Are we SHARP enough? The importance of adequate patient selection in sorafenib treatment for hepatocellular carcinoma

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ORIGINAL ARTICLE

Are we SHARP enough? The importance of adequate patient selection in sorafenib treatment for hepatocellular carcinoma

Tim A. Labeur[a,b] ![ORCID], David W. G. Ten Cate[c] ![ORCID], R. Bart Takkenberg[d] ![ORCID], Hicham Azahaf[d] ![ORCID], Martijn G. H. van Oijen[a,b] ![ORCID], Otto M. van Delden[e] ![ORCID], Robert A. de Man[f], Jeroen L. A. van Vugt[c] ![ORCID], Jan N. M. IJzermans[d] ![ORCID], Ferry A. L. M. Eskens[g] and Heinz-Josef Klümpen[a,b] ![ORCID]

aCancer Center Amsterdam, Amsterdam, The Netherlands; bDepartment of Medical Oncology, Academic Medical Center, Amsterdam, The Netherlands; cDepartment of Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands; dDepartment of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands; eDepartment of Radiology, Academic Medical Center, Amsterdam, The Netherlands; fDepartment of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands; gDepartment of Medical Oncology, Erasmus University Medical Center, Rotterdam, The Netherlands

ABSTRACT

Background: Upon FDA/EMEA registration for hepatocellular carcinoma (HCC), sorafenib received a broader therapeutic indication than the eligibility criteria of the landmark SHARP trial. This allowed treatment of SHARP non-eligible patients in daily clinical practice.

Aim: To assess sorafenib efficacy and safety in SHARP eligible and non-eligible patients, and determine the validity of the current therapeutic indication as described by the FDA/EMEA.

Patients and methods: Consecutive patients treated with sorafenib for advanced HCC at two Dutch tertiary referral centers between 2007 and 2016 were analyzed retrospectively. Primary outcome was overall survival (OS). Secondary outcomes were time to progression (TTP), response rate, adverse events and reasons for discontinuation. Outcomes were compared between SHARP eligible and non-eligible patients.

Results: One hundred and ninety-three of 257 (75%) patients were SHARP eligible. SHARP eligible patients (9.5 months, 95% CI 7.7–11.3) had a longer median OS than non-eligible patients (5.4 months, 95% CI 3.6–7.1) (log-rank $p < .001$). SHARP non-eligible patients were more often Child–Pugh B, had higher AST and ALT levels and developed more grade 3–4 liver dysfunction (44 versus 23%, $p < .001$) during treatment. SHARP ineligibility remained the strongest predictor of OS (HR 1.78, 95% CI 1.32–2.41) and an independent predictor of TTP (HR 1.45, 95% CI 1.05–2.00) in multivariable analysis.

Conclusions: Landmark trial outcomes of sorafenib for HCC are reproducible in daily practice, provided that the SHARP eligibility criteria are respected. Based on the findings of this and previous studies, sorafenib usage should be restricted to Child–Pugh A patients.

Introduction

For almost a decade, the multikinase inhibitor sorafenib has been the only registered treatment for advanced hepatocellular carcinoma (HCC). Implementation of sorafenib as standard treatment for advanced HCC is based on the results of two randomized phase III trials: the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial and the parallel Sorafenib Asian-Pacific (AP) trial [1,2]. Both studies demonstrated a sorafenib survival benefit of 3 months compared with placebo in strictly selected patients. HCC develops mostly in patients with liver cirrhosis, thus only patients with well-preserved liver function (Child–Pugh A) were eligible for study participation. Presence or absence of underlying cirrhosis was not specified. Accordingly, the current guidelines recommend sorafenib treatment for advanced HCC in patients with Child–Pugh A liver function only, without specifying the presence or absence of underlying cirrhosis [3,4]. Nonetheless, the Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) gave sorafenib a broader therapeutic indication than the eligibility criteria of the landmark SHARP trial [5]. The guideline endorsed Barcelona Clinic Liver Cancer (BCLC) staging system does not exclude Child–Pugh B patients for sorafenib treatment [6]. Consequently, several real-life studies showed that sorafenib is currently prescribed to a broad spectrum of patients, including substantial numbers (12.5–34%) of Child–Pugh B patients [7–16]. It is well-established that patients with Child–Pugh B liver function have significantly poorer outcomes, although sorafenib toxicity seems not related to Child–Pugh status [9,12,15]. Still, in absence of randomized-controlled trials, the exact benefit in patients not-meeting the SHARP eligibility criteria, specifically in Child–Pugh B patients, remains controversial. Real-life studies in some tumor types (i.e., colorectal and prostate

