Research Article

Impact of Baseline Characteristics on the Overall Survival of HCC Patients Treated with Sorafenib: Ten Years of Experience

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Keywords

Real-life conditions · Baseline factors · ALBI grade · Etiologies · Child-Pugh · ECOG · Neutrophil-to-lymphocyte ratio · Lactate dehydrogenase · Prognostic factor · Transaminases

Abstract

Background: Sorafenib has been established as the standard of care for patients with advanced hepatocellular carcinoma (HCC) since 2007 on the basis of two landmark trials (SHARP and Asia-Pacific). Ten years have passed since then and, despite much research in the field,

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still no validated real-life prognostic markers are available for HCC patients treated with this drug. Therefore, going through 10 years of research into sorafenib of several Italian Cancer Centers, we conducted a field-practice study aimed at identifying baseline clinical factors that could be significantly associated with overall survival (OS). **Method:** Univariate/multivariate analyses were conducted to retrospectively identify the impact of baseline characteristics on the OS of 398 advanced HCC patients treated with sorafenib. **Results:** Based on univariate analysis, α -fetoprotein (AFP), albumin, AST, bilirubin, Child-Pugh, ECOG, systemic immune-inflammation index (SII), albumin-bilirubin (ALBI) grade, and portal vein thrombosis were significantly associated with shorter OS. Following adjustment for clinical covariates positive in univariate analysis, the multivariate analysis including AFP, age, etiology, albumin, aspartate transaminase (AST), bilirubin, Child-Pugh, LDH, platelet-to-lymphocyte ratio, ECOG, ALBI grade, portal vein thrombosis, SII, and BCLC stage identified increase in LDH, age >70 years, no viral etiologies, ECOG >0, albumin <35, ALBI grade 2, and AST >40 as prognostic factors for poorer OS based on the 5% significance level. **Conclusion:** Our study highlights that baseline hepatic function, patient-centered variables, and etiology have prognostic value. These findings might have implications in terms of therapeutic decision-making and patient counseling.

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Introduction

Hepatocellular carcinoma (HCC), the most frequent primary liver malignancy, ranks as the sixth cancer worldwide in terms of incidence and represents the second leading cause of cancer-related death [1–3]. A peculiarity of this neoplasm is its tendency to develop in the context of an advanced liver disease in the vast majority of cases. Etiologies vary from well-known predisposing conditions such as chronic viral infections (HCV and HBV) and alcohol abuse, to more recent and increasing risk factors which are part of the spectrum of the metabolic diseases (non-alcoholic steatohepatitis [NASH], non-alcoholic fatty liver disease, obesity, diabetes) [4, 5].

Sorafenib has represented the cornerstone of HCC systemic treatment since 2007 and the only FDA-approved agent for frontline therapy of advanced HCC until 2018. In the phase III SHARP trial, sorafenib demonstrated a significant improvement in overall survival (OS) in comparison to placebo for the treatment of advanced HCC (10.7 vs. 7.9 months; hazard ratio [HR] 0.69, 95% CI: 0.55–0.87; $p < 0.001$) [6]. The most frequent adverse events (AEs) were hand-foot syndrome and diarrhea, with a manageable toxicity profile [6]. These data were subsequently confirmed in another phase III, placebo-controlled trial involving HCC patients of the Asia-Pacific area, with an OS benefit of 2.3 months reported in the sorafenib arm [7]. The role of sorafenib for HCC treatment under real-life practice conditions has been further assessed in the GIDEON trial (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and of its treatment with sorafenib) [8]. This observational study involving more than 3,200 unresectable HCC patients, showed that sorafenib tolerability was not significantly different between Child-Pugh (C-P) A and B subgroups [8], but C-P B patients exhibited poorer survival outcomes compared to C-P A group [8]. In this study, no analysis on prognostic or predictive factors to sorafenib was performed.

