ORIGINAL RESEARCH

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Unresectable Hepatocellular Carcinoma and Prognostic Factors of Sorafenib Treatment: A Real-Life Experience

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ABSTRACT Objective: Sorafenib is the first targeted therapy for patients with advanced hepatocellular carcinoma (HCC). This multicenter study primarily aimed to assess real-life experiences of sorafenib in patients with advanced HCC in Türkiye and to determine the prognostic factors. **Material and Methods:** Patients treated with sorafenib for HCC treatment were included in a retrospective collection of demographic, clinical, and laboratory data. Overall survival (OS) and progression-free survival (PFS), safety data, and prognostic factors were analyzed. **Results:** A total of 147 patients receiving sorafenib from six tertiary oncology centers were included. Approximately 88.4% and 11.6% of patients were Child-Pugh (CP) classes A and B, respectively. The median PFS was 5.1 (95% CI, 4.3 to 5.9) and 2.9 months (95% CI, 2.3 to 3.5), and OS was 9.8 (95% CI, 6.4 to 13.2) and 5.3 months (95% CI, 4.1 to 6.5) in patients with CP-A and CP-B, respectively. There was a difference in OS between CP-A and B (p=<0.001). The most common adverse event was diarrhea (19.7%, Grade 1-2; 6.8%, Grade 3). The eastern cooperative oncology group (ECOG) performance score, CP score, neutrophil-lymphocyte ratio (NLR), and alpha-fetoprotein (AFP) values were found to be independent prognostic factors. **Conclusion:** OS and PFS were similar in routine clinical practice compared to Phase III pivotal SHARP and Asia-Pacific trials. The median survival was longer in those with a better ECOG performance score, CP-A, and lower NLR and AFP levels.

Keywords: Hepatocellular carcinoma; prognostic factors; sorafenib; real-life experience

Sorafenib, a multi-kinase inhibitor agent, has been used in hepatocellular carcinoma (HCC) treatment for almost one and a half decades. It was the gold standard treatment based on two randomized Phase III trials.[1,2] Sorafenib remained the only agent used in systemic therapy from 2008 to 2017. However, since then, many agents, including tyrosine kinase inhibitors, vascular endothelial growth factor-targeted therapies, and immune checkpoint inhibitors alone or in combination have been approved for systemic treatment. Regorafenib was approved for second-line treatment by the RESOURCE trial in 2017, while lenvatinib was approved for the first-line treatment by the REFLECT trial in 2018.[3,4] In the recently published Phase III IMBrave150 trial, atezolizumab and bevacizumab combination treatments

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have demonstrated superiority to sorafenib in the first-line treatment.[5] There may be inconsistencies between data collected in controlled clinical trials and practice. Regardless of etiology, cirrhosis is the most important risk factor for HCC development, and clinical trials were conducted in HCC patients with Child-Pugh (CP) class A (preserved liver function) owing to strict inclusion criteria.[6] However, many patient groups not included in clinical trials require treatment in real-life. For example, the benefit and efficacy of sorafenib in patients with CP-B are controversial owing to the lack of randomized trials. Therefore, real-life studies are considered important because they include such patients.

Although the atezolizumab plus bevacizumab treatment was demonstrated to be more effective by the IMBrave150 trial, a substantial proportion of individuals cannot obtain this treatment. Thus, sorafenib is still the "gold standard" therapy at such places. After determining the standard treatment for a disease, the next step is to identify the patients for whom that treatment will be most beneficial. HCC has a poor prognosis as it commonly presents with an advanced stage. The median survival has been reported to be between 5 and 20 months.[7-10] Treatment outcomes are improved using prognostic factors. By prognostic factor determination, patient selection is more accurate, and the patient group that benefitted from the treatment can be selected. These prognostic factors can be identified using randomized clinical trials, retrospective analyzes, and real practice. The treatment selection can be better managed using treatment algorithms based on prognostic factors. Prognostic factors defined in HCC include macroscopic vascular invasion, CP stage, high alpha-fetoprotein (AFP), Barcelona clinic liver cancer (BCLC) stage, viral status, and high neutrophil-leukocyte ratio.[11,12] Although sorafenib was more effective than placebo in these groups, it may be insisted with atezolizumab and bevacizumab combination therapy for a patient with a poor prognosis instead of sorafenib owing to its lower efficacy.

