Original Paper

Sorafenib: Experience and Better Management of Side Effects Improve Overall Survival in Hepatocellular Carcinoma Patients: A Real-Life Retrospective Analysis

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Keywords

Sorafenib · Hepatocellular carcinoma · Learning curve · Prognosis · Adverse events

Abstract

Background: Sorafenib is the first-line treatment for advanced hepatocellular carcinoma (HCC). The management of its side effects is improving. This study aimed to assess, in real life, if this translates into a better prognosis. **Methods:** This was a retrospective study of advanced HCC patients treated with sorafenib between 2007 and 2017. **Results:** 188 advanced HCC patients received >4 weeks of sorafenib. Median treatment duration was 5.4 months and median overall survival (mOS) 10 months (95% confidence interval 15–27). Sorafenib was initiated in 65 patients in 2007–2012 and 123 in 2013–2017. Both groups were comparable except for Barcelona Clinic liver cancer class. Tumor progression, disease control (DC) rate, and incidence of toxicity were similar in the 2 periods, but the duration of treatment (4.3 vs. 5.9 months; $p < 0.01$) and mOS (8 vs. 12 months; $p < 0.002$) differed. Among progressive disease patients, mOS was similar (7 months) but for those who had DC at 8 weeks, mOS was longer in the recent period (13 vs. 27 months; $p < 0.0001$). In the univariate analysis of OS, the period of treatment had a prognostic value. **Conclusion:** When comparing 2 periods of treatment in advanced HCC patients under sorafenib, duration of treatment and mOS were higher in the recent period. While mOS did not differ for patients who progressed, it was 2-fold higher in the recent period for those who had tumor control. Improvements in the use of sorafenib seem to be associated with better outcomes limited to patients with DC.

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Introduction

Sorafenib has been the global gold standard, first-line systemic treatment for advanced hepatocellular carcinoma (HCC) since 2007, when 2 large-scale, randomized controlled trials [1, 2] demonstrated a survival benefit over placebo, despite a low radiological response rate. Surprisingly, adoption of sorafenib in the USA was particularly low, with no clear explanation for this [3]. In the phase I studies, dose-limiting toxicities of sorafenib were diarrhea, fatigue, and a very unusual skin toxicity (palmoplantar erythrodysesthesia and rash) [4]. In the phase II study, dedicated to HCC [5], a modified grading scale, specific dose delays, and modification rules for skin toxicity were implemented; nevertheless, grade 3 drug-related dermatologic adverse events (AEs) were observed in 6% of the patients and almost half had dermatologic events of any grade. In the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial [1], demonstrating an improvement in median overall survival (mOS) (from 7.9 months with placebo up to 10.7 months with sorafenib), the same guidelines with dose delays and modifications to treat side effects, particularly dermatologic toxicities, were provided. Despite these precautions, dermatologic events were the most frequent cause of grade 3–4 drug-related AEs, the second cause of dose reduction in the SHARP trial, and the most common cause in the Asia-Pacific trial [2, 6].

In HCC as well as in renal-cell cancer [6], dermatologic toxicity mainly occurs early (2–4 weeks following treatment initiation), and its prevalence decreases after 6–8 weeks, with fewer cases reported after 3 months [7]. It seems logical to expect that improving the management of these dermatologic side effects could translate into a longer duration of treatment, and at a higher dose, resulting in a better outcome. Year after year, the management of side effects (particularly dermatologic events) [8, 9], constitutional syndrome (asthenia, anorexia, and weight loss), and patient education have undergone continuous improvements as a result of new publications [10] and “empirical” improvements to physicians’ practices [11] for dealing with dose reductions/interruptions/reintroductions. In parallel, guidelines in phase 3 trials have evolved, emphasizing preventive measures, and, in more recent trials, allowing dose reescalation of sorafenib after skin toxicity, at the physician’s discretion (e.g., the Adjuvant Sorafenib for Hepatocellular Carcinoma after Resection or Ablation [STORM] trial) [12]. Moreover, it is now clear that toxicities, particularly dermatologic side effects, are correlated with sorafenib efficacy, leading to better OS [13]. The possibility of long-lasting responses or stabilization as well as very long survival [14] encourages patients and physicians to continue treatment even when there are side effects.

This retrospective study aimed to determine whether improvement in the use of sorafenib based on experience, and particularly on better strategies for managing the side effects, was associated with better outcomes. We retrospectively analyzed patients treated with sorafenib in our institution by comparing two 5-year periods: 2007–2012 (the learning period) and 2013–2017 (the recent period). Obviously, as this is a real-life retrospective survey, many data are lacking, but we consider that it nonetheless provides an interesting snapshot of sorafenib use and outcomes across different time periods in a French Hepatology Unit.