Among the new available agents for HCC treatment, lenvatinib, an oral inhibitor of multiple receptor tyrosine kinases, received FDA approval as first-line therapy for advanced HCC in 2018, after its non-inferiority in comparison to sorafenib was reported in the REFLECT trial [9]. In September 2017, the FDA granted accelerated approval to the fully human IgG4

monoclonal antibody programmed death receptor-1 (PD-1) inhibitor nivolumab for the treatment of HCC patients previously treated with sorafenib, based on the results of the phase I/II CheckMate-040 trial [10]. Now, great expectation is addressed towards the ongoing phase III CheckMate-459 trial (NCT02576509), which compares nivolumab and sorafenib as first-line therapy for advanced-stage HCC patients [11].

Despite this evolving scenario, the role of sorafenib remains pivotal, also because of more than 10 years' experience gained in the management of its activity and safety profile [4]. Unfortunately, the main results obtained to date come from 2 important randomized trials and from different subanalyses and pooled analyses, rather than from normal clinical practice. With that in mind, exploring the characteristics and the possible prognostic factors in a population of HCC patients treated with sorafenib under real-life conditions in the last 10 years becomes of paramount importance.

After 10 years of research into sorafenib, there are still no validated prognostic or predictive factors of response to the drug in HCC [12]. The aim of the present study was to summarize 10 years of research into sorafenib in the real-life experience of several Italian Cancer Centers, looking for clinical factors that could be significantly associated with survival outcomes in this setting of patients.

Patients and Methods

Patients and Treatment

This multicenter Italian study was conducted on HCC patients consecutively treated and derived from our retrospective studies conducted in these years [13–22]. Patients receiving sorafenib with advanced-stage and intermediate-stage HCC refractory to or unsuitable for locoregional therapies, either histologically proven or diagnosed according to the AASLD (American Association for the Study of Liver Diseases 2005) guidelines, were eligible for our analysis. None of the patients had received previous systemic therapy. Eligibility criteria were the same as those of Llovet's pivotal study on sorafenib in HCC [6].

All patients received sorafenib according to standard schedule (400 mg b.i.d. continuously) or physician choice; dose reduction was applied as clinically indicated. Follow-up consisted of CT/MRI scan every 8 weeks or as clinically indicated. Tumor response was evaluated by modified Response Evaluation Criteria in Solid Tumors (mRECIST). Treatment with sorafenib was continued until disease progression, unacceptable toxicity, or death.

Statistical Analysis

The aim of this analysis was to examine the association between baseline characteristics and OS in patients with HCC treated with sorafenib. All hematologic blood tests were carried out at baseline the day before the start of the treatment. Association between categorical variables was assessed using Fisher's exact test, when appropriate.

OS was defined as the time interval between the time from the start date of treatment to the date of death or last follow-up visit. OS were estimated by the Kaplan-Meier method and curves were compared by the log-rank test.

The multivariate analyses were conducted using seven models. Model 1 included all basal positive analysis that we found in univariate analysis plus age and gender. In the other models, we added in various steps all other analyses (model 2: model 1 plus previous treatment; model 3: model 1 plus response to sorafenib; model 4: model 1 plus starting dosage; model 5: model 1 plus treatment in second line; model 6: model 1 plus skin toxicity; model 7: model 1 plus all toxicity).

Backward selection was used with a threshold level of 10% to select variables to evaluate in the MV analysis. The significance level of 5% was used to determine statistical significance. MedCalc package (MedCalc® version 16.8.4) was used for all statistical analysis.

Fig. 1. Overall survival in relation to ECOG (a), portal vein thrombosis (b), starting dosage (c), and age (d).

Results

Between June 7th, 2007, and August 8th, 2018, 398 patients with HCC and treated with sorafenib were included in our analysis. The study sample included 356 males (89.4%) and 42 females (10.6%) with a median age at diagnosis of 69 years (range 25–88). Median OS was 12 months (95% CI: 11.1–14.6). Median follow-up was 36 months (range 1–65).

C-P class A was the most represented ($n = 255$; 88.1%). 263 patients (71.2%) had BCLC-C disease stage. 28.2% patients had an α -fetoprotein (AFP) level >400 ng/mL. The most common underlying etiology was hepatitis infection from C virus (52.6%) and B virus (20.1%).

