Clinical Cancer Research

Sorafenib in Patients with Hepatocellular Carcinoma—Results of the Observational INSIGHT Study

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Abstract

Purpose: Sorafenib is the only currently approved systemic therapy for advanced hepatocellular carcinoma (HCC). We aimed to evaluate the safety and efficacy of sorafenib therapy in patients with HCC under real-life conditions regarding patient, tumor characteristics, and any adverse events at study entry and at follow-up visits every 2 to 4 months.

Experimental Design: The current INSIGHT study is a non-interventional, prospective, multicenter, observational study performed in 124 sites across Austria and Germany between 2008 and 2014.

Results: Median overall survival and time to progression (RECIST) were found to be dependent on baseline Barcelona Clinic Liver Cancer (BCLC) tumor stage (A: 29.2, B: 19.6, C: 13.6, D: 3.1 and A: 6.0, B: 5.5, C: 3.9, and D: 1.7 months, respectively), Child–Pugh liver function (A: 17.6, B: 8.1, C: 5.6 and A: 5.3, B: 3.3, C: 2.5 months, respectively), and performance status of the patient; however, age did not affect prognosis. Sorafenib-related adverse events at any grade occurred in 64.9% of patients, with diarrhea (35.4%), hand–foot–skin reaction (16.6%), nausea (10.3%), and fatigue (11.2%) occurring most frequently.

Conclusions: Sorafenib treatment was shown to be effective in a real-life setting, in agreement with previously reported clinical trial data. The therapy was found to have an acceptable safety profile, with predominantly mild to moderate side effects. *Clin Cancer Res; 23(19); 5720–8. ©2017 AACR.*

Introduction

Liver cancer is the fifth most common cancer worldwide in men, and the ninth most common in women, with incidence expected to increase in the coming years (1–3). Hepatocellular carcinoma (HCC) is the most common histologic subtype, accounting for around 80% of liver cancers (4). The main causes of HCC vary across the world, with hepatitis B infection prevailing in the Asia–Pacific (AP) region, while hepatitis C infection and alcohol abuse are the predominant etiologies in the western world (5–7). The survival rate of patients with HCC is particularly low owing to late diagnosis, the chemoresistant nature of such tumors, and the presence of underlying liver disease. Potentially curative treatment strategies, such as tumor resection, liver transplantation, or percutaneous local ablation, are only possible at an early stage (7, 8). Once the disease has progressed, transarterial chemoembolization (TACE) and systemic sorafenib therapy can only prolong survival (9). Sorafenib is a multikinase inhibitor that has demonstrated significant antiproliferative and antiangiogenic activity, as well as induction of tumor cell apoptosis in an HCC model (10, 11). It acts by disrupting the Raf/MEK/ERK pathway by inhibiting Raf-1, in addition to targeting a number of receptor tyrosine kinases, including VEGFRs (VEGFR-2 and VEGFR-3), platelet-derived growth factor receptor-β (PDGFR-β), Flt-3, cKIT, and RET.

In July 2006, sorafenib gained EMA approval for the treatment of HCC, with the FDA following in November 2007. This was as a result of a large multicenter, double-blind, placebo-controlled, phase III trial involving 602 patients with advanced HCC in Europe, North and South America, and Australia. The Sorafenib Hepatocarcinoma Assessment Randomized Protocol (SHARP, NCT00105443) trial demonstrated an increase in median overall survival time and time to radiologic progression, as well as a manageable safety profile, when patients were treated with sorafenib (12, 13). A separate trial in the AP region gave similar promising results. The AP trial involved a total of 226 patients with unresectable or metastatic HCC and demonstrated significantly longer overall survival for those who were treated with sorafenib (14, 15).

Noninterventional studies are important postapproval trials designed to characterize the safety and effectiveness of new therapies in a real-life setting. They have the advantage of including patient populations that are not usually enrolled in controlled

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Translational Relevance

The current INSIGHT study is a noninterventional, prospective, multicenter, observational study performed in 124 sites across Austria and Germany between 2008 and 2014. A total of 788 patients were included. Noninterventional studies are important postapproval trials designed to characterize the safety and effectiveness of new therapies in a real-life setting. They have the advantage of including patient populations that are not usually enrolled in controlled clinical trials, and the collected results are very important for the use in everyday clinical practice. With this study, we aimed to evaluate the safety and efficacy of sorafenib therapy in patients with hepatocellular carcinoma under real-life conditions outside the framework of a randomized clinical trial. In agreement with previously reported clinical trial data, sorafenib treatment was shown to be effective. The therapy was found to have an acceptable safety profile, with predominantly mild to moderate side effects.

clinical trials, such as those with Child–Pugh B status or of an older age. Here, we report on INSIGHT, a large multicenter, noninterventional study of sorafenib treatment in a broad HCC population. We describe the baseline characteristics of the patients, and their influence on safety and efficacy under real-life clinical conditions.