Patients and Methods

Patients

This single-center, retrospective study included all HCC patients in our institution treated with sorafenib between November 2007 and December 2017. Only patients who received at least 4 weeks of sorafenib with full follow-up at our institution were retained for the analysis of the prognostic impact of the treatment period. The follow-up was closed on March 1st 2018.

After treatment initiation, patients had a safety follow-up at least twice a month for 2 months and then on a monthly basis. Biological tests (blood count, Na⁺, K⁺, Mg⁺⁺, P⁺⁺, liver tests, INR, and albumin) were performed on days 14 and 28 and then monthly, TSH was measured every other month, and tumor parameters (contrast-enhanced CT scan and α -fetoprotein [AFP] blood level) were assessed every 8 weeks. Tumor response was defined according to Response Evaluation Criteria in Solid Tumor (RECIST) and then (beginning in 2011) modified (m)RECIST [15]. Disease control (DC) rate was the percentage of patients without tumor progression (objective response plus stable disease) and was assessed after 8 and 16 weeks of treatment. No central review of tumor response was done. As RECIST and mRECIST gave similar results in assessing disease progression [16, 17] (and then DC, our major radiologic parameter), we did not reread the CT scans.

Dose modifications due to AEs were based on their severity. In the learning period, we strictly followed the dose reduction guidelines from the SHARP trial; in brief, this consisted of a dose delay in the case of grade 3–4 nondermatologic side effects or grade 2 dermatologic toxicities, in most cases a decrease of 1 (200 mg $\times$ 2/day) or possibly 2 (400 mg every 2 days) dose levels, without any possibility of dose reescalation. No preventive measure was systematically proposed.

At the end of 2012, we decided to modify these rules. Briefly, we proposed symptomatic treatment without sorafenib dose modification for grade 1 toxicity, with a dose reduction for grade 2 AEs, and with a dose interruption for grade 3. In cases of fatigue, anorexia, or weight loss, after excluding other explanations by means of biological tests (hemoglobin, Na⁺, K⁺, Mg⁺⁺, P⁺⁺, and TSH), the dose was decreased to 400 mg/day for 7 days. If the patient experienced an improvement, this dose was continued for another week, and then increased to 800 mg/day. If the patient was still symptomatic on day 7, the treatment was stopped for at least 1 week; in the case of improvement, 400 mg/day (at dinnertime) was proposed and maintained. These rules were explained to the patients and a phone number was available if they had any questions. If the performance status remained poor, sorafenib was stopped and a CT scan was performed to rule out an early progression. All patients routinely received diosmectite, 1–3 doses of 3 g per day to prevent and treat diarrhea. Dermatologic toxicity was proactively managed by pretreatment with urea creams (50 and 10%) twice a day, beginning 1 week before the initiation of sorafenib. In case of a grade 2 dermatologic event, the sorafenib dose was decreased to 400 mg/day and local treatment was intensified. If dermatologic signs persisted, sorafenib was withheld for at least 1 week; when dermatologic toxicity resolved, the dose was progressively increased (from 400 mg/day for 1 week to 600 mg/day for another week, and then 800 mg/day if all went well). During the entire course of therapy, patients could alternate between periods of receiving 800, 600, or 400 mg/day, and pauses.

Sorafenib was stopped in cases with severe side effects that recurred and impaired quality of life when reintroducing the dose of 400 mg/day, when toxicity was associated with tumor progression, or when the tumor progressed in the absence of symptomatic progression if a second-line trial was available.

Statistical Tests

Qualitative variables are expressed as frequencies and percentages and compared using the χ^2 test or the Fisher exact test when required. Quantitative variables are expressed as means (range) and compared using the Student parametric test under the normality assumption or else the nonparametric Wilcoxon test. The normality assumption was assessed using the Shapiro-Wilk test. Data relative to time durations and survivals are expressed using medians (95% confidence interval [CI]). Survival analyses were performed using Kaplan-Meier curves and compared by log-rank tests. Univariate and multivariate analyses were performed for detecting independent factors of OS. For quantitative variables, the cutoff values were set at 200 ng/mL for AFP serum level and at the median value of the entire group for platelets, albumin, and bilirubin serum levels. Variables that were significant in the univariate analysis were included in the multivariate analysis (except for period of treatment). A *p* value <0.05 was used to indicate statistical significance. All statistical tests were performed using SAS v9.4 software (SAS Institute Inc, Cary, NC, USA).