Sorafenib was started at the standard dose of 800 mg/day in 69.6% of patients. AEs of any grade were reported in 273 patients (74.5%); 32.2% of patients reported hand-foot skin toxicity (grade 1: 27.9%; grade 2: 50%; grade 3: 20.3%). Best response to sorafenib treatment was represented by 2 complete responses (0.7%), partial response in 36 patients (11.5%),

Table 1. Univariate analysis of basal characteristics

	Patients, <i>n</i>	Events, <i>n</i>	Median OS, months (95% CI)	HR	95% CI	<i>p</i> value
Age at diagnosis (c.v.)	396	314		1.00	0.98–1.01	0.4683
Age at diagnosis						
<80 years	355	281	12.3 (11.1–14.9)	1		
>80 years	41	33	11.7 (6.1–17.8)	1.29	0.86–1.91	0.2136
Sex						
1 (M)	356	281	12.4 (10.8–14.9)	1		
2 (F)	42	35	12.3 (11.0–16.1)	1.01	0.71–1.44	0.9459
BCLC stage						
B	106	80	15.6 (12.4–19.0)	1		
C	263	209	11.8 (9.2–13.5)	1.20	0.94–1.55	0.1382
Etiology						
Alcohol	37	30	13.9 (7.9–20.8)	1		0.5594
Others	39	32	12.0 (9.2–15.1)	1.34	0.80–2.26	
HBV	79	65	11.3 (8.8–15.0)	1.18	0.76–1.81	
HCV	207	161	13.5 (11.1–15.8)	1.01	0.69–1.48	
NASH	31	24	12.9 (6.1–15.6)	1.02	0.60–1.72	
Body mass index (c.v.)	237	180		0.99	0.95–1.03	0.7956
Body mass index						
Low	8	6	10.8 (7.7–26.3)	1.23	0.50–3.01	0.8845
Normal	208	157	13.2 (12.0–15.6)	1		
High	21	17	11.8 (8.0–22.8)	1.00	0.61–1.66	
Performance status						
0	208	158	15.8 (14.3–18.0)	1		<0.0001
>0	160	131	8.5 (7.7–10.3)	1.72	1.34–2.20	
Portal vein thrombosis						
No	209	151	15.1 (12.9–17.8)	1		0.0065
Yes	118	99	8.5 (6.1–10.8)	1.45	1.11–1.90	
Sorafenib dosage (800 vs. other)						
800	147	112	15.1 (12.7–17.9)	1		0.0015
Other	64	54	8.7 (5.3–12.0)	1.82	1.26–2.63	

stable disease in 145 patients (46.5%), and progression disease in 129 patients (41.3%); the disease control rate was 58.5%. 44.5% of patients received other treatments after sorafenib progression/intolerance.

Basal Characteristics and Clinical Outcome

For basal characteristics, the univariate analysis identified ECOG >0 (vs. 0; HR 1.72; $p < 0.0001$) (Fig. 1a), portal vein thrombosis yes (vs. no; HR 1.45; $p = 0.0065$) (Fig. 1b) and starting dosage <800 mg (vs. 800 mg; HR 1.82; $p = 0.0015$) (Fig. 1c) as potential prognostic factors for poorer OS (Fig. 1d). At univariate analysis, no differences were found for age (Fig. 1d), gender, etiology and body mass index (Table 1).

For hepatic function, the univariate analysis identified C-P B (vs. A; HR 1.57; $p = 0.0220$) (Fig. 2a), albumin <35 (vs. >35; HR 1.47; $p = 0.0317$) (Fig. 2b), bilirubin >normal value (NV) (vs. <NV; HR 1.43; $p = 0.0297$) (Fig. 2c), albumin-bilirubin (ALBI) grade 2 (vs. 1; HR 1.76; $p =$

Fig. 2. Overall survival in relation to Child-Pugh (a), albumin (b), bilirubin (c), ALBI (d), AST (e), and α -fetoprotein (f).