Patients and Methods

The INSIGHT study is a noninterventional, prospective, multicenter, observational study performed in 124 sites across Austria and Germany. The study ran from April 2008 to April 2014, with the final data collection cutoff for primary output being October 2013. Written informed consent was provided and ethical approval was obtained from the Ethical Committee of University Clinic Duisburg, Germany (no. 08-3611). The study was conducted in accordance with the Declaration of Helsinki.

Objectives

The objective of this study was to evaluate the safety and efficacy of sorafenib therapy, including overall survival and time to progression, in patients with HCC under real-life conditions. Further objectives were documentation of the duration of treatment and reports of adverse events (AEs).

Patients and treatment

The study included patients with HCC who were diagnosed according to the American Association for the Study of Liver Diseases (AASLD) guidelines 2005, and the subsequent 2011 update (16, 17), were aged 18 years or older, and were candidates for systemic therapy with sorafenib (7). The observation period for each patient was the time between the initial visit, where sorafenib therapy was commenced, and the time point of disease progression (according to RECIST criteria), death or unacceptable AEs leading to sorafenib discontinuation.

Sorafenib was administered orally with the dose and duration chosen at the discretion of the treating physician, complying with local product information. Although dosing was generally 800 mg daily, some patients were also started on a lower daily dose of 200, 400, or 600 mg.

Documentation

At each follow-up visit during sorafenib therapy, tumor and patient status evaluation, and the occurrence of AEs were documented. Data were collected at the start of sorafenib treatment, and then at intervals of 2 to 4 months. AEs were categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) v.3.0. A serious AE (SAE) was classed as an event that resulted in death, hospitalization, disability/incapacity, was life threatening, or was assessed to be an important medical event.

Statistical analysis

Data are given as percentages or means with SDs. Variables were considered on an available case basis, and the number of documentations available for each is noted in the results tables. Overall survival and time to progression are represented by Kaplan–Meier curves to illustrate outcomes over time. Univariate and multivariate Cox regression analyses were used to identify baseline characteristics associated with overall survival and time to progression. Factors included were age, gender, extrahepatic spread, and vascular invasion. Alpha-fetoprotein was excluded from the analysis owing to the high number of missing values.

Results

During the study period, 791 patients were enrolled in the trial. Of these, one patient received no treatment, and two patients had missing documentation. This resulted in a total of 788 patients for the safety analysis set. Another six patients were excluded from the efficacy analysis set: one patient had no written informed consent, one patient was misdiagnosed, and for four patients, no follow-up information was available. Therefore, a total of 782 patients were finally evaluated regarding efficacy.

The end of the study observation period was a result of disease progression for 284 patients (36.0%), death for 212 patients (26.9%), and unacceptable AEs leading to treatment discontinuation in 122 patients (15.5%).

Patient characteristics

The mean age (±SD) of the efficacy set was 66.7 years (±9.6), and the mean body mass index was 26.9 kg/m^2 (±4.6); 14.6% were female. The characteristics of the patients, including clinical background, are shown in Table 1. The majority of patients had Child–Pugh A liver cirrhosis (56.7%), predominantly due to chronic alcohol abuse (43.5%) or hepatitis B (11.6%) or C (13.9%). Most tumors were at Barcelona Clinic Liver Cancer (BCLC) stage C (50.1%), with 53.2% limited to the liver. A small proportion of patients were treated with sorafenib even though it was not indicated in the EASL guidelines (7). About half of the patients had undergone prior treatment for HCC, including surgery (21.5%) and locoregional treatment with TACE, RFA, or percutaneous ethanol injection (34.8%).

Efficacy

Median overall survival for the total population was 15.1 months, while time to progression was 4.2 months. The efficacy of sorafenib was further analyzed according to BCLC stage. As

Table 1. Patient characteristics (efficacy analysis set)

	$n = 782$	Mean ± SD or %
Age (years)	782	66.7 ± 9.6
>70 years	297	38.0
Female gender	114	14.6
Body mass index (kg/m^2)	739	26.9 ± 4.6
TNM[a]		
Stage I	9	1.2
Stage II	30	3.8
Stage IIIA	69	8.8
Stage IIIB	97	12.4
Stage IIIC	52	6.6
Stage IV	224	28.6
BCLC[b]		
Stage A	101	12.9
Stage B	194	24.8
Stage C	392	50.1
Stage D	14	1.8
Child–Pugh[c]		
A	443	56.6
B	182	23.3
C	26	3.3
ECOG[d]		
(0) Fully active	243	31.1
(1) Physically restricted	404	51.7
(2) Capable of self-care	126	16.1
(3) Capable of limited self-care	8	1.0
Prior treatment		
Surgical	168	21.5
Locoregional treatment	272	34.8
Percutaneous ethanol injection	16	2.0
Transarterial chemoembolization	213	27.2
Radiofrequency ablation	46	5.9
Tumor spread[e]		
Tumor limited to liver	416	53.2
Extrahepatic spread	283	36.2
Vascular invasion	171	21.9
Etiology[f]		
Hepatitis B	91	11.6
Hepatitis C	109	13.9
NASH	91	11.6
Alcohol	340	43.5
Aflatoxin	1	0.1
Other	204	26.1
Alpha fetoprotein		
≥400 ng/mL	252	32.2
Missing	112	14.3