This multicenter study primarily aimed to evaluate real-life experiences with sorafenib and determine the prognostic factors of sorafenib treatment in the Turkish population.

MATERIAL AND METHODS

PATIENTS AND DATA COLLECTION

This retrospective cross-sectional study used the demographic, clinical, and laboratory data collected retrospectively. Ethical approval was obtained from Ankara City Hospital Ethics Committee (date: October 13, 2021, no: E2-21-903). This study was conducted according to Helsinki Declaration and good clinical practice recommendations. Each investigator provided written informed consent before the study initiation. This multicenter study included six tertiary oncology centers that are high-volume, covering almost the whole of Ankara and reflecting the Turkish population. After the screening between 2010 and 2021, 147 patients with adequate records were identified for the study. Patients treated with at least one dose of sorafenib for HCC were included. Patients without restriction for their previous treatment were included. Overall survival (OS) and progression-free survival (PFS), response rates, prognostic factors, and safety were analyzed. The OS was defined as the time from initiation of sorafenib treatment to death. The PFS was defined as the time from initiation of sorafenib treatment to disease progression or death. The response rates were determined radiologically according to RECIST 1.1. The neutrophil-lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count. Based on the median value of NLR, it was divided into high and low. The values above the median value were grouped as high.

STATISTICAL ANALYSIS

Statistical analyses were performed using the IBM SPSS Statistics Version 25 program (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized with median values and ranges. The categorical variables were summarized with absolute frequency and percentages. Differences between groups were evaluated using the chi-square test. Kaplan-Meier survival analysis was performed for PFS and OS. Univariate analysis was performed with Kaplan-Meier. Multivariate analysis was performed with Cox regression. The p values less than or equal to 0.05 were considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS AND SURVIVAL OUTCOMES

A total of 147 patients receiving sorafenib from six centers were included. The median age of patients before sorafenib administration was 63.6 (21-92) years. The eastern cooperative oncology group (ECOG) performance status of the majority of patients was 0-1 (84.1%). The most common etiology was hepatitis B virus with an occurrence of 58.9%. At the beginning of sorafenib treatment, 88.4% of patients were CP-A, and 11.6% were CP-B. The detailed patient characteristics are presented in Table 1.

The median follow-up of patients was 6.6 (0.6-101.8) months. The median PFS was 4.8 months (95% CI, 4.0-5.5), and the median OS was 8.5 months (95% CI, 6.5-10.4) (Figure 1). The median PFS was 5.1 (95% CI, 4.3-5.9) and 2.9 months (95% CI, 2.3-3.5), the median OS was 9.8 months (95% CI, 6.4-13.2) and 5.3 months (95% CI, 4.1-6.5) in patients with CP-A and CP-B, respectively. There was a difference in survival between patients with CP-A and CP-B (p=<0.001). The objective response rate was 11.3%, with complete (n=1) and partial response (n=13), and 36.3% of patients had stable disease (n=45) as the best tumor response. Approximately 48.5% (n=63) of patients could receive treatment after sorafenib. The most common subsequent treatments were chemotherapy (55.5%) and regorafenib (39.7%).

PROGNOSTIC FACTORS

Patient characteristics were thought to be prognostic factors, including etiology, ECOG performance status, presence of extrahepatic disease, history of local treatment, CP score, BCLC stage, tumor size, NLR, alanine transaminase, total bilirubin, and AFP, were evaluated using univariate analysis. The median OS was 9.8 months (95% CI, 7.0-12.6) and 3.8 months (95% CI, 2.7-4.8) in patients with an ECOG performance status of 0-1 and 2-3, respectively. It was 9.8 months (95% CI, 6.4-13.2) in patients with CP score A, and 5.3 months (95% CI, 4.1-6.5) in patients with B. The median OS of patients with NLR levels higher than the median value was 5.3 months (95% CI, 4.2-

TABLE 1: Patients and treatment characteristics.