Results

Patients

From 2007 to 2017, treatment with sorafenib was initiated in 227 consecutive HCC patients. In 39 patients, sorafenib was stopped early, mainly because another therapeutic option was proposed at our multidisciplinary team meeting (*n* = 27 patients: 18 underwent

transarterial chemoembolization, 4 had best supportive care, and 5 entered a clinical trial), there were major side effects/refusal of treatment ($n = 6$), or no clear explanation ($n = 6$). Our analysis is therefore based on 188 patients treated with sorafenib for >4 weeks who had their entire follow-up in our institution.

This population was composed of 21 women and 167 men with a median age of 66 (95% CI 63–68; range 31–89) years. Only 2 patients had moderate liver fibrosis; all others had severe chronic liver disease, at the stage of cirrhosis in most cases. Etiology of the underlying liver disease was C virus infection in 38%, alcoholism in 30%, nonalcoholic steatohepatitis in 19%, B virus infection in 7%, and other etiologies or the absence of a diagnosis in 6%. Most patients ($n = 127$, 68%) had previously received another treatment for HCC: 62 transarterial chemoembolization, 24 resection, and 11 percutaneous treatments; sorafenib was used as the front line in 61 patients.

At sorafenib initiation, 145 patients (77%) were Child-Pugh A and 43 (23%) were Child-Pugh B. According to the Barcelona Clinic liver cancer (BCLC) classification, 15 (8%) were intermediate stage (TACE failures) and 173 (92%) were advanced stage. Macrovascular invasion was present in 91 patients (48%), and extrahepatic metastases were observed in 36 (19%) in the lymph nodes ($n = 9$), bone ($n = 10$), lung ($n = 11$), adrenal glands ($n = 3$), or peritoneum ($n = 3$). ECOG performance status was 0 in 93 patients and 1 in 95 patients, respectively.

Treatment Efficacy and Toxicity

The median duration of sorafenib treatment was 5.4 (95% CI 4.5–6.0; range 1.0–70) months. mOS was 10 (95% CI 8–12) months. Seventy-six patients (40%) had DC at 8 weeks, and 45 (24%) at 16 weeks; the mOS of these subgroups was, respectively, 18 (95% CI 15–27) months and 19 (95% CI 15–37) months. Of note, the DC rate at 8 weeks was 41% among BCLC C patients and 47% among BCLC B patients (ns). An objective response (RECIST or mRECIST) was obtained in 16 patients (8.5%), including 2 cases with a complete response (mRECIST). The mOS of these 16 responders was 47 (95% CI 19–74) months.

AEs (of any grade) occurred in 137 patients (73%), mainly dermatologic toxicities ($n = 55$; 29%), diarrhea ($n = 19$; 10%), fatigue and weight loss ($n = 24$; 13%), hypertension ($n = 3$; 2%), and worsening of liver function ($n = 42$; 22%). In particular, a hand-foot skin reaction requiring treatment was observed in 58% of the patients who reached 16 weeks of DC versus 20% ($p < 0.0001$) of those who progressed early (before 8 weeks).

Comparison of the 2007–2012 and 2013–2017 Data

Sorafenib was initiated in 65 patients in 2007–2012 and in 123 in 2013–2017. The characteristics of these patients are summarized in Table 1. Both groups were comparable for most parameters, but BCLC stage differed significantly: 12% were intermediate stage in the recent period versus none in the learning period ($p < 0.003$). All other major parameters (performance status, liver disease etiology, Child-Pugh class, tumor extension, and biological tests) were similar in both periods. Therefore, even if better patient selection was likely in the recent period, this difference was not statistically significant for any parameters other than BCLC stage.

The incidence of dermatologic side effects was not statistically different ($p = 0.31$) between the 2 periods; it was 25% in the learning period and 32% in the recent period, respectively.

The median duration of sorafenib treatment (Table 2) was 4.3 (95% CI 3.0–5.4) months in the learning period, and significantly longer ($p < 0.0009$), i.e., 5.9 (95% CI 4.7–6.7) months, in the recent period (2013–2017). We do not have precise enough data to describe dose modifications, suspensions, and reintroductions in either of the groups (particularly in the recent period).