Abbreviations: *n*, number of applicable patients; NASH; nonalcoholic steatohepatitis; TNM, tumor–nodes–metastases.
[a]Data missing/nonevaluable for 301 patients.
[b]Data missing/nonevaluable for 81 patients.
[c]Data missing/nonevaluable for 131 patients.
[d]Data missing/nonevaluable for one patient.
[e]Data missing/nonevaluable in one patient.
[f]Data missing/nonevaluable in 14 patients.

shown in Fig. 1A, the median overall survival for patients at BCLC stage A was 29.2 months. Median overall survival decreased to 19.6, 13.6, and 3.1 months for BCLC stages B, C, and D, respectively ($P < 0.0001$). Time to progression also significantly differed between the different BCLC stages (Fig. 1B; $P = 0.0001$; Table 2).

For patients with HCC and Child–Pugh A liver cirrhosis ($n = 443$), the median overall survival was 17.6 months (Fig. 2A). Overall survival for patients with Child-Pugh B ($n = 182$) and C ($n = 26$) significantly decreased, at 8.1 and 5.6 months, respectively ($P < 0.0001$). Time to progression was also dependent on Child–Pugh status, with values of 5.3, 3.3, and 2.5 months noted for patients with Child–Pugh A, B, and C, respectively ($P < 0.0001$; Fig. 2B). Median overall survival and time to progression did not differ significantly between patients with Child–Pugh A and B with BCLC stage A ($P = 0.19$ and $P = 0.17$, respectively; Fig. 2C and D). However, there was a significant variation in both of these parameters for patients with HCC at BCLC stage B or C (Fig. 2E–H). Owing to the small number of patients with Child–Pugh C status, this population was excluded from the subgroup analysis.

Patients with Child–Pugh B were further subdivided into those with Child–Pugh scores of 7, 8, and 9. Patients with Child–Pugh B score at 7 and 8 points demonstrated similar overall survival and time to progression. However, patients with Child–Pugh B with worse liver function (9 points) not only showed significantly shorter overall survival ($P = 0.003$) but also a significantly shorter time to progression ($P = 0.0001$; Fig. 2I and J).

The median overall survival and time to progression for patients >70 years of age was 13.3 months ($n = 297$) and 4.1 months ($n = 297$), respectively, which did not differ significantly from that of patients ≤70 years of age (overall survival 16.3 months, $n = 485$, $P = 0.39$, time to progression 5.0 months, $n = 485$, $P = 0.66$, Fig. 3A and B).

Baseline performance status [Eastern Cooperative Oncology Group (ECOG)] had a significant effect on overall survival (Fig. 3C), with distinguishable survival curves for ECOG 0, 1, 2, and 3 ($P < 0.0001$). The time to progression was similar in patients with ECOG 0, 1, and 2, but was significantly shorter in eight patients with ECOG 3 (Fig. 3D, $P < 0.0001$). In fully active patients (ECOG 0), median time to progression under sorafenib was 5.8 months, compared with 1.7 months for patients capable of only limited self-care (ECOG 3).

Multivariate analysis identified extrahepatic spread as independently associated with overall survival [HR, 1.64; 95% confidence interval (CI), 1.29–2.08; $P < 0.0001$] as was vascular invasion (HR, 1.45; 95% CI, 1.10–1.91; $P = 0.0081$] (Table 2). Extrahepatic spread was also independently associated with overall survival (HR, 1.40; 95% CI, 1.18–1.66; $P = 0.0001$) as was vascular invasion (HR, 1.40; 95% CI, 1.15–1.70; $P = 0.0009$). Age and gender were not associated with overall survival or time to progression in the multivariate analysis.

Safety

Out of the 788 patients included in the safety set, 688 patients (87.3%) experienced an AE during the follow-up period. For 394 of these patients, the AE was considered to be serious (50.0%), with diarrhea the most common of these AEs (6.0%) (Table 3). A total of 511 patients (64.9%) experienced an AE attributed to sorafenib [adverse drug reaction (ADR)], and for 77 (9.8%) of these patients, an ADR was considered to be serious. Again, diarrhea was the most frequently experienced serious ADR (5.2%). Of the total safety analysis set ($n = 788$), 279 patients (35.4%) suffered from diarrhea to some degree. The majority of cases (266) were considered to be drug related. The other most commonly experienced ADRs were hand–foot–skin reaction (HFSR; 16.5% of patients), nausea (8.0%), and fatigue (7.9%).