CONTACT Heinz-Josef Klümpen h.klumpen@amc.nl Department of Medical Oncology, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

Supplemental data for this article can be accessed here.

cancer) have shown decreased outcomes when systemic therapies are given outside the landmark trial eligibility criteria [17,18], whereas outcomes were comparable in patients with bile tract cancer [19]. A direct comparison between SHARP eligible and non-eligible subgroups in advanced HCC has not been conducted. Hence, it remains unknown whether sorafenib treatment of a substantial numbers of SHARP ineligible patients, which are exposed to sorafenib toxicity and results in significant healthcare costs, is beneficial. Hence, this retrospective multicenter study aims to assess the real-life efficacy and safety of sorafenib in advanced HCC, comparing SHARP eligible and non-eligible subgroups; and to determine whether the current sorafenib therapeutic indication as described by EMEA/FDA is valid based on the current evidence.

Patients and methods

Study population

All consecutive patients, ≥18 years old, evaluated at two tertiary HCC referral centers in the Netherlands [Academic Medical Center (AMC), Amsterdam, and Erasmus University Medical Center (EMC), Rotterdam] who received at least one dose of sorafenib for advanced HCC between May 2007 and December 2016 were included in this retrospective study. Study-based sorafenib was allowed, but patients who received study-based selective internal radio-embolization therapy (SIRT) combined with sorafenib were excluded from this analysis [20].

HCC diagnosis was established histologically or by the American Association for the Study of Liver Diseases (AASLD) imaging criteria [21]. Absence or presence of underlying cirrhosis was established on criteria proposed by Mittal et al. [22]. Patients were staged by four-phase computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI) and discussed at a multidisciplinary meeting. Patients were considered for treatment with sorafenib according to the BCLC guidelines [3]. HIV infection was not a contraindication for treatment. Following the indications provided by the manufacturer, patients received sorafenib 400 mg twice daily (BID), but were allowed to receive lower starting doses (200 mg twice daily), toxicity-adjusted dosing and treatment interruptions at the discretion of the medical oncologist to cope with drug-related adverse events [5]. The Institutional Review Board (IRB) of the AMC (reference number W17_420#17.488) approved the study and a waiver for informed consent was given.

Data collection

Potential patients were identified using keywords and diagnostic codes from the electronic patient record and pharmacy records. Included keywords were 'hepatocellular carcinoma', 'HCC', 'malignancy liver', 'liver neoplasm' and 'liver malignant neoplasm'. Medical records were reviewed and clinical data was manually extracted. Extracted data included previous treatments, baseline patient and tumor characteristics and treatment details including treatment emergent adverse events (AE), which was prospectively monitored as part of standard care. Efforts were made to collect missing data, for example by contacting referring hospitals for additional data on referred patients.

SHARP eligibility criteria

Subgroups were made based on meeting or not meeting the eligibility criteria of the SHARP trial [2]. These criteria are shown in Figure 1. In summary, patients were required to have advanced stage HCC or intermediate stage HCC which was not or no longer eligible for surgical or locoregional therapies, without previous systemic therapy for HCC. SHARP eligible patients were required to have an ECOG PS 0-2, Child–Pugh A liver function and adequate renal and hematological function. The actual life expectancy was not mentioned in the files, but was considered to be within the limits of the SHARP eligibility criteria (≥12 weeks) based on descriptive data. Patients violating one or more SHARP eligibility criteria were assigned to the 'SHARP non-eligible subgroup and patients meeting all criteria were assigned to the 'SHARP eligible' subgroup. Patients who could not be assigned to a subgroup due to missing data were excluded from this study.

Outcome measures

The primary outcome, overall survival (OS), was calculated from the date of the first dose of sorafenib until death or censored on the last known date to be alive. Survival status was checked in the electronic medical record and verified by using the municipal records database on 17 January 2018.

Time to progression (TTP) was defined as the time from start of sorafenib treatment until clinical or radiological disease progression. Radiological response evaluation was performed every 2–3 months as part of standard of care and assessed by experienced abdominal radiologists using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [23]. Progression-free patients were censored at the time of last radiological evaluation. Patients who died or were lost to follow-up before first radiological evaluation, were excluded from TTP analysis. In response evaluation, all patients who showed clinically progressive disease in the absence of radiological evaluation were considered to have progressive disease. All adverse events were classified according to the National Cancer Institute's Common Toxicity Criteria (NCI-CTC v4.03) [24]. Liver dysfunction was defined as occurrence or deterioration of hyperbilirubinemia, ascites or encephalopathy.