	No. (n=147)	(%)
Median age before sorafenib, yr median (range)	63.6 (21-92)	
Male	130	88.4
ECOG PS*		
0-1	122	84.1
2	22	15.2
3	1	0.7
Cause of disease		
HBV	86	58.5
Cryptogenic cirrhosis	36	24.5
HCV	10	6.8
NAFLD	8	5.4
Alcohol	5	3.4
Other	2	1.4
Child-Pugh class*		
A	129	88.4
B	17	11.6
BCLC stage		
B (intermediate)	48	32.7
C (advanced)	99	67.3
Previous treatment**		
TACE	43	29.3
Chemotherapy	42	28.6
RF ablation	25	17
TARE	11	7.5
Other	4	2.7
No treatment	39	26.5
Extrahepatic disease		
No	56	38.1
Yes	91	61.9
Extrahepatic disease sites**		
Lymph nodes	60	40.8
Lung	24	16.3
Bone	14	9.5
Peritoneal	9	6.1
Surrenal gland	8	5.4
No extrahepatic disease	56	38.1
Median albumin-g/dL, range	3.7 (2.2-5.2)	
Median total bilirubin-mg/dL, range	0.9 (0.2-5.0)	
Median alpha-fetoprotein-ng/mL, range	106.5 (1-521,379)	
Median alanine transaminase-U/L, range	43 (9-251)	
Median INR, range	1.1 (0.7-2.2)	
Median NLR	2.95 (0.27-16.50)	
Tumor size, cm		
<10	91	61.9
≥10	56	38.1

*In the available data; **The total is over 100% because there is more than one feature in one patient; ECOG PS: Eastern cooperative oncology group performance status; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NAFLD: Non-alcoholic fatty liver disease; BCLC: Barcelona clinic liver cancer; TACE: Transarterial chemoembolisation; RF ablation: Radiofrequency ablation; TARE: Transarterial embolization; INR: International normalized ratio; NLR: Neutrophil-to-lymphocyte ratio.

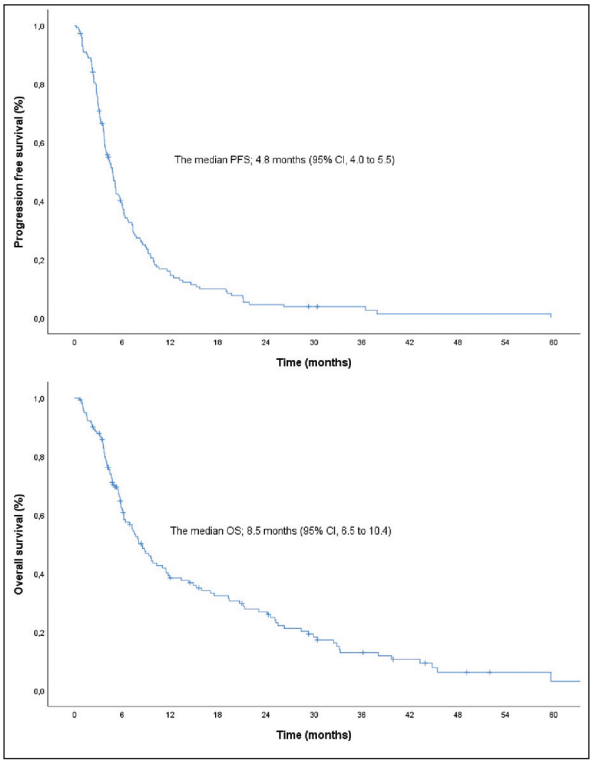

FIGURE 1: Kaplan-Meier curves for progression-free and overall survival of all patients.