The ADRs that occurred were further analyzed according to the Child–Pugh status of the patient (Table 4). Of the 445 patients with Child–Pugh A, 322 patients (72.4%) experienced an ADR, 10 of which (2.3%) were classed as life threatening, and five (1.1%) of which resulted in death. Patients with Child–Pugh B and C

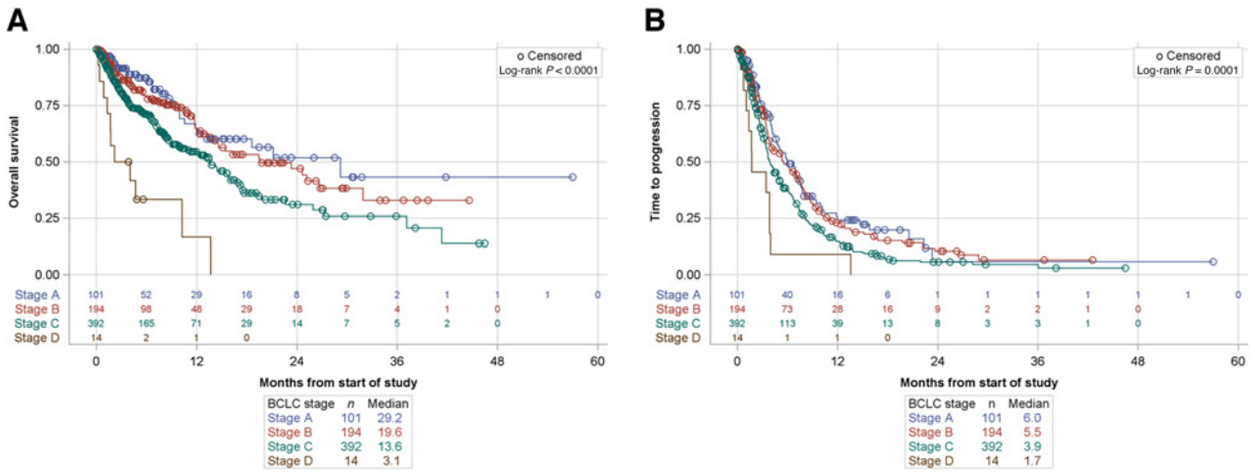

Figure 1.
Sorafenib efficacy according to BCLC classification.

experienced fewer ADRs compared with patients who had Child–Pugh A (50.8% and 30.8% for B and C, respectively).

Dosage and duration of treatment

A total of 307 patients (39.3%) received a lower starting dose than the recommended 800 mg/day. This was for a variety of reasons, most notably, comorbidities or a decision by the physician to evaluate the tolerability of the patient to sorafenib prior to escalating the dosage. The starting dose did not vary significantly with Child–Pugh score.

During the study, 517 patients (66.1%) underwent a change in the dose of sorafenib. This was a reduction for 458 patients (58.6%) and an increase for 145 patients (18.5%). The dose was reescalated in the cases of 196 patients (25.1%). The occurrence of an AE was the most common reason for a dose decrease.

Treatment duration was highest for the patients with Child–Pugh A, with a median value of 26.1 weeks in comparison with 14.5 and 17.1 weeks for patients with Child–Pugh B and C, respectively (Table 5). The proportion of patients who received sorafenib for $\leq$12 weeks was higher for the Child–Pugh B and C groups (45.6% and 42.3%, respectively) in comparison with Child–Pugh A (26.9%), while 34.5% of this latter group remained on treatment for over 36 weeks. At the time of the final analysis, five (1.1%) patients with Child–Pugh A were still receiving treatment, while all patients with Child–Pugh B and C had discontinued the therapy or had died.

Discussion

Two large randomized, double-blind phase III trials previously demonstrated improvements in overall survival and time to progression for patients who were administered sorafenib in comparison with placebo (12, 14). This resulted in the approval of the drug for the treatment of HCC. As clinical trials have strict inclusion and exclusion criteria, a wide variety of patients were not included in these prior studies. Both the SHARP and AP phase III trials predominantly included patients of BCLC stage C, Child–Pugh class A, and with an ECOG status of 0 or 1; this excluded a large number of patients. Owing to the format of the current study, patients with other BCLC stages, a Child–Pugh class of B or C, or patients who required significant care, could be included if the attending physician deemed sorafenib treatment to be appropriate. Therefore, patients with a range of HCC severities, varying liver function, and poorer performance statuses were represented in the current trial. The main objectives of this postmarketing, surveillance study were to assess the efficacy and safety of sorafenib in a real-life clinical setting.