Statistical analysis

Continuous variables were expressed as medians and ranges, and categorical variables as absolute and relative frequencies. The Pearson's chi-square or Fisher's exact test where appropriate, were used to compare categorical data in the SHARP eligible and non-eligible subgroups. Continuous data was compared using the Student's t-test or Mann–Whitney
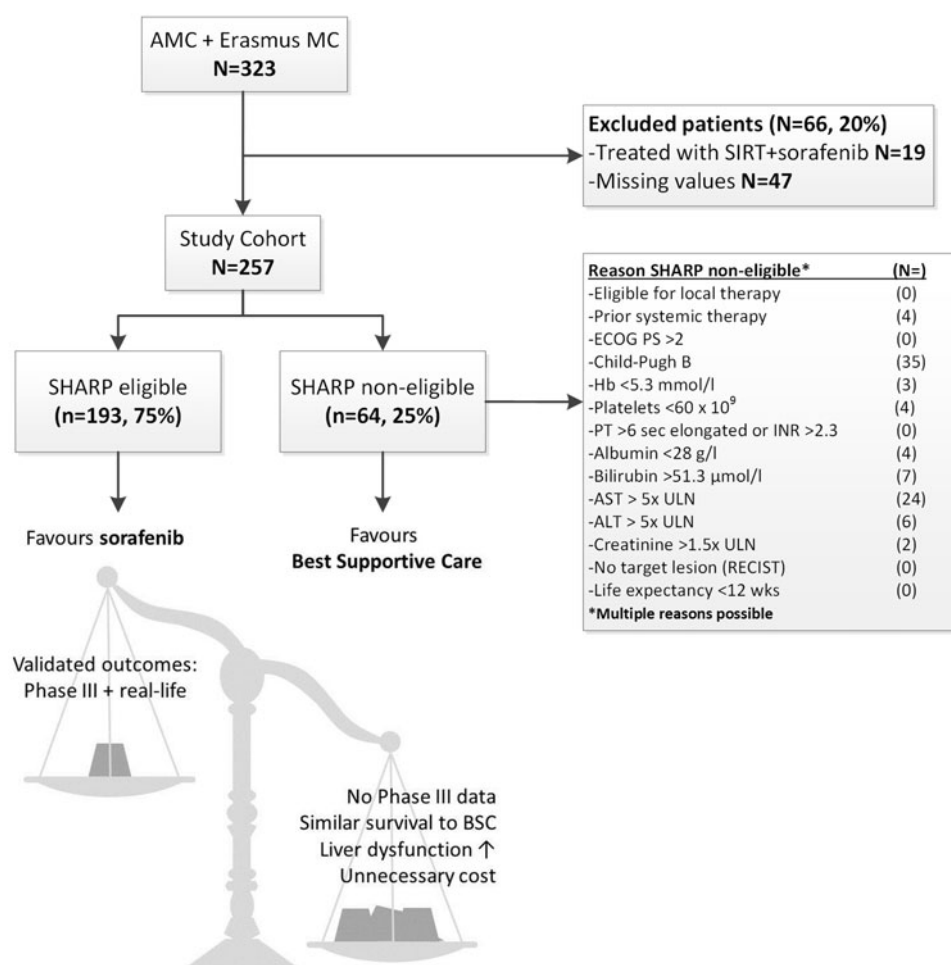
Figure 1. Study flowchart.

U-test, where appropriate. The Kaplan–Meier method and log-rank tests were used to estimate and compare OS and TTP curves. Cox proportional hazard regression analysis was used to calculate hazard ratios (HRs) and assess the association of baseline variables, including literature reported predictors, with OS and TTP. All predictors with a two-sided p value $<.05$ in univariate analysis were included in a subsequent multivariable model in which correlated predictors were adjusted to reduce overlapping variance. In order to identify the impact of the separate SHARP eligibility criteria, we performed an exploratory univariate analysis of the individual criteria separately. A two-sided p value $<.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS statistics (version 23.0; IBM Corp., Armonk, NY).

Results

Patient characteristics

Between May 2007 and December 2016, a total of 323 patients with advanced HCC were treated with sorafenib. Of these, 66 patients (20%) were excluded due to incomplete data ($n = 47$) or because they received combined SIRT and sorafenib treatment ($n = 19$) (Figure 1). The remaining 257 patients formed the study cohort of whom baseline patient

and tumor characteristics are summarized in Table 1. The majority of patients had liver cirrhosis (79%), and 218 patients (85%) were in the Child–Pugh A class. The most common etiological factors were alcohol (34%), followed by hepatitis B virus infection (HBV; 16%) and hepatitis C virus infection (HCV; 16%). At the start of sorafenib treatment, most patients had advanced stage HCC (73%) and 93 patients (36%) received prior treatment for HCC, mainly TACE (21%). In total, 193 of the 257 (75%) were considered SHARP eligible. Reasons for non-eligibility of the other 64 patients are listed in Figure 1. SHARP non-eligible patients had more often Child–Pugh B liver function with lower albumin and higher bilirubin, aspartate transaminase (AST) and alanine transaminase (ALT) levels. Less common reasons for SHARP ineligibility were prior systemic treatment for HCC ($n = 4$), low platelet count ($n = 4$) or low hemoglobin ($n = 3$). SHARP non-eligible patients were younger (63 versus 66 years, $p = .040$), but other baseline clinical and tumor characteristics were comparable between subgroups.