6.4), and with lower NLR levels was 14.3 months (95% CI, 8.8-19.9); it was 7.2 months (95% CI, 5.7-8.7) and 11.9 months (95% CI, 6.6-17.1) in patients with AFP values higher and lower than the median values. While the median OS was 5.7 months (95% CI, 5.0-6.4) in patients with high total bilirubin, it was 11.9 months (95% CI, 6.0-17.7) in those with normal total bilirubin, which all were significantly different (Table 2). We included the variables of the ECOG performance status, CP score, NLR, total bilirubin, and AFP values in multivariate analysis. We found that ECOG performance status, CP score, NLR value, and AFP value were independent prognostic factors (Table 3).

SAFETY

Adverse events were reported in 57.8% of patients. The most common adverse event was diarrhea (19.7%, Grade 1-2; 6.8%, Grade 3), fatigue, and hand-foot syndrome were reported in 10.2% and 18.4% of Grade 1-2, and 12.2% and 4.1% of Grade 3-4, respectively (Table 4). While 33.8% of patients required dose discontinuation, 39.8% had to be treated with a dose lower than the standard 800 mg dose. The treatment was discontinued most commonly owing to disease progression (74.1%). An adverse event that led to discontinuation occurred in 9.5% of patients.

DISCUSSION

This study aimed to evaluate the efficacy and tolerability of sorafenib treatment and prognostic factors in Turkish patients with HCC. This study is one of the largest real-life cohorts in Europe. In this study, the median OS was detected to be 8.5 months. It was 9.8 months in patients with CP-A. In the pivotal trials,

TABLE 2: The univariate analysis of variables for overall survival.

		Univariate analysis	
Baseline variables		**HR (95% CI)**	**p value**
Etiology	Viral hepatitis vs. others	1.005 (0.68-1.48)	0.97
ECOG PS	0-1 vs. 2-3	0.32 (0.19-0.52)	<0.001
Extrahepatic disease	No vs. yes	0.86 (0.58-1.26)	0.45
Local treatment	No vs. yes	0.79 (0.49-1.25)	0.32
Child-Pugh score	A vs. B	0.36 (0.20-0.63)	<0.001
BCLC stage	B vs. C	0.85 (0.58-1.26)	0.44
Tumor size	≥10 cm vs. <10 cm	1.33 (0.91-1.93)	0.13
NLR	>Median vs. ≤median	1.97 (1.33-2.92)	0.001
ALT	Normal* vs. high	1.16 (0.79-1.71)	0.43
Total bilirubin	Normal** vs. high	0.56 (0.37-0.84)	0.006
AFP	≤Median vs. >median	0.60 (0.41-0.88)	0.01

*Normal ALT value was defined as ≤40 U/L; **Normal total bilirubin value was defined as ≤1.2 mg/dL; HR: Hazard ratio; ECOG PS: Eastern cooperative oncology group performance status; BCLC: Barcelona clinic liver cancer; NLR: Neutrophil-to-lymphocyte ratio; ALT: Alanine transaminase; AFP: Alpha fetoprotein.

TABLE 3: The multivariate analysis of variables for overall survival.

		Multivariate analysis	
Baseline variables		**HR (95% CI)**	**p value**
ECOG PS	2-3 vs. 0-1	3.94 (2.21-7.04)	<0.001
Child-pugh score	B vs. A	3.23 (1.73-6.05)	<0.001
NLR	>Median vs. ≤median	1.74 (1.13-2.67)	0.011
Total bilirubin	High vs. normal*	1.43 (0.91-2.24)	0.117
AFP	>Median vs. ≤median	2.23 (1.46-3.39)	<0.001

*Normal total bilirubin value was defined as ≤1.2 mg/dL; HR: Hazard ratio; ECOG PS: Eastern cooperative oncology group performance status; NLR: Neutrophil-to-lymphocyte ratio; AFP: Alpha fetoprotein.

