unit, CIBERehd, Institut d'Investigacions Biomèdiques, August Pi i Sunyer (IDIBAPS), Hospital Clínic Barcelona, Barcelona, Spain;* [4]*Medizinische Hochschule Hannover, Abteilung fur Gastroenterologie, Hepatologie und Endokrinologie, Hannover, Germany;* [5]*Toronto General Hospital, Toronto, ON, Canada;* [6]*National Cancer Institute, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Foundation, Milan, Italy;* [7]*University Hospital of Essen, Essen, Germany;* [8]*Medizinische Klinik "Charite", Campus Benjamin Franklin, Berlin, Germany;* [9]*Innere Klinik (Tumorforschung), West German Cancer Center, Universitätsklinikum Essen, Essen, Germany;* [10]*AHEPA University Hospital, First Department of Medicine, Thessaloniki, Greece;* [11]*Centre Oscar Lambret, Departement de Cancerologie Digestive et Urologique, Lille, France;* [12]*St. Chiara University Hospital, Milan, Italy;* [13]*Bayer HealthCare Pharmaceuticals, Montville, NJ, USA;* [14]*Bayer Schering Pharma, Milan, Italy;* [15]*Mount Sinai Liver Cancer Program, Mount Sinai School of Medicine, New York, NY, USA;* [16]*Institució Catalana de Recerca I Estudis Avançats, Catalonia, Spain*

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.
Received 3 October 2011; received in revised form 6 December 2011; accepted 12 December 2011; available online13 January 2012

☆ Presented in part in abstract form at: (1) American Gastroenterological Association (AGA) Institute/American Society of Clinical Oncology (ASCO)/American Society for Radiation Oncology (ASTRO)/Society of Surgical Oncology (SSO) 2010 Gastrointestinal Cancers Symposium; Orlando, Florida, USA, January 22–24, 2010; (2) 46th ASCO Annual Meeting; Chicago, Illinois, USA, June 4–8, 2010; (3) 4th Annual International Liver Cancer Association (ILCA) Conference; Montreal, Québec, Canada, September 10–12, 2010; (4) European Society for Medical Oncology (ESMO) Annual Meeting; Milan, Italy, October 8–12, 2010.

* Corresponding author. Address: Institut Paoli-Calmettes, 232 Boulevard Ste Marguerite, 13009 Marseille, France.
E-mail address: raouljl@marseille.fnclcc.fr (J.-L. Raoul).

† On behalf of the SHARP Investigators Study Group (The names of the investigators in the SHARP Investigators Study Group are listed in the Appendix).

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.