Table 2. Univariate analysis of liver function

	Patients, <i>n</i>	Events, <i>n</i>	Median OS, months (95% CI)	HR	95% CI	<i>p</i> value
Child-Pugh						
A	327	255	13.5 (11.8–15.6)	1		0.0220
B	44	41	8.0 (3.7–10.9)	1.57	1.07–2.33	
Albumin (c.v.)	198	157		0.94	0.91–0.98	0.0066
Albumin						
<35	68	58	10.0 (7.9–11.7)	1.47	1.03–2.09	0.0317
>35	125	94	15.6 (12.7–18.0)	1		
Bilirubin (c.v.)	262	215		1.32	1.02–1.71	0.0317
Bilirubin						
<1.2	193	155	13.5 (11.8–15.6)	1		0.0297
>1.2	71	61	9.2 (6.8–13.6)	1.43	1.03–1.98	
ALBI grade (c.v.)	194	155		1.76	1.19–2.60	0.0040
ALBI grade						
1	164	127	14.9 (12.0–16.3)	1		0.0008
2	30	28	7.7 (3.0–10.8)	2.47	1.46–4.20	
ALT (c.v.)	190	148		1.00	0.99–1.00	0.1433
ALT						
<41	79	58	13.5 (9.6–18.5)	1		0.4356
>41	107	86	12.9 (10.8–15.8)	1.14	0.81–1.60	
AST (c.v.)	162	124		1.00	1.00–1.00	0.0094
AST						
<40	41	27	24.0 (13.5–34.1)	1		0.0010
>40	118	94	12.0 (10.4–15.6)	1.92	1.30–2.85	
Ascites						
No	59	45	13.9 (10.4–17.8)	1		0.0045
Yes	35	30	4.1 (2.2–9.7)	2.16	1.27–3.68	
Alkaline phosphatase (c.v.)	59	43		1.00	0.99–1.00	0.3421
Alkaline phosphatase						
<129	23	17	14.6 (8.7–20.9)	1		0.6684
>129	36	26	9.6 (3.1–17.8)	1.14	0.61–2.11	
GGT (c.v.)	61	44		1.00	0.99–1.00	0.7878
GGT						
<61	4	4	5.8 (2.2–14–6)	2.55		0.1877
>61	57	40	13.5 (5.6–17.8)	1	0.63–10.25	
MELD (c.v.)	347	272		1.04	0.99–1.08	0.1132
MELD						
<12	295	224	12.8 (11.3–15.0)	1		0.5322
>12	52	48	10.9 (6.8–17.8)	1.11	0.80–1.54	

Table 3. Univariate analysis of other basal blood tests

	Patients, <i>n</i>	Events, <i>n</i>	Median OS, months (95% CI)	HR	95% CI	<i>p</i> value
AFP (c.v.)	372	296		1.00	1.00–1.00	0.9032
AFP						
<400	264	202	14.3 (11.4–16.1)	1		0.0028
>400	105	91	9.6 (7.9–12.7)	1.51	1.15–1.98	
Serum calcium (c.v.)	155	123		0.84	0.61–1.16	0.2994
Serum calcium						
<8.6	14	12	11.2 (4.2–16.3)	1.45	0.73–2.88	
>8.6	131	102	12.9 (10.9–15.6)	1		0.2907
Creatinine (c.v.)	267	219		1.11	0.69–1.79	0.6612
Creatinine						
<1.2	237	190	12.0 (11.3–14.9)	1.02		0.9111
>1.2	30	29	11.1 (6.7–22.8)	1	0.69–1.52	
Hb (c.v.)	221	176		0.98	0.90–1.06	0.5887
Hb						
<NV	111	91	11.2 (8.5–12.7)	1.10	0.81–1.48	0.5330
NV	110	85	15.6 (12.0–18.0)	1		
INR (c.v.)	209	168		1.19	0.83–1.70	0.3444
LDH (c.v.)	174	143		1.00	1.00–1.00	0.0210
LDH						
<225	63	48	14.7 (10.4–18.0)	1		0.6538
>225	111	95	12.0 (8.5–15.1)	1.08	0.76–1.53	
Serum sodium (c.v.)	196	160		0.96	0.93–1.00	0.0524
Serum sodium						
<136	41	33	9.2 (6.0–16.1)	1.36	0.89–2.07	0.1559
>136	155	127	12.0 (11.0–15.1)	1		