TABLE 4: The most common AEs during sorafenib treatment.

AE	All grades, n (%)	Grade 3-4, n (%)
Any AE	57.8	21.1
Diarrhea	26.3	6.8
Hand-foot syndrome	22.5	4.1
Fatigue	22.4	12.2
Nausea	3.4	0.7
Anorexia	2.7	0
Hyperbilirubinemia	2.7	0.7
Thrombocytopenia	2	0
Constipation	1.4	0

AE: Adverse event.

the median OS was 10.7 and 6.5 months in the SHARP and Asia-Pacific trials.[1,2] While the median PFS was 4.8 months in all patients, it was 5.1 months in those with CP-A. The median PFS in the SHARP and Asia-Pacific trials were 5.5 and 2.8 months, respectively. Consequently, survival outcomes were comparable with pivotal phase 3 trials. Survival of 5 to 25 months has been reported in real-life data.[7-9,13-15] The primary reason for this wide range is the differences in patient selection. Tak et al. reported that 782 Korean patients with HCC were evaluated and the median patient survival was 7.7 months.[13] Longo et al. reported the median OS as 25.5 months (95% CI 17.0-34.1) in a study evaluating 103 patients.[14] This difference in survival may be owing to differences in race, etiology, and CP rates. In real-life data from Türkiye published in 2013, where all patients had CP-A, survival was reported as 48 weeks.[15]

In the SHARP and Asia-Pacific trials, more than 95% of the patients were CP-A. In our study, 88.4% of the patients were CP-A. No patients received previous systemic therapy in both Phase 3 trials. However, 28.6% of the patients received systemic treatment before sorafenib in this study. In addition, the proportion of patients with ECOG performance status 0-1 was slightly lower than that in other studies (84% vs. >92%). Thus, the patients in our study were more advanced and had a worse prognosis than those in clinical studies.

In this study, the disease control rate (complete, partial, and stable response) was 47.6%, which was higher than that in the SHARP trial (43%). However, it was slightly lower (53%) than that in the Asia-Pacific trial.

Sorafenib was generally well tolerated in our study, with fewer side effects reported than those in other studies (57.8% vs. 80% in the SHARP trial). Diarrhea, hand-foot syndrome, and fatigue were most frequently reported. These adverse events were predominantly in Grade 1-2. An adverse event causing treatment discontinuation developed in 9.5% of patients. This rate was significantly lower than that in the SHARP trial (38%). This may be owing to the low number of side effects reported in retrospective studies.

Many clinical and biological prognostic factors have been identified in patients with HCC treated using sorafenib. Among these, there are markers such as CP stage, BCLC stage, viral status, diabetes history, AFP levels, and NLR and platelet-to-lymphocyte ratio values.[12] In our multivariate analysis, four parameters had a significant impact on prognosis. Moreover, patients with a better ECOG performance score had better survival. This has been demonstrated in real-life data.[16] Almost all of the patients included

in clinical trials comprised those with CP-A. In contrast, observational studies involve larger patient groups. The GIDEON study, a large observational study, evaluated the survival of sorafenib in patients with CP-A (n=1,968) and CP-B (n=666).[17] The median OS was 13.6 (95% CI 12.8-14.7) and 5.2 months (95% CI 4.6-6.3) in patients with CP-A and CP-B, respectively. In our study, a slightly lower OS was found in patients with CP-A (9.8 months), while a similar OS was found in those with CP-B (5.3 months).