Table 1. Main characteristics of the 188 patients treated with sorafenib for >1 month and followed up in our institution in 2007–2017

	Sorafenib 2007–2012 (n = 65)	Sorafenib 2013–2017 (n = 123)	p value
Age, years	63.8±10.2	65.7±9.5	0.21
ECOG performance status			0.34
0	35 (54)	58 (47)	
1	30 (46)	65 (53)	
Etiology of HCC			0.20
Hepatitis C	23 (35)	48 (39)	
Alcohol abuse	25 (38)	31 (25)	
Hepatitis B	7 (11)	6 (5)	
Nonalcoholic steatohepatitis	7 (11)	30 (24)	
Other	3 (5)	8 (7)	
Child-Pugh grade			0.30
A	47 (72)	98 (80)	
B	18 (28)	25 (20)	
Vascular invasion	29 (44.5)	62 (50.5)	0.45
Metastasis ^a	13 (20.0)	23 (18.5)	0.83
BCLC class			0.0033
B	0 (0)	15 (12)	
C	65 (100)	108 (88)	
Platelets, × 10 ⁹ /L	145±79	165±124	0.76
Bilirubin, μmol/L	27±16	23±18	0.054
Albumin, g/L	33±6	35±9	0.48
AFP, ng/mL	2,331±5,865	7,208±35,078	0.60

Values are expressed as n (%) or mean ± SD. ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic liver cancer; AFP, α-fetoprotein.

^a Lymph nodes, bone, lung, adrenal, peritoneum.

Table 2. Efficacy of sorafenib in HCC in the 2 periods: 2007–2012 and 2013–2017

	2007–2012 (n = 65)	2013–2017 (n = 123)	p value
Treatment duration, months	4.3 (3.1–5.1)	5.9 (4.7–6.7)	0.0009
Patients with dermatologic AEs	16 (25)	39 (32)	ns
OS, months	8 (6–11)	12 (9–15)	0.002
DC at 8 weeks			
Patients	22 (34)	54 (44%)	ns
OS, months	13 (8–15)	27 (18–44)	0.0001
DC at 16 weeks			
Patients	12 (18)	33 (27)	ns
OS, months	13 (5–24)	25 (16–47)	0.0075
PD at 8 weeks			
Patients	43 (66)	69 (56)	ns
OS, months	7 (5–9)	7 (6–9)	ns

Values express n (%) or median (95% confidence interval). Bold type denotes statistical significance. AEs, adverse events; OS, overall survival; DC, disease control; PD, progressive disease.

In both periods, the proportion of patients who progressed early (<8 weeks) or who achieved DC was the same. The mOS differed significantly between the 2 periods, from 8 (95% CI 6–11) months in the learning period to 12 (95% CI 9–15) months in the recent period ($p = 0.002$) (Fig. 1a). DC at 8 and 16 weeks was observed in 22 (34%) and 12 patients (18%), respectively, in the learning period, and in 54 (44%) and 33 patients (27%) in the recent period. However, these patients had statistically significant differences in survival between the 2 periods: 13 versus 27 months ($p < 0.0001$) for those with DC at 8 weeks (Fig. 1b) and 13 versus 25 months ($p = 0.0075$) for those with DC at 16 weeks. Respectively, 43 (66%) and 69 patients (56%) had progressive disease at 8 weeks; the mOS of these groups was similar in the 2 periods (at 7 months) (Fig. 1c).

Fifty-seven patients received other treatment after sorafenib, 13 (20%) during the learning period and 44 (36%) in the recent period. In the learning period, the second-line treatments were: systemic chemotherapy in 2, TACE in 3, radioembolization in 1, surgery in 1, and palliative irradiation for bone or lymph node metastases in 6. In the recent period, 19 received regorafenib, but only in the last months of 2017 [18] and 10 of these were early progressors, 3 included in a second-line trial, and 1 received systemic chemotherapy; 10 received TACE second-line, and 11 underwent palliative irradiation of metastases.

Prognostic Factors

Univariate analysis of OS (Table 3) identified the following prognostic factors: Child-Pugh class, bilirubin serum level, albumin serum level, AFP serum level, performance status (PS) (0 vs. 1–2), vascular invasion, metastasis, and period of treatment. The BCLC class did not reach significance as a prognostic factor in this small cohort of 188 patients, meaning that the impact of the difference in BCLC frequency between the 2 groups did not significantly affect the difference in OS.

These variables (but not the period of treatment) were introduced in the multivariate analysis of prognostic factors of OS (Table 4). Only 2 variables had statistically significant prognostic value for OS: AFP ($p < 0.01$) and Child-Pugh class ($p = 0.01$). PS (0.051) and vascular invasion ($p = 0.08$) were not far from significance.