Overall survival

After a median follow-up of 45.8 months (range 0.2–63.2), 232 of 257 (90%) patients had died. The median OS for all patients receiving sorafenib was 8.4 months (95% CI 6.9–9.9). The median OS in the SHARP eligible subgroup was

Table 1. Baseline characteristics of all, SHARP eligible and non-eligible patients.

Variable	All patients, $N = 257$	Eligible, $N = 193$	Non-eligible, $N = 64$	p value[a]
Age, median (range) (years)	65 (26–84)	66 (26–84)	63 (27–79)	**.040**
Male, n (%)	208 (81)	161 (83)	47 (73)	.098
Etiology, n (%)				
Alcohol	87 (34)	67 (35)	20 (31)	.650
HBV	40 (16)	30 (15)	10 (16)	.998
HCV	41 (16)	31 (16)	10 (16)	.934
NAFLD/NASH	20 (8)	17 (9)	3 (5)	.420
Other/unknown	15 (6)	9 (5)	6 (9)	.215
Cirrhosis, n (%)	203 (79)	148 (77)	55 (86)	.081
Child–Pugh class, n (%)[b]				**<.001**
A	218 (85)	193 (100)	25 (39)	
B	35 (14)	NA (0)	35 (55)	
ECOG performance status, n (%)				.558
0	81 (32)	64 (33)	17 (27)	
1	153 (60)	113 (59)	40 (63)	
2	23 (9)	16 (8)	7 (11)	
BCLC stage prior to start sorafenib, n (%)				.300
B (intermediate)	69 (27)	55 (29)	14 (22)	
C (advanced)	188 (73)	138 (72)	50 (78)	
Number of nodes, n (%)				.097
1 node	53 (21)	41 (21)	12 (19)	
2–3 nodes	60 (23)	66 (34)	14 (22)	
>3 nodes or diffuse infiltrating	20 (8)	86 (45)	38 (59)	
Size of largest node, mm (range)	72 (10–230)	70 (12–225)	77 (10–230)	.143
Macroscopic vascular invasion, n (%)	107 (42)	79 (41)	28 (44)	.692
Extend of disease				.085
Confined to liver	108 (42)	87 (45)	21 (33)	
Extrahepatic spread	149 (58)	106 (55)	43 (67)	
Laboratory analysis				
AFP, ng/ml, median (range)	179 (2–1201500)	158 (2–1201500)	244 (3–688200)	.137
AFP ≥400 ng/ml, n (%)	109 (42)	81 (42)	28 (44)	.727
Hemoglobin (mmol/L), median (range)	8.2 (4.9–10.8)	8.3 (5.6–10.8)	7.8 (4.9–10.5)	.001
Thrombocytes ($\times 10^9$), median (range)	187 (52–846)	188 (62–672)	175 (52–846)	.761
PT (sec), median (range)	12.5 (9.8–17.5)	12.3 (9.8–16.4)	13.0 (10.7–17.5)	**<.001**
Creatinine (μmol/L), median (range)	72 (41–247)	74 (41–151)	68 (41–247)	.227
Albumin (g/dl), median (range)	40 (23–50)	40 (30–50)	35 (23–47)	**<.001**
Bilirubin (μmol/L), median (range)	14 (3–75)	13 (3–40)	22 (3–75)	**<.001**
AST (U/L), median (range)	69 (17–697)	64 (17–198)	126 (29–697)	**<.001**
ALT (U/L), median (range)	47 (9–493)	45 (9–224)	51 (20–493)	.012
Received prior treatment, n (%)	93 (36)	75 (39)	18 (28)	.121
Liver transplantation	5 (2)	5 (3)	0 (0)	.336
Surgical resection	26 (10)	23 (12)	3 (5)	.149
RFA	36 (14)	28 (15)	8 (13)	.836
TACE	53 (21)	41 (21)	12 (19)	.669
SIRT	1 (<1)	1 (<1)	0 (0)	1.00
Systemic therapy	4 (2)	NA	4 (6)	**.004**