0.004) (Fig. 2d), and aspartate transaminase (AST) >NV (vs. <NV; HR 1.92; $p = 0.001$) (Fig. 2e) as potential prognostic factors for poorer OS. No differences were found for alanine transaminase (ALT), alkaline phosphatase, GGT (gamma glutamyl transferase), Meld score, and BCLC stage (Table 2). For other parameters, only AFP >400 (vs. <400; HR 1.51; $p = 0.0028$) (Fig. 2f) and LDH as continuous variable (HR 1.00; $p = 0.021$) were found as potential prognostics factors (Table 3).

For inflammatory index, the univariate analysis identified platelet-to-lymphocyte ratio (PLR) as continuous variable (HR 4.94; $p = 0.026$) and systemic immune-inflammation index (SII) >360 (vs. <360; HR 1.36; $p = 0.041$) as potential prognostic factor for poorer OS. Conversely, neutrophil-to-lymphocyte ratio (NLR) (cut off of 3) was not associated with a different clinical outcome.

Other Parameters and Clinical Outcome

Regarding previous treatments, the univariate analysis identified previous treatment with radiofrequency (RFA) (vs. no RFA; HR 1.67; $p = 0.0017$) (Fig. 3a) and transarterial chemoembolization (TACE) (vs. no TACE; HR 1.40; $p = 0.0060$) (Fig. 3b) as potential prog-

Fig. 3. Overall survival in relation to previous treatment with RFA (a), TACE (b), all toxicity (c), hand-foot skin toxicity (d), diarrhea (e), and second-line treatment (f).

Table 4. Multivariate analysis

AFP >400	0.1335	0.3171	0.8571	0.0957	0.4283	0.1833	0.2667
LDH	0.0414	0.0742	0.0383	0.0480	0.0613	0.0463	0.0689
Age <70	0.0007	0.0001	0.0414	0.0039	0.0018	0.0004	0.0005
Etiology							
HCV							
HBV	0.2004	0.0656	0.0832	0.2638	0.7268	0.0886	0.1658
Others	0.0038	0.0198	0.0031	0.0039	0.0028	0.0023	0.0014
PS >1	0.0305	0.2400	0.0579	0.0302	0.0331	0.0347	0.0548
Portal vein thrombosis	0.5814	0.9398	0.8212	0.6105	0.2057	0.5893	0.7544
PLR >16	0.4666	0.5075	0.7603	0.3811	0.9062	0.6422	0.5831
SII <360	0.3499	0.2440	0.5673	0.4088	0.2896	0.3068	0.4079
Child-Pugh B	0.1304	0.2885	0.0030	0.1181	0.1940	0.1466	0.1688
Albumin <35	0.0004	0.0018	0.0987	0.0013	0.0021	0.0007	0.0007
Bilirubin >1.2	0.6055	0.2961	0.7319	0.7118	0.5484	0.9362	0.6926
ALBI 2	<0.0001	<0.0001	0.0001	<0.0001	<0.0001	<0.0001	<0.0001
AST <40	0.0074	0.0885	0.0023	0.0131	0.0567	0.0027	0.0101
BCLC B	0.8875	0.4047	0.6065	0.8442	0.9231	0.7806	0.9488
Thermoablation		0.0077					
TACE		0.7452					
Response PD			0.0131				
Dosage <800 mg				0.1327			
Subsequent treatments					0.1375		
Skin toxicity						0.6407	
Any toxicity							0.1553

nostic factors for greatest OS. The number of TACE and the best response were not associated with different clinical outcome.

For toxicity, we found a correlation between toxicity (all toxicity [Fig. 3c], hand-foot skin toxicity [Fig. 3d], and diarrhea [Fig. 3e]) and good prognosis. No second-line treatment was associated with a lower survival (HR 2.07; $p < 0.0001$) (Fig 3f).