Discussion

In the last 2 decades, many new drugs, targeted therapies and, more recently, immunotherapies have been added to the therapeutic arsenal available to medical oncologists. These new and effective therapies come with impressive costs as well as new and somewhat surprising adverse effects, completely different from what was experienced in the past [18]. Clinicians have had to adapt to these new toxicities and learn how to recognize them early, prevent them, and decide to stop treatment when they are severe. This period corresponds to a learning curve which can be quite steep, particularly if one treats only a few cases annually.

This retrospective analysis performed in the real-life setting, in a single center, provides important information on sorafenib-prescribing practices in HCC and patient outcomes.

First, in most cases, the inclusion/exclusion criteria of the SHARP trial were met [1]: all of our patients were PS 0–1 and we did not treat any patients with end-stage HCC. However, almost a quarter of our patients were Child-Pugh B when initiating sorafenib, independent of

Fig. 1. Survival curves of patients treated with sorafenib for hepatocellular carcinoma (HCC) in 2007–2012 (dotted line) and 2013–2017. **a** Prognosis improved in the recent cohort ($p < 0.002$). **b** Patients who had disease control at 8 weeks. The prognosis improved in the recent cohort ($p < 0.0001$). **c** Patients who progressed early (<8 weeks). The prognosis remained stable.

Table 3. Prognostic factors for overall survival in the cohort of 188 hepatocellular carcinoma patients treated with sorafenib

Parameters	Univariate analysis	
	median survival, months (95% CI)	p value (log rank)
Sex		0.90
Male	10 (8–13)	
Female	12 (5–24)	
Child-Pugh class		<0.0001
A	12 (9–13)	
B	5 (3–8)	
BCLC class		0.29
B	11 (8–18)	
C	10 (8–12)	
Platelets		0.18
≤130 × 10 ⁹ /L	11 (8–13)	
>130 × 10 ⁹ /L	8 (7–11)	
Bilirubin		0.03
≤18.3 μmol/L	13 (9–15)	
>18.3 μmol/L	8 (6–11)	
Albumin		0.01
≤33 g/L	8 (6–11)	
>33 g/L	13 (8–15)	
AFP		0.001
≤200 ng/mL	13 (11–16)	
>200 ng/mL	8 (6–10)	
PS		<0.0001
0	13 (11–15)	
1	7 (5–8)	
Vascular invasion		<0.0001
No	13 (11–16)	
Yes	7 (6–9)	
Metastasis		0.01
No	9 (8–12)	
Yes	17 (8–27)	
Period of treatment		0.002
2007–2012	8 (6–11)	
2013–2017	12 (9–15)	

Bold type denotes statistical significance. BCLC, Barcelona Clinic liver cancer; AFP, α-fetoprotein; PS, performance status.

the period. These figures are close to what was observed in the observational registry, and we confirm that the mOS of Child-Pugh B patients is poor (5 months in our retrospective analysis as well as in the GIDEON study) [6].

Second, we observed DC at 8 weeks in 76 patients (40%) and an objective response in 16 (8.5%). These figures are also very close to those reported in the literature. Both situations are associated with a better outcome, with mOS reaching 18 and 47 months, respectively. In agreement with recent literature data, most of our patients who achieved tumor control experienced dermatologic toxicity requiring treatment, a rate 3 times higher than those who progressed (58 vs. 20%).

Third, when we split our study into 2 periods, there was a significant improvement in OS in the recent period (i.e., from 8.0 months in 2007–2012 up to 12.0 months in 2013–2017) which was confirmed ($p = 0.002$) in a univariate analysis.

Table 4. Multivariate analysis of overall survival in the cohort of 188 hepatocellular carcinoma patients treated with sorafenib in 2007–2017

Parameters	OR (95% CI)	p value
Child-Pugh, A vs. B	1.82 (1.07–3.10)	<0.03
Bilirubin, ≤18.3 vs. >18.3 μmol/L	0.84 (0.55–1.31)	0.44
Albumin ≤33 vs. >33 g/L	1.02 (0.65–1.59)	0.95
AFP, ≤200 vs. >200 ng/mL	2.03 (1.34–3.07)	<0.001
PS, 0 vs. 1	1.46 (0.96–2.21)	0.07
Vascular invasion, yes vs. no	1.54 (1.00–2.37)	<0.05
Metastases, no vs. yes	0.78 (0.42–1.47)	0.44
Period of treatment, 2007–2012 vs. 2013–2017	0.66 (0.44–1.00)	0.05

Bold type denotes statistical significance. AFP, α-fetoprotein; PS, performance status.