[a]p value applies to the 'meeting' versus 'not meeting' groups. p values <0.05 are highlighted in bold.
[b]Missing in four patients.
AFP: α-fetoprotein; ALT: alanine transaminase; AST: aspartate transaminase; BCLC: Barcelona Clinic Liver Cancer classification; ECOG: Eastern Cooperative Oncology Group; HBV: hepatitis virus B; HCV: hepatitis virus C; NA: non-applicable; NAFLD/NASH: non-alcoholic fatty liver disease/non-alcoholic steatohepatitis; PT: prothrombin time; RFA: radiofrequent ablation; SHARP: Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol; SIRT: selective internal radiation therapy; TACE: transcatheter arterial chemoembolization.

9.5 months (95% CI 7.7–11.3) compared with 5.4 months (95% CI 3.6–7.1) in the SHARP non-eligible subgroup (log-rank $p < .001$; Figure 2A).

In univariable Cox regression analysis (Table 3), not meeting the SHARP inclusion criteria was the strongest predictor of an increased risk of mortality [hazard ratio (HR) = 1.81, 95% CI 1.35–2.44]. Other baseline factors that were associated with an increased risk of mortality were ECOG performance status 2, tumor size >72 mm (above median), macrovascular invasion (MVI) and α-fetoprotein (AFP) ≥ 400 ng/ml, whereas patients that received prior HCC treatment had a better prognosis (HR 0.67, 95% CI 0.51–0.88). In

subsequent multivariable analysis, not meeting the SHARP inclusion criteria (HR = 1.78, 95% CI 1.32–2.41), MVI (HR = 1.34, 95% CI 1.02–1.76) and AFP ≥400 (HR = 1.60, 95% CI 1.22–2.11) were independently associated with reduced survival. An additional exploratory analysis aimed at assessing the impact of the individual SHARP eligibility criteria (Supplementary Table S1), showed that Child–Pugh B (HR 2.03, 95% CI 1.40–2.95), hemoglobin <5.3 mmol/l (HR 13.85, 95% CI 4.16–46.06), bilirubin >51.3 μmol/L (HR 2.46, 95% CI 1.16–5.25), AST >5× ULN (HR 2.66, 95% CI 1.72–4.11), ALT >5× ULN (HR 1.18, 95% CI 0.52–2.67) and creatinine >1.5× ULN (HR 8.57, 95% CI 2.08–35.39) were associated with
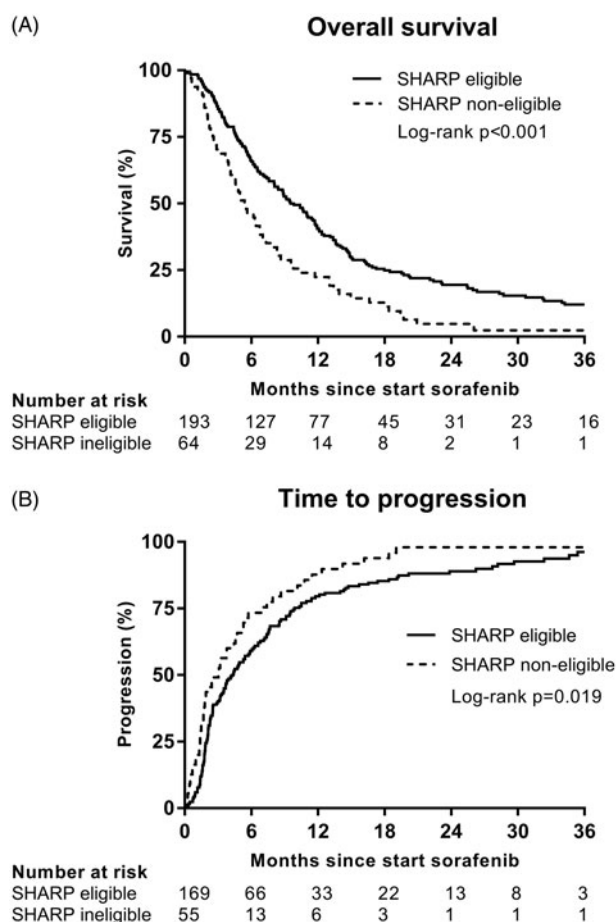
(A)

Overall survival

Number at risk						
SHARP eligible	193	127	77	45	31	23	16
SHARP ineligible	64	29	14	8	2	1	1

(B)

Time to progression

Number at risk						
SHARP eligible	169	66	33	22	13	8	3
SHARP ineligible	55	13	6	3	1	1	1

Figure 2. (a) Overall survival and (b) time to progression in SHARP eligible and SHARP non-eligible subgroups. Thirty-three patients were not evaluable for TTP analysis.

reduced OS. A multivariable analysis was not conducted due risk of collinearity of multiple violations, and limited sample size of subgroups.