Efficacy

Overall survival and time to progression were both found to be significantly higher for patients at less advanced HCC stages according to BCLC. However, BCLC stage was not found to be

Table 2. Uni- and multivariable predictors of overall survival and time to progression

	Overall survival (univariable)		Overall survival (multivariable)	
Baseline characteristics	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age >70 years	1.11 (0.88–1.41)	0.39		
Female	1.03 (0.74–1.44)	0.85		
Extrahepatic spread	1.59 (1.26–2.02)	0.0001	1.64 (1.29–2.08)	<0.0001
Vascular invasion	1.38 (1.05–1.81)	0.0218	1.45 (1.10–1.91)	0.0081
	Time to progression (univariable)		**Time to progression (multivariable)**	
Baseline characteristics	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age >70 years	1.04 (0.88–1.23)	0.66		
Female	0.95 (0.75–1.20)	0.67		
Extrahepatic spread	1.37 (1.16–1.63)	0.0003	1.40 (1.18–1.66)	0.0001
Vascular invasion	1.36 (1.12–1.66)	0.002	1.40 (1.15–1.70)	0.0009

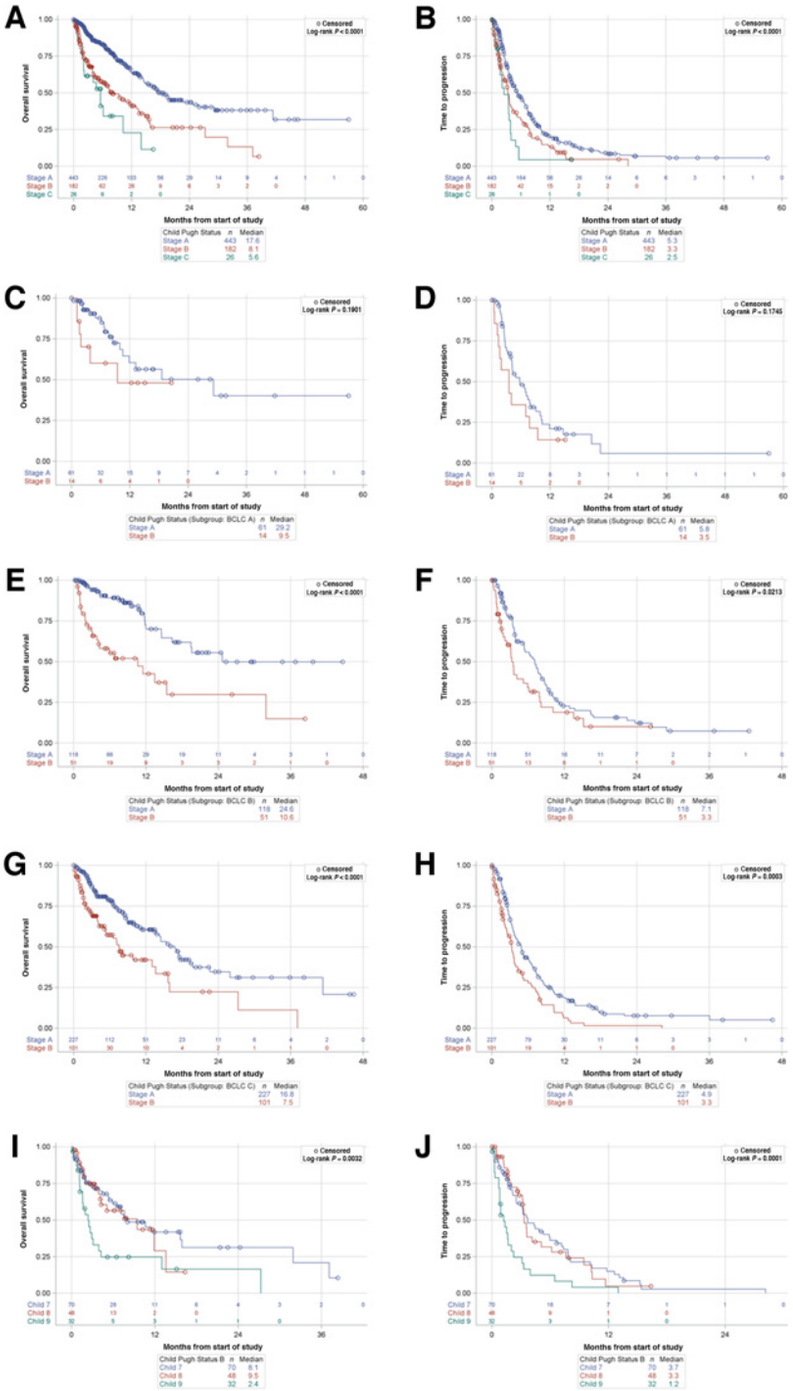

Figure 2.
Sorafenib efficacy according to liver function.

independently associated with prognosis. The efficacy of the drug for patients with a BCLC stage D was found to be much poorer than that for the other patients. This is in agreement with a study by Ozenne and colleagues, who reported that BCLC stage correlated with survival time for patients receiving sorafenib treatment (18). These data demonstrate that the BCLC stage of HCC is a good prognostic marker, and that, due to their short survival, HCC patients with BCLC stage D do not benefit to the same extent from sorafenib treatment.