Systemic inflammation is closely associated with invasion and metastasis in HCC.[18-20] Calculation of NLR, which is an indirect and easy technique used to detect the systemic inflammatory response, can be used to determine the prognosis.[12] However, high NLR has been demonstrated to have a poor prognosis in many prospective and retrospective studies.[16,21] Personeni et al. demonstrated that high NLR (cut-off value=3) was an independent prognostic biomarker in a Phase 2 trial evaluating tivantinib as second-line therapy in patients with HCC.[21] Lué et al., in a retrospective study of 154 patients, found that high NLR (when cut-off ≥2.3) adversely affected survival in European patients with HCC.[16] However, the cut-off value of the NLR is ambiguous. While there are studies with a cut-off value higher than the median NLR value, some studies report a lower cut-off value, as aforementioned. Bruix et al. used the cut-off value of 3 (median NLR value) as the cut-off in the prognostic factor analysis of the SHARP and Asia-Pacific trials.[11] In this study, high NLR was found as a negative prognostic factor. In our study, we determined the cut-off value for high NLR as the median NLR value (2.95). This value is consistent with other studies. In our study, patients with NLR>2.9 (high NLR) had a worse prognosis than those with a lower hazard ratio of 1.74 (95% CI, 1.13-2.67).

The AFP is a critical tumor marker used both to support the diagnosis and predict treatment response. Simultaneously, its basal level is associated with tumor volume. In the SHARP study, patients with AFP levels >200 ng/mL had lower survival than those with AFP<200 ng/mL.[1] This information was also confirmed by Bruix et al.[11] Some studies also used >400 ng/mL as a cut-off. In this study, it was demonstrated that AFP was not effective in survival when the cut-off value was 400.[22] In our study, the lower median AFP value (106.5 ng/mL) was used, which we found significant in the univariate analysis. Thus, the significance was thought to increase. We found that a high AFP value was a negative prognostic factor in multivariate analysis, with a hazard ratio of 2.23 (95% CI, 1.46-3.39).

This study has some limitations. First, this study was retrospective. Owing to the lack of data, especially adverse events, drug compliance information may have been underestimated. The second was the lack of a control group for comparison. Therefore, the results were indirectly compared with clinical trials and historical information. Finally, some patient subgroups, especially the CP-B group, may have weak statistical power owing to the smaller number of patients.

CONCLUSION

In conclusion, the survival outcomes were consistent with real-life data and clinical trials of sorafenib in the Turkish population in this study. Fewer side effects were reported than those in other studies. The median survival was longer in those with a better ECOG performance score, CP-A, and lower NLR and AFP levels.

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During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Cihan Erol, Mehmet Ali Nahit Şendur;* ***Design:*** *Cihan Erol, Mehmet Ali Nahit Şendur;* ***Control/Supervision:*** *Öztürk Ateş, Didem Şener Dede, Muhammed Bülent Akıncı, Nuri Karadurmuş, Öznur Bal, Yüksel Ürün, Şuayib Yalçın, Bülent*

Yalçın, Muhammed Ali Nahit Şendur; ***Data Collection and/or Processing:*** *Cihan Erol, Murat Bardakçı, Mutlu Hızal, Seda Kahraman, Emre Yekedüze, Deniz Can Güven, Musa Barış Aykan, Recep Ak, Öztürk Ateş, Didem Şener Dede, Muhammed Bülent Akıncı, Nuri Karadurmuş, Öznur Bal, Yüksel Ürün, Şuayib Yalçın, Bülent Yalçın, Mehmet Ali Nahit Şendur;* ***Analysis and/or Interpretation:*** *Cihan Erol, Mutlu Hızal;* ***Literature Review:*** *Cihan Erol, Mehmet Ali Nahir Şendur;* ***Writing the Article:*** *Cihan Erol, Mehmet Ali Nahir Şendur;* ***Critical Review:*** *Cihan Erol, Murat Bardakçı, Mutlu Hızal, Seda Kahraman, Emre Yekedüze, Deniz Can Güven, Musa Barış Aykan, Recep Ak, Öztürk Ateş, Didem Şener Dede, Muhammed Bülent Akıncı, Nuri Karadurmuş, Öznur Bal, Yüksel Ürün, Şuayib Yalçın, Bülent Yalçın, Mehmet Ali Nahit Şendur.*

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