TTP and response rate

Data on TTP (Figure 2(b)) was available in 224 patients (87%); 33 patients (13%) died or were lost to follow-up before clinical or radiological disease progression. Overall, the median TTP was 3.8 months (95% CI 2.9–4.6). SHARP eligible patients had a significant longer TTP (4.3 months, 95% CI 3.1–5.6) than non-eligible patients (3.0 months, 95% CI 1.7–4.4) (log-rank $p = .019$). After correction for other univariable predictors (HBV, MVI and AFP ≥ 400), not meeting the SHARP eligibility criteria remained an independent predictor of poor TTP (HR 1.45, 95% CI 1.05–2.00) (Supplementary Table S2). The best radiological response according to RECIST 1.1 was not statistically different between eligible and non-eligible subgroups (Table 2).

Treatment details and adverse events

Treatment details and adverse events are summarized in Table 2. Median duration of sorafenib treatment was 13 weeks (range 0–225 weeks) with a median maximum-

tolerated dose of 200 mg twice daily, reflecting that the majority of patients (59%) did not reach the maximum dose. The most common treatment emergent AE's (all grades) were gastrointestinal (37%), liver dysfunction (35%), asthenia (30%) and skin toxicity (34%). The most common grade III/IV AE's were liver dysfunction (28%), followed by gastrointestinal (13%) skin toxicity (11%). During sorafenib treatment, liver dysfunction occurred more frequently in the SHARP non-eligible patients (56 versus 28%, $p < .001$) compared with SHARP eligible patients. Non-eligible patients developed more often grade 3–4 liver dysfunction (44 versus 23%, $p = .001$), but maximum-tolerated sorafenib dose and AE's were comparable between subgroups. Patients who were SHARP non-eligible showed a trend towards shorter treatment duration (9 versus 13 weeks, $p = .052$) and terminated treatment more often due to combined progression and AE's (38 versus 22%, $p = .030$). In SHARP eligible patients, the main reason for permanent discontinuation was disease progression (54%).

Discussion

We showed that SHARP eligible patients treated in daily clinical practice had an OS similar to those treated in the SHARP trial (9.5 versus 10.7 months, respectively), whereas SHARP non-eligible patients had significantly reduced survival (5.4 months), reduced TTP and more liver dysfunction during treatment.

In our cohort, a minority of patients (25%) did not meet the SHARP eligibility criteria, mainly due to Child–Pugh class B liver function or serum AST/ALT values exceeding five times the upper limit of normal. This suggests that the observed survival difference, between SHARP eligible and non-eligible patients can be explained by more compromised liver function in the latter subgroup. Likewise, there was an increased occurrence of (severe) liver dysfunction whereas maximum-tolerated dose and other toxicity types were comparable. Hence, this study confirms the remarks made by the authors of both sorafenib landmark studies, which stressed that restricting enrollment to Child–Pugh A patients, could have potentially prevented deaths related to advanced liver disease masking the effects of sorafenib [1,2].

Despite these remarks and the guidelines advising sorafenib treatment of advanced HCC in Child–Pugh A patients only [3], multiple cohort studies showed that prescription to Child–Pugh B patients has not been uncommon (12–44%, Table 4) in the past decade [9,12,15]. As sorafenib toxicity in these patients is comparable to Child–Pugh A patients, sorafenib seems a safe treatment option; however, safety alone is not enough to consider sorafenib as standard of care. Our study validates the findings of a series of previous studies, both retrospective and prospective (Table 4), showing that Child–Pugh B patients have a poor outcome on sorafenib treatment. Interestingly, the outcomes of SHARP non-eligible patients treated with sorafenib were inferior to historic cohorts of SHARP eligible patients receiving placebo (7.9 months) [2] and comparable to patients with Child–Pugh B receiving best-supportive care (BSC) only (5 months) [3,25].

Table 2. Treatment details and adverse events of SHARP eligible and non-eligible patients.