This is not related to major differences between treated patients from the 2 periods. As in most hepatology centers, the proportion of HCC from nonalcoholic steatohepatitis increased. In the recent period, 12% of the patients who received sorafenib were intermediate stage; this can be related to a modification of our stopping transarterial chemoembolization, with a more rapid shift to medical treatment in cases of an absence of tumor response after 2 sessions. This higher frequency of BCLC B patients in the recent period certainly contributed to the improvement of survival but its impact was likely minimal because median OS between BCLC B and C patients was similar as the same percentage of patients progressed at 8 weeks in both groups, and BCLC stage did not reach significance in the univariate analysis of OS prognostic factors.

However, the period was associated with a major impact on survival for patients who achieved DC (mOS: 13 vs. 27 months for those with DC at 8 weeks), probably related to a longer treatment duration of this first line (4.3 vs. 5.9 months; $p < 0.0009$).

The second-line treatment could have had an impact on this improved mOS, but this would undoubtedly have been minimal, as regorafenib (the only efficient second-line treatment) was initiated in only 19 patients just before the end of this survey, and had only a small impact (increased mOS, from 7.8 to 10.6 months; hazard ratio = 0.63), and most of these patients were early progressors without obvious improved survival when compared to the learning period.

We therefore assumed that this gain in survival between periods is probably a reflection of improvements in our strategy for managing sorafenib side effects, thereby allowing a longer duration of treatment (4.3 vs. 5.9 months; $p < 0.009$), and thus longer tumor control. The incidence of dermatologic AEs remained high in both periods, indicating that the efficacy of preventive and palliative measures was mainly with regard to the severity and tolerability of these toxicities. It is also plausible that a succession of pauses and dose reductions improves overall tolerance, allowing patients to stay on sorafenib for a longer time with a greater likelihood of benefit. This improvement was also observed in different first-line trials that included a sorafenib arm. Intertrial comparisons are always difficult, particularly when different populations (e.g., Asian or Western patients) are involved. Nevertheless, trial after trial, there has been a decrease in discontinuation rates for serious AEs related to sorafenib (33% in SHARP [1], 33% in the brivanib trial [19], 25.4% in the linifanib trial [20, 21], 12.7% in the sunitinib trial [22] and, more recently, 7% in the lenvatinib trial [21]). In parallel, the mOS in Western or non-Asian populations in these trials, initially at 10.7 months in the SHARP trial, increased to 11.6 months in the brivanib trial, 12.4 months in the linifanib trial, 15.1 months in the sunitinib trial, and 14.2 months in the lenvatinib trial (but with more restrictive inclusion criteria).

Further analysis of the efficacy data reveals that the incidence of patients who experienced progressive disease remained stable at around 60% in the 2 periods examined; the mOS of these progressors was unchanged and very poor (7 months) despite frequent use of regorafenib. On the other hand, the benefits observed in the recent period mainly concern the patients who experienced DC (at 8 and at 16 weeks), with a doubling of mOS between the 2 periods (from 13 to 27 months). Second-line regorafenib may have contributed to this, although this drug was only given a few months before ending our analysis, and without any impact on the population of early progressors.

To summarize, when comparing 2 periods in a real-life population of HCC patients treated with sorafenib, the indications remained stable and dermatologic toxicities occurred at the same rate, but the duration of treatment and OS improved. This improvement was only observed in patients who achieved DC at 8 weeks, a population that had a higher rate of dermatologic toxicities, while those who progressed early (globally, 60% of the cases without any differences between the 2 periods) had a poor and similar outcome in the 2 periods. These data support the association between toxicity (particularly skin toxicity) and efficacy of sorafenib, suggesting that improving the management of these toxicities at the discretion of the physician allows patients to stay on treatment longer, and thereby achieve a more favorable outcome. However, it is possible that this will not affect our ability to achieve DC and transform an early progressor to a responder or a patient with stable disease. These points as well as the costs of the drugs should be taken into account when planning a first-line treatment in the coming months with the arrival of new drugs [23].

Disclosure Statement

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Author Contributions

JLR and XA were involved in study design and interpretation of data. XA, HP, PC, VO, and MB were in charge of the patients and participated in interpretation of data. XA collected data. GP performed the statistical analysis and participated in interpretation of data. All authors reviewed and approved the final version of the manuscript.

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