The presence of extrahepatic spread (EHS) was associated with poorer overall survival but not time to progression. Similar results were found in a subanalysis of the SHARP trial, with shorter overall survival reported for the sorafenib-treated patients with EHS than those without (8.9 vs. 14.1 months), while time to progression was similar (5.3 vs. 5.8 months; ref. 13). In the current study, vascular invasion was independently linked to both outcomes, which is again in agreement with the SHARP trial, where shorter overall survival (8.1 vs. 14.1 months) and time to

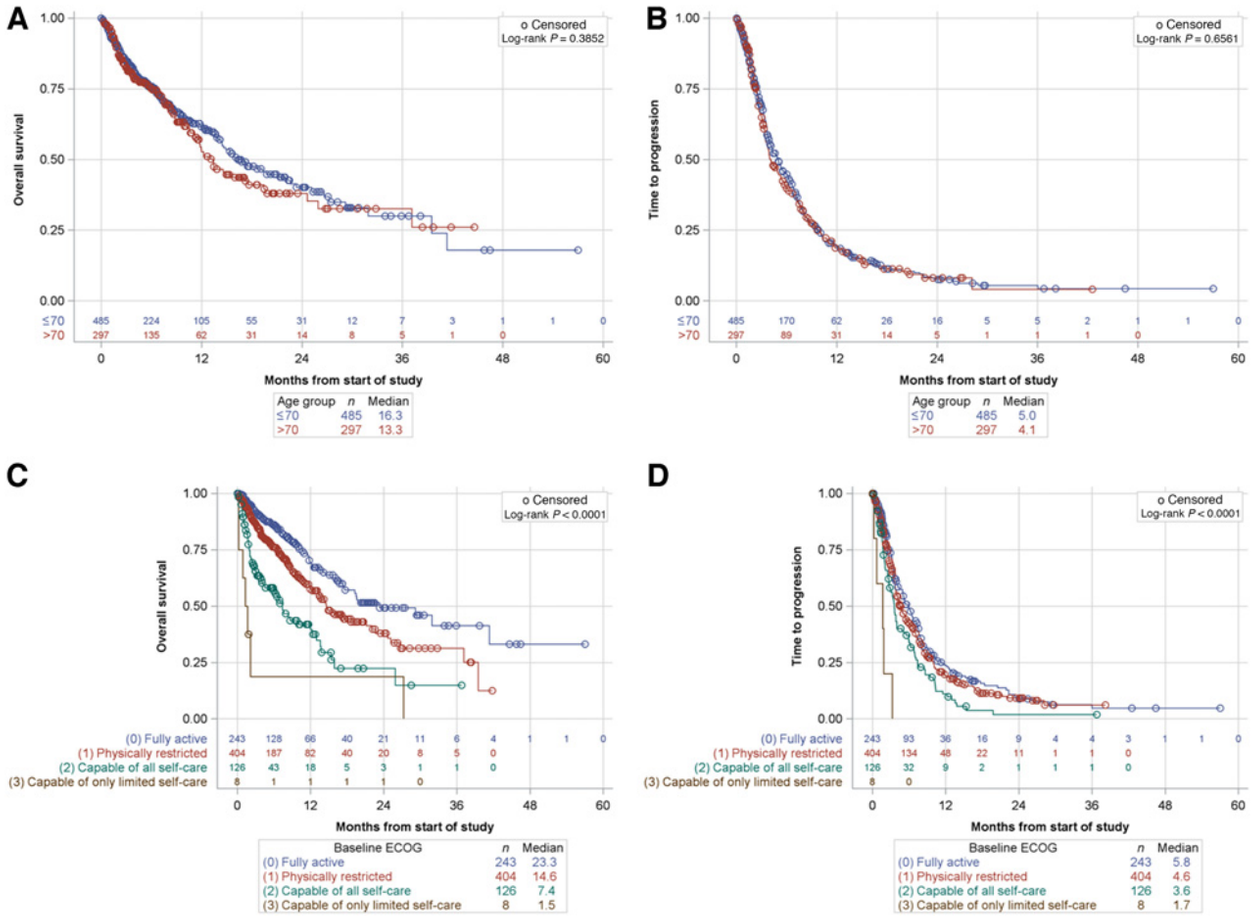

Figure 3.
Sorafenib efficacy according to age and ECOG.

progression (4.1 vs. 7.3 months) were identified when microvascular invasion was present (13).

Liver function was also found to correlate with the efficacy of sorafenib. As Child–Pugh status increased from A to C, both overall survival and time to progression decreased significantly. Furthermore, Child–Pugh status was found to be independently associated with both overall survival and time to progression. A study by Yada and colleagues investigating patients with BCLC stage C HCC found that overall survival for patients with Child–Pugh A was higher than for patients with Child–Pugh B, although, in contrast to our data, they reported no significant difference in time to progression (19). In the current study, for patients with single or small tumors (BCLC A), there was little difference in overall survival or time to progression between patients with Child–Pugh A and Child–Pugh B. This might be due to the lower number of patients with stage A BCLC in our cohort. For more severe disease (BCLC B and C), however, sorafenib treatment resulted in a superior prognosis for patients with better liver function (Child–Pugh A). Owing to the Child–Pugh scoring system, patients with Child–Pugh B cirrhosis represent a rather heterogeneous population. A study reported by Wörns and colleagues suggested that sorafenib treatment was not suitable for patients with Child–Pugh C, while a larger sample size was required to determine the benefits to patients with Child–Pugh B, as their results were inconclusive (20). It has been speculated that subdivision of this Child–Pugh stage would allow for more detailed assessment of the benefits of a treatment for patients on an individual level, potentially resulting in a more appropriate treatment strategy (21). Consequently, the Child–Pugh B category was subdivided according to scores of 7, 8, and 9. It was found that while patients with a score of 7 or 8 demonstrated good overall survival and time to progression, those with a slightly higher score of 9 had a much poorer prognosis. This suggests that there may be a cut-off point in terms of liver function, above which patients do not benefit substantially from sorafenib treatment.