Regarding best response to sorafenib, we found a correlation between them and clinical outcome (complete response HR 1.00; partial response HR 1.61; stable disease HR 2.75; progression disease HR 7.51; $p < 0.0001$). Finally, we analyzed six categories of concomitant drug, but no correlation between them and clinical outcome was found.

Multivariate Analysis

The multivariate analysis using model 1 (including AFP [cut off 400], age [$<$ or ≥ 70 years], etiology [HBV, HCV and other], albumin [$<$ or $> \text{NV}$], AST [$<$ or $> \text{NV}$], bilirubin [$<$ or $> \text{NV}$], C-P [A vs. B], LDH as a continuous variable, PLR [$<$ or > 16], ECOG [0 vs. > 0], ALBI grade [1 vs. 2], portal vein thrombosis [yes vs. no], SII [< 360 vs. > 360], and BCLC stage [B vs. C]) identified increase in LDH, age ≥ 70 years, other etiology, ECOG > 0 , albumin < 35 , ALBI grade 2, and AST > 40 as prognostic factors for poorer OS based on the 5% significance level. The results of other models of multivariate analysis are shown in Table 4.

Discussion

In this retrospective study, we evaluated the OS of advanced HCC patients treated with sorafenib in real-life clinical setting. The analysis showed that age > 70 years, performance status ECOG > 0 , HCC etiologies other than HCV or HBV infection, high levels of LDH, albumin

<35, ALBI grade 2, and AST >40 were associated with poorer OS. Our study demonstrates that, in real-life setting, hepatic function is the real indicator of the prognosis.

Despite the different type of analysis, the characteristics of the population of our study are consistent with the data of the SHARP trial [6]. Males were definitely more prevalent than females (89.4 and 10.6% vs. 87 and 13%, respectively), median age of patients was 69 years (vs. 65 years), an ECOG Performance status of 0 was represented by 52.2% of patients (vs. 54%). A lower proportion of patients (71.2 vs. 83%) were BCLC stage C and C-P A (88.1 vs. 97%). Of note, median OS of 12.3 months described here is similar to that of 10.7 months reported in the above-mentioned landmark trial, thus suggesting that real-life benefit of sorafenib is similar to that reported in randomized clinical trials. The multivariate analysis showed that ALBI grade, age, and etiology were the only always positive factors.

Compared to C-P score, ALBI grade has been established by Johnson et al. [23] as a simple, evidence-based, and objective method of assessing liver function in HCC. Incorporating only serum bilirubin and albumin, it stratifies patients with HCC into three categories (with grade 3 considered the worse) and it is able to highlight distinct prognostic subgroups within C-P grade A. In our study, ALBI grade 2, rather than any grade of C-P score, was identified as a negative prognostic factor suggesting its stronger role in evaluating hepatic impairment. Our study outlines the superiority of ALBI grade over C-P score; in the univariate analysis, C-P B (vs. A) and ALBI grade 2 (vs. 1) were identified as potential prognostic factor for poorer OS, but C-P disappears when considered in multivariate analysis, whereas ALBI grade constantly remains. Although not in a real-life setting, Abdel-Rahman [24] also reported a positive effect on OS of lower ALBI.

Regarding the 2 factors comprised in the ALBI score (bilirubin and albumin), both albumin and bilirubin were identified as potential prognostic factors for poorer OS in the univariate analyses, but in the multivariate context only albumin <35 g/L emerged as an independent prognostic factor. Therefore, we show that albumin, rather than bilirubin, is the most relevant factor able to make ALBI grade the strongest prognostic factor in the multivariate analysis. This is partially in line with previously reported paper, such as that from Bruix et al. [25] in which not only albumin but also bilirubin was identified in the MV analysis.