Variable	All patients, N = 257	Eligible, N = 193	Non-eligible, N = 64	p value[a]
Weeks of treatment, median (range)	13 (0–225)	13 (0–209)	9 (0–225)	.052
Total tolerated daily dose, median (range)	400 (200–1400)	400 (200–1400)	400 (200–1000)	.203
Treatment emergent adverse events				
Any, all grades	203 (79)	150 (78)	53 (83)	.082
Any, grade 3/4	140 (55)	104 (54)	36 (56)	.742
Asthenia, all grades	76 (30)	56 (29)	20 (31)	.734
Asthenia, grade 3/4	14 (5)	12 (6)	2 (3)	.528
Dermatological, all grades	88 (34)	72 (37)	16 (25)	.072
Dermatological, grade 3/4	29 (11)	24 (12)	5(8)	.370
Gastrointestinal, all grades	94 (37)	69 (36)	25 (39)	.634
Gastrointestinal, grade 3/4	32 (13)	27 (14)	5 (8)	.274
Hematological, all grades	26 (10)	21 (11)	5 (8)	.634
Hematological, grade 3/4	8 (3)	6 (3)	2 (3)	1.000
Hypertension, all grades	16 (6)	15 (8)	1 (2)	.130
Hypertension, grade 3/4	5 (2)	5 (3)	0 (0)	.336
Liver dysfunction, all grades	90 (35)	54 (28)	36 (56)	**<.001**
Liver dysfunction, grade 3/4	72 (28)	44 (23)	28 (44)	**.001**
Other, all grades	28 (11)	20 (10)	8 (13)	.634
Other, grade 3/4	14 (5)	9 (5)	5 (8)	.347
Treatment interruptions				.998
None	172 (67)	129 (67)	43 (67)	
1–2 interruptions	77 (30)	58 (30)	19 (30)	
≥3 interruptions	8 (3)	6 (3)	2 (3)	
Reason termination				**.030**
Ongoing	6 (2)	6 (3)	0 (0)	
Progression	127 (49)	104 (54)	23 (36)	
Toxicity	34 (13)	25 (13)	9 (14)	
Progression and adverse event	66 (26)	42 (22)	24 (38)	
Other/unknown	24 (9)	16 (8)	5 (16)	
Best radiological response (RECIST 1.1)				.373
Complete response	0 (0)	0 (0)	0 (0)	
Partial response	20 (8)	13 (7)	7 (11)	
Stable disease	98 (38)	79 (41)	19 (30)	
Progressive disease	106 (41)	77 (40)	29 (45)	
Not evaluable	33 (13)	9 (9)	6 (19)	

[a]p value applies to the 'meeting' versus 'not meeting' groups. p values <.05 are highlighted in bold.
RECIST: Response Evaluation Criteria in Solid Tumors; SHARP: Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol.

Table 3. Hazard ratios for overall survival in univariable and multivariable analysis.

Variable name, n (%)	Univariable analysis			Multivariable analysis		
	HR	95% CI	p value[a]	HR	95% CI	p value[a]
Not meeting SHARP inclusion criteria	1.81	1.35–2.44	**<.001**	1.78	1.32–2.41	**<.001**
Female sex	1.27	0.92–1.75	.152			
Age >65 years	0.96	0.74–1.24	.729			
HBV	1.02	0.71–1.47	.929			
HCV	0.87	0.60–1.25	.437			
Alcohol abuse	0.96	0.73–1.26	.747			
Cirrhosis	1.11	0.81–1.53	.520			
ECOG PS 2 (ref = ECOG 0-1)	1.57	1.01–2.44	**.045**	1.36	0.86–2.15	.191
BCLC stage C (ref: B)	1.23	0.91–1.65	.180			
Number of nodes (ref =1 node)			.087			
2–3 nodes	0.86	0.60–1.24				
>3 nodes/diffuse infiltrating	1.20	0.86–1.68				
Tumor size >72 mm	1.53	1.17–1.98	**.002**	1.27	0.95–1.70	.111
Macroscopic vascular invasion	1.44	1.11–1.88	**.006**	1.34	1.02–1.76	**.036**
Extrahepatic spread (ref = liver confined)	1.11	0.85–1.44	.456			
AFP ≥400	1.76	1.35–2.30	**<.001**	1.60	1.22–2.11	**.001**
Received previous treatments	0.67	0.51–0.88	**.004**	0.84	0.61–1.15	.264

[a]p values <.05 are highlighted in bold.
AFP: α-fetoprotein; BCLC: Barcelona Clinic Liver Cancer classification; ECOG PS: Eastern Cooperative Oncology Group Performance status; HBV: hepatitis virus B; HCV: hepatitis virus C; NAFLD/NASH: non-alcoholic fatty liver disease/non-alcoholic steatohepatitis; SHARP: Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol.

This suggests that sorafenib is non-superior to BSC in patients with more advanced liver disease. Despite the multitude of studies counting almost 5000 patients treated with sorafenib, including more than 1100 Child–Pugh B patients, the conclusions on the usage in these patients remain conflicting (Table 4). Ideally a randomized placebo-controlled trial should be conducted to determine the efficacy in Child–Pugh B patients. Unfortunately, such an initiative (BOOST trial) had to be terminated prematurely due to slow enrollment, demonstrating the difficulty in recruiting these

Table 4. Studies comparing sorafenib outcomes in Child–Pugh A and B subgroups in advanced HCC.