We also found that age did not have a significant effect on survival of patients being treated with sorafenib. Neither overall survival nor time to progression varied between patients $\leq$70 years and >70 years, and age was not found to be independently associated with either outcome. In contrast, ECOG status had a strong influence on survival of sorafenib-treated patients, with patients who were only capable of limited self-care demonstrating low survival and time to progression. The multivariate analysis identified that both outcome parameters were poorer for patients with even just low levels of physical restriction in their daily lives

Table 3. Overall safety profile of sorafenib

	[*N* (%) = 788]
AE (all grades)	688 (87.3)
ADR (all grades)	511 (64.9)
Serious AE	394 (50.0)
Serious ADR	77 (9.8)
Grade 3 AE	267 (33.9)
Grade 3 ADR	143 (18.2)
Grade 4 AE	81 (10.3)
Grade 4 ADR	18 (2.3)
Deaths[a]	240 (30.5)
Drug-related deaths	9 (1.1)
AE (all grades) ≥5% of patients	
Diarrhea	279 (35.4)
HFSR	131 (16.6)
General physical health deterioration	90 (11.4)
Fatigue	88 (11.2)
Nausea	81 (10.3)
Ascites	59 (7.5)
Decreased appetite	58 (7.4)
Rash	52 (6.6)
Vomiting	46 (5.8)
Weight decrease	43 (5.5)
AE (grade 3/4) ≥5%	
Diarrhea	47 (6.0)
ADR (all grades) in ≥5% of patients	
Diarrhea	266 (33.8)
HFSR	130 (16.5)
Nausea	63 (8.0)
Fatigue	62 (7.9)
Rash	50 (6.4)
ADR (grade 3/4) ≥5%	
Diarrhea	41 (5.2)

[a]Overall 260 patients died, of which for 240, a CTC grade was available.

(ECOG ≥ 1). Koschny and colleagues and Iavarone and colleagues reported similar findings, with a poor ECOG score being predictive of a decrease in overall survival (22, 23).

Safety

The SHARP and AP phase III trials reported similar incidences of ADRs (80% and 81.9%, respectively; refs. 12, 14). In the current study, the overall incidence of ADRs was comparably low (64.9%), which is likely due to the inclusion of patients with Child–Pugh B and C, who were excluded from the phase III trials. Compared with the patients with Child–Pugh A, patients with Child–Pugh B and C had lower incidences of ADRs. The observational GIDEON study also included a proportion of patients with Child–Pugh B who were being treated with sorafenib (24). At the final analysis, they noted a similar rate of ADRs (66%) to that reported here; however, no great difference in overall rates of ADRs between patients with Child–Pugh A and B was found (25). We found that patients with lower Child–Pugh scores experienced more ADRs of grade 1–3 and a comparable number of grade 4 and 5 ADRs to those with higher Child–Pugh scores. Similar data were found in the GIDEON study, although the differences are more pronounced in the current work (25). This may be attributed to the shorter duration of treatment and overall survival of the patients with Child–Pugh C with a shorter sorafenib exposure time. Furthermore, in both the current study and the GIDEON study, the numbers of enrolled patients with Child–Pugh C were low ($n = 26$ and $n = 74$, respectively). A larger population would be needed to determine significance.

The nature of the ADRs found in the current study was similar to those reported in the aforementioned phase III trials and the GIDEON study, with diarrhea and HFSR being the most frequent (12, 14, 25). The only ADR that was found at grade 3/4 in more than 5% of patients was diarrhea. The SHARP and AP trials also reported significant proportions of patients with this ADR at this severity; however, in contrast with the current study, they also identified a similar or higher percentage with HFSR (12, 14).

Dosage and duration of treatment

A relatively high proportion of patients were started on sorafenib therapy at a lower dosage than the recommended 800 mg per day. Although in some cases, comorbidities or general poor health were the reasons behind such practice, in many cases, the treating physician initiated a lower dose to assess tolerability prior to performing a planned dose escalation. Further investigation into the resulting efficacy and safety associated with a lower starting dose would help to clarify the appropriateness of such an approach.

Many patients underwent either permanent or temporary dose changes during the course of the study. A high proportion of these were dose decreases as a result of an AE; however, in many cases, the dose was increased again once the AE had subsided or been treated effectively. Discontinuation of sorafenib treatment owing to unacceptable AEs was recorded for 15.5% of patients.