Regarding age, our results show that patients with age ≥ 70 years had an independent prognostic factor able to impact negatively on OS. This information has its relevance since, with the aging population, the treatment of HCC in elderly patients is becoming a global health issue. Sorafenib is the standard of care for patients with advanced HCC, regardless of age, following the results of SHARP and Asia Pacific (AP) trials; no specific results related to age were reported in the publications of those trials. In the univariate analysis of our study, no difference was identified between age <70 and ≥ 70 years; therefore, sorafenib can be considered effective and safe also in elderly patients. When considering age in the context of a multivariate setting, older-age patients appear to have worse prognosis. Several and not available factors may contribute to explain this result; one of these may be represented by comorbidities, which were absent in our database and which may increase treatment-related toxicity. To date, only few studies reported the use of sorafenib in elderly patients. With the premise that the cutoff used to define “elderly” patients is varying across studies, the only prospective cohort study comparing treatment with sorafenib in two different age groups (<70 vs. ≥ 70 years) of cirrhotic patients with HCC reports that sorafenib is more effective in the elderly group in terms of time to progression and OS, but results are not statistically significant [26]. Several retrospective studies found similar results, in other words no difference in terms of OS [27].

Our analysis shows that etiology other than HBV/HCV infection, alcohol abuse, or NASH is an independent prognostic factor for worse OS. This information could be explained, at least for what concerns viral infections, by the fact that patients without known risk factors

have not been subjected to HCC screening and therefore have been diagnosed with advanced-stage HCC with worse liver function [28]. Moreover, again with regard to HCC viral etiology, subgroup analysis of the SHARP and AP trials seems to suggest a different efficacy of sorafenib in HBV- or HCV-positive subjects. There is no evidence of any improvement in OS attributable to sorafenib for patients positive for HBV and negative for HCV. The mechanism of action of the drug, together with the diversity in tumor microenvironment characteristics on the basis of HBV or HCV infection, could explain the different antitumor profile [29–31]. Other parameters that were found having a good correlation with the prognosis were AST, ECOG, and LDH.

AST but not ALT was an independent prognostic factor for poorer prognosis. Pathological processes that can lead to a higher proliferative state, tissue damage, and high tumor cell turnover tend to increase AST but not ALT, at least not to the same extent [32]; thus, probably explaining why in our study AST, and not ALT, negatively correlates with prognosis. In subset analyses of phase III SHARP and AP trials [33], no difference was found between ALT/AST, but we think that, in real life practice conditions, aminotransferases levels may naturally be greater and therefore their prognostic role may emerge.

ECOG >0 is an independent prognostic factor for poorer OS, in line with the above-mentioned paper by Abdel-Rahman [24], which shows a significant survival difference based on ECOG score of 0 versus 1 and indicates that even minor differences in performance might impact the overall outlook of HCC patients undergoing treatment with sorafenib. Another paper by Samawi et al. [34] identified the independent prognostic role of ECOG PS (2–3 vs. 0–1).

As already described in several papers [35, 36], elevated levels of LDH are significantly associated with poor prognosis. The biological link between hypoxia, LDH levels, and the tumor-driven angiogenesis pathway through the abnormal activation of the hypoxia inducible factor-1 is well established, and data from several analyses on different cancers seem to suggest that LDH levels may be a significant prognostic factor. Regarding LDH in HCC treated with systemic therapies, preclinical studies reported that high levels of LDH predict resistance to several tyrosine kinase inhibitors (TKIs), including sorafenib [37], through the maintenance of the glycolytic flow, and therefore the competition between ATP and TKI inhibition at the ATP enzymatic site on the protein kinase target of their activity. Recently, given the heterogeneity of studies and results and in order to produce the best estimate of effect size, Kong et al. [38] performed a meta-analysis of 10 studies to evaluate the prognostic role of LDH, confirming that elevated LDH is a risk factor for different survival outcomes in HCC patients.

Another interesting finding from our study is the prognostic impact of previous treatments. RFA or TACE appear as potential prognostic factors for greatest OS. The positive impact of prior locoregional treatments is in line with the recently published report by Abdel-Rahman [24]. It can be easily imagined that, probably, previously treated patients had a biologically different (more favorable) HCC. Our study suggests that even >3 TACE did not negatively impact on OS and did not negatively influence the possibility of receiving sorafenib; this is a remarkable information, since we would expect that a higher number of TACE can worsen patient prognosis.