First author	Year	Design	No. of patients (% Child–Pugh B)	Overall survival Child A versus B (mo.)	Conclusion on Child–Pugh B
Pinter [14]	2009	Retrospective	59 (39%)	8.3 versus 4.3	More data needed
Wörns [16]	2009	Prospective	34 (44%)	7.2 versus 3.3	Treat with caution
Abou-Alfa [7]	2011	Retrospective	127 (30%)	9.5 versus 3.2	More data needed
Hollebecque [9]	2011	Prospective	120 (17%)	13 versus 4.5	Treat with caution
Iavarone [10]	2011	Prospective	296 (12%)	12.7 versus 7.7	–
Pressiani [15]	2012	Prospective	297 (21%)	10.0 versus 3.8	Treat with caution
Da Fonseca [11]	2015	Retrospective	120 (17%)	9.7 versus 2.5	More data needed
Ogasawara [13]	2015	Prospective	89 (34%)	11.1–14.5 versus 4.6–8.7	Child–Pugh B7 is eligible
Marrero [12]	2016	Prospective	2717 (25%)	13.6 versus 5.2	Treat with caution
Edeline [8]	2016	Retrospective	905 (20%	7.0–10.2 versus 3.6	Limit indication to Child–Pugh A

patients and carrying out such a trial [26]. Still, healthcare authorities increasingly demand validation of (expensive) drugs and both clinicians and patients are facing dilemmas when considering treatment. The significant costs of sorafenib therapy, which proved only to be cost-effective in patients with compensated liver disease and when applying proper dose adjustments, underlines the need of strict patient selection [27,28]. Therefore, we conclude that currently there is insufficient evidence for sorafenib treatment beyond the SHARP eligibility criteria, specifically in patients with Child–Pugh B liver function, and that the registered therapeutic indication and the BCLC staging system should restrict treatment to Child–Pugh A patients. The limitations of Child–Pugh A as a selection criterion and alternatives [i.e., Albumin-Bilirubin (ALBI) score] have been discussed previously [8,29]. Our findings support adherence to the current guidelines with careful patient selection and dose-adjustments according to the current evidence. This may reduce non-beneficial exposure of patients to sorafenib toxicity and the unnecessary healthcare costs.

Still, even in SHARP eligible patients further optimization of sorafenib usage is possible, indicated by low response rates, heterogeneity in survival outcomes and lack of a significant improvement in patient-reported quality of life variables [2]. In the future, molecular biomarkers, i.e., tumor profiling or biochemical serum markers, might aid in further selecting the optimal candidates for sorafenib or future trials.

Our study has several limitations, including the retrospective design with its inherent drawbacks. Non-availability of key parameters (i.e., Child–Pugh classification) led to exclusion of some patients, as adherence to the SHARP eligibility criteria could not be assessed. Furthermore, the retrospective assessment of parameters that are subject to inter-observer variability, such as ECOG PS or life expectancy, might have caused inaccurate assessment. Strengths of our study include the focus on unselected patients in the daily clinical practice of two tertiary referral centers for HCC, covering roughly 30–40% of the Dutch HCC population. The construction of a robust dataset was possible due to the standardized evaluation of all patients in a multidisciplinary team meeting, prospective monitoring of drug toxicity and standardized RECIST 1.1 response monitoring.

In conclusion, our results confirm that the trial outcomes of sorafenib in advanced HCC are reproducible in daily clinical practice, provided that the SHARP eligibility criteria are respected. Based on our findings and the results of previous studies, sorafenib usage should be restricted to Child–Pugh A patients.

ORCID

Tim A. Labeur 🆔 http://orcid.org/0000-0002-9988-5077
David W. G. Ten Cate 🆔 http://orcid.org/0000-0002-8013-9701
R. Bart Takkenberg 🆔 http://orcid.org/0000-0003-2179-1385
Hicham Azahaf 🆔 http://orcid.org/0000-0002-4303-2315
Martijn G. H. van Oijen 🆔 http://orcid.org/0000-0001-7897-1710
Otto M. van Delden 🆔 http://orcid.org/0000-0003-3342-9367
Jeroen L. A. van Vugt 🆔 http://orcid.org/0000-0003-0033-9947
Jan N. M. IJzermans 🆔 http://orcid.org/0000-0003-3558-1039
Heinz-Josef Klümpen 🆔 http://orcid.org/0000-0002-7290-1823

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