In comparison with patients with Child–Pugh B and C, those with Child–Pugh A underwent treatment with sorafenib for a longer duration. Furthermore, five patients with Child–Pugh A remained on sorafenib treatment at the time of the final analysis, while none of the patients with Child–Pugh B or C did. A similar trend was found in the observational GIDEON study, although the median treatment duration was lower for all patient categories (24, 25). The prolonged treatment is,

Table 4. Incidence of a adverse drug reactions by Child–Pugh score (based on $N = 788$ patients of the safety set)

	Total *N* (%)	CP-A *n* (%)	CP-B *n* (%)	CP-C *n* (%)	Data missing
Total patients	788	445	183	26	134
ADR					
Yes	511 (64.9)	322 (72.4)	93 (50.8)	8 (30.8)	88 (65.7)
CTCAE grading					
Grade 1 (mild)	258 (32.7)	158 (35.5)	44 (24.0)	3 (11.5)	53 (39.6)
Grade 2 (moderate)	331 (42.0)	208 (46.7)	57 (31.2)	7 (26.9)	59 (44.0)
Grade 3 (severe)	143 (18.2)	89 (20.0)	28 (15.3)	1 (3.9)	25 (18.7)
Grade 4 (life threatening)	18 (2.3)	10 (2.3)	6 (3.3)	1 (3.9)	1 (0.8)
Grade 5 (death)	9 (1.1)	5 (1.1)	4 (2.2)	0 (0.0)	0 (0.0)
Missing	43 (5.5)	29 (6.5)	10 (5.5)	1 (3.9)	3 (2.2)

Abbreviation: CP, Child–Pugh.

Table 5. Duration of treatment stratified by Child–Pugh subgroups and BCLC stage

	Patients	Median treatment duration [weeks (Q1, Q3)]	≤12 weeks [*n* (%)]	>12–24 [*n* (%)]	>24–36 [*n* (%)]	>36 [*n* (%)]	Patients continuing Tx [*n* (%)]
Total	782	22.0 (10.1, 44.7)	245 (31.3)	176 (22.5)	116 (14.8)	236 (30.2)	9 (1.2)
Child–Pugh							
A	443	26.1 (11.9, 48.9)	119 (26.9)	99 (22.3)	67 (15.1)	153 (34.5)	5 (1.1)
B	182	14.5 (5.7, 33.1)	83 (45.6)	42 (23.1)	22 (12.1)	35 (19.2)	0 (0.0)
C	26	17.1 (7.4, 24.4)	11 (42.3)	5 (19.2)	7 (26.9)	3 (11.5)	0 (0.0)
Missing	131	26.0 (13.6, 54.1)	32 (24.4)	30 (22.9)	20 (15.3)	45 (34.4)	4 (3.1)
BCLC							
Stage A	101	26.0 (13.1, 57.6)	28 (27.7)	20 (19.8)	17 (16.8)	34 (33.7)	2 (2.0)
Stage B	194	26.7 (9.9, 52.1)	54 (27.8)	42 (21.7)	25 (12.9)	70 (36.1)	3 (1.5)
Stage C	392	19.6 (9.2, 39.6)	138 (35.2)	91 (23.2)	57 (14.5)	105 (26.8)	1 (0.3)
Stage D	14	13.1 (5.7, 21.0)	7 (50.0)	4 (28.6)	1 (7.1)	2 (14.3)	0 (0.0)
Missing	81	26.1 (14.3, 51.3)	18 (22.2)	19 (23.5)	16 (19.8)	25 (30.9)	3 (3.7)

Abbreviations: Q, quartile; Tx, treatment.

however, not related to the rates of ADRs, as the frequencies of severe events were similar for all Child–Pugh statuses. Treatment duration did not vary between patients with a BCLC stage of A or B, whereas those with C or D received treatment for shorter periods. The proportions of patients who were treated with sorafenib for over 36 weeks was comparable between those of BCLC stage A and B, with only a small proportion of patients with stage D BCLC remaining on the therapy for this length of time.

Conclusions

Sorafenib treatment was shown to be effective in a real-life setting, in agreement with previously reported clinical trial data. Disease stage (BCLC classification), liver function (Child–Pugh stadium), and performance status (ECOG score) correlated with longer overall survival and time to progression. The therapy was found to have an acceptable safety profile, with predominantly mild to moderate side effects. The data obtained in this observational study agree well with those of previously reported clinical trials, validating the results in a real-life setting.

Disclosure of Potential Conflicts of Interest

T.M. Ganten and E. Schott report receiving speakers bureau honoraria from and are consultant/advisory board members for Bayer. P.R. Galle reports receiving speakers bureau honoraria from Bayer and is a consultant/advisory board member for Bayer, Bristol-Myers Squibb, Lilly, MSD, Sillajen, and Sirtex. R. Koschny reports receiving commercial research support from Bayer. No potential conflicts of interest were disclosed by the other authors.

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