Second-line treatment was associated with a highest survival. It has to be underlined that our analysis covers a period of time prior to the authorization of the use of new experimental drugs; thus, second-line treatment in our hospitals was essentially represented by metronomic capecitabine which seems to be an efficient and safe systemic therapy for patients who either did not tolerate sorafenib or progressed during sorafenib treatment [18, 19]. Nowadays, we face a completely different therapeutic landscape since three new drugs received approval, based on phase III clinical trials, for the treatment of patients with HCC who previously received sorafenib: regorafenib (RESORCE [39]), cabozantinib (CELESTIAL [40]), and ramu-

circumab (REACH-2 [41]). It would be of particular interest to see how the introduction of those drugs will change the survival in a real-life experience.

We found a statistically significant correlation between all toxicity, dermatologic AEs, diarrhea, and good prognosis. This is not surprising, since several papers have highlighted this peculiar concept, both in retrospective and prospective studies [42–48]. The consistency of this association led Di Costanzo et al. [20] to even construct and validate a scoring system (OTE score), comprising HFSR, hypertension, and diarrhea, able to predict sorafenib effectiveness in sorafenib-treated HCC patients.

Several factors of impaired liver function, such as elevated levels of AFP or high C-P score, have been shown to be negative prognostic indicators in patients with HCC independent of the type of treatment; some of those factors, together with tumor-related variables (portal vein thrombosis, etc.), have been incorporated in a variety of staging and prognostic systems, such as BCLC [34, 49]. Some of these baseline characteristics could also be identified as negative prognostic indicators for the OS on sorafenib treatment in univariate analyses of the phase III SHARP trial [50, 25]. Consistently, AFP >400, C-P B, presence of portal vein thrombosis, and BCLC stage C were associated with poorer OS in the univariate analysis of our cohort, but their effect on OS disappeared when considered in the context of the multivariate analyses. Of note, C-P B (vs. A) was associated with shorter OS, in line with the prospective and real-life GIDEON study [8].

Finally, no correlation was found between immune inflammation indicators and prognosis in multivariate analysis. As reported in our previous paper [22], NLR was not associated with a different clinical outcome, in contrast to what was observed in the subanalysis of SHARP and AP trials conducted by Bruix et al. [25] in which high NLR had a detrimental effect on OS. This difference may be at least in part explained by the different populations in exams; prevalence of cirrhosis in our study is much higher, and this disease stage is associated with a low number of neutrophils, lymphocytes, and platelet levels.

The main strengths of our study are the large sample size and the multicenter enrollment of patients in a field-practice setting. We analyzed medical data collected under real-life conditions, therefore mimicking routine care and thus providing high external validity and high generalizability. The main weakness of our study is, on the other hand, the retrospective nature of data, which implicates collection of studies with different characteristics and endpoints, missing data, etc. To overcome, at least in part, this aspect, cases were consecutively selected, thus reducing potential bias. Another limit is represented by the fact that, given the homogeneity of the population, the applicability of the current results is restricted to non-Asian patients.

Conclusion

In advanced HCC patients, the prediction of prognosis is extremely complex because survival is affected by both tumor burden and liver function. In our study, we have provided insights into the impact of baseline characteristics on the OS of sorafenib-treated HCC patients in real-life setting, highlighting that hepatic function, patient-centered variables, and HCC etiology, rather than tumor stage, AFP, and immune inflammation indicators, have prognostic value. These findings might have implications in terms of therapeutic decision-making and patient counseling, especially now that, after 10 years of sorafenib solitude, the therapeutic scenario for advanced HCC is becoming more and more multifaceted.

Statement of Ethics

The study protocol was reviewed and approved by the local Ethics Committee (CEIIAV: Ethics Committee IRST IRCCS AVR). Study number IRST B041, protocol number 5482/v.1, intern. code L3P1192. All patients signed their written informed consent.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

A.C.G.: conception and design of the work; analysis and interpretation of data; review, drafting, and final approval of the manuscript. G.O. and G.R.: writing the paper. All authors: acquisition, analysis, and interpretation of data; review and final approval of the manuscript.

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