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Real-World Single-Center Clinical Data on Sorafenib in Patients with Unresectable Hepatocellular Carcinoma

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Abstract

Introduction. Hepatocellular carcinoma (HCC) is a malignant tumor that frequently develops in conjunction with chronic liver disease and cirrhosis, and is often identified late in its course, with a median survival of around 6 to 20 months following diagnosis. Although surgical excision is the gold standard of treatment, most patients are ineligible due to tumor size or underlying liver disease. The hepatic reserve of the patient, as determined by the Child-Turcotte-Pugh classification, frequently influences treatment options.

Method. Between January 2016 and June 2018, 42 patients admitted to Fundeni Clinical Institute's Department of Medical Oncology who had previously been treated with Sorafenib for more than two months were recruited in this retrospective analysis. We evaluated the etiology and stage of illness (BCLC), residual liver function (CHILD), performance status (ECOG), treatment response and side effects, progression-free survival, and overall survival.

Results. The study group had good short and long-term outcomes: median progression-free survival was 7.7 months and median overall survival was 11.6 months. The most frequently-reported adverse effects were skin rashes, diarrhea, hypertension, and hand-foot skin reaction.

Conclusion. This retrospective, single-center study confirmed the benefit of sorafenib in the treatment of advanced HCC, particularly in patients with good liver function and performance status.

Keywords: *Sorafenib, hepatocellular carcinoma, BCLC stage, ECOG performance status, overall survival, progression free survival.*

Original Research

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1. Introduction

According to World Health Organization (WHO), hepatocellular carcinoma (HCC) is one of the most common malignancies, being the sixth most common cancer worldwide and the fourth leading cause of cancer-related deaths. There are around 841.000 new cases diagnosed every year, with an increasing incidence globally and 782.000 HCC-related deaths annually (1).

Major risk factors for HCC include cirrhosis (regardless of etiology), chronic infection with the hepatitis B virus (HBV) or hepatitis C virus (HCV), foods that are contaminated with aflatoxins, nonalcoholic fatty liver disease (obesity, diabetes and/or insulin resistance), alcohol consumption and smoking (2).

Hepatectomy can be used for patients with early-stage HCC. However, these cases are less common because patients with HCC often present with advanced-stage disease. Consequently, many of them require systemic therapies or palliative treatment (3).

Sorafenib is a tyrosine kinase inhibitor with activity against many protein kinases (RAF kinases), vascular endothelial growth factor receptors (VEGFR) and platelet-derived growth factor receptor (PDGFR), which also blocks tumor cell proliferation and tumor angiogenesis (4).

Sorafenib is generally well tolerated, with a manageable side effect profile. Diarrhea and hand-foot skin reaction are the most common side effects (5). The efficiency of sorafenib in patients with unresectable HCC has been evaluated in several clinical trials. In registration trials, sorafenib improved median overall survival (OS) in patients with advanced HCC by a median of 2.3-2.8 months (6,7). In the SHARP study, a randomized controlled trial, the median OS in the sorafenib-treated group was 10.7 months compared with 7.9 months in the placebo group, with a good safety profile (7). Based on the results of the two landmark trials (6,7), sorafenib is indicated only in patients with good liver function (Child-Pugh A) and advanced tumors (Barcelona Clinic Liver Cancer (BCLC) C) or intermediate stage tumors (BCLC B) who are not eligible or who progressed after locoregional therapy. However, sorafenib is sometimes used outside of these criteria in the real-world setting, mainly due to the absence of alternative treatment options (8,9). As these patient subgroups were not evaluated in registration trials, only observational, non-randomized cohort studies can inform clinical practice. Therefore, we performed a retrospective real-world cohort study of patients with advanced HCC treated with sorafenib to investigate its efficacy and safety profile.

2. Materials and methods

This was a retrospective cohort study conducted between January 2016 and June 2018, including 42 patients admitted to the Department of Medical Oncology, Fundeni Clinical Institute, Bucharest. To be included in the study, patients with HCC needed to have been treated with sorafenib for at least two months. Patients received a daily dose of 800 mg of sorafenib, 400 mg (two tablets of 200 mg) taken twice daily, in the morning and in the evening. The treatment was continued for as long as the patients had clinical benefit or until unacceptable toxicity or death. In the case of toxicity, the dose was either reduced to 400 mg/day or stopped. The study was performed in accordance with standard ethical guidelines approved by the local institutional review board and with the Declaration of Helsinki (10).

Individual medical records were reviewed for demographic and clinical information, as all patients gave written informed consent prior to treatment, according to our institutional guidelines. Data on the clinical profile at admission, etiology and stage of the disease (BCLC), liver function (Child-Pugh score), Eastern Cooperative Oncology Group (ECOG) performance status, portal vein thrombosis, lymphadenopathy, the presence of extrahepatic disease at diagnosis, alpha-fetoprotein (AFP) values, and previous treatments were recorded. The primary outcome was overall survival (OS) from the initiation of sorafenib. Secondary outcomes were progression-free survival (PFS), the frequency of specific adverse effects and requirements for dose reduction or drug cessation due to intolerability. Tumor response assessment was performed every 6 months

with CT-scan or MRI and was evaluated according to mRECIST criteria (11). Complete blood count, liver and kidney function tests, coagulation tests and serum AFP were assessed every month. The treatment with sorafenib was continued for patients with clinical or radiological benefit.

Statistical analysis

The Kaplan-Meier method was used to estimate curves corresponding to the average patient follow-up period, progression-free survival, and overall survival. The obtained curves were compared using log-rank tests (Mantel-Cox test) to determine the prognostic factors for longer survival. OS was defined as the time from treatment initiation to death. Patients alive at the time of last follow-up were censored in the OS analysis. PFS was calculated as the time from treatment initiation to the date of disease progression or death from any cause. The patients alive at the time of last follow-up were censored. Univariate analysis was performed for the main known prognostic factors of advanced HCC: age, sex, performance status (ECOG), liver function (Child-Pugh), HCC stage (BCLC), and AFP value.

The following programs were used for data processing and graphical representation of results: Hipocrate Clinic, IBM SPSS 23, and XLSTAT-Biomed 2016. The database was closed for analysis in June 2018. The threshold for statistical significance was 5%. All p-values are two-sided and reported with 95% confidence intervals. The mean follow-up time was 12.9 months (95% CI: 9.8-14.8 months). The Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) was used to evaluate and grade adverse events (AE).

3. Results

Among the 42 patients included in our study, HCC occurred more often in male patients (33 patients – 78.57%), with a mean age at diagnosis of 60.9 years (range 33-78). Regarding the etiology, HCV infection was the most common risk factor that led to the development of HCC (17 patients - 40%), followed by HBV (14 patients - 33.33%), while the rest of the cases (11 patients – 26.2%) were due to HBV + hepatitis D virus (HDV) infection, NASH and toxic hepatitis (see Table 1).

According to the Barcelona Clinic Liver Cancer staging system, most patients (29 patients – 69%) were BCLC stage C. Twenty-eight (66.66%) patients were ECOG 1 at the time of diagnosis. 32 (76.2%) patients were Child-Pugh A. We also found that 18 (42.86%) patients had AFP levels of over 400 ng/ml, 16 (38%) of them had AFP levels of 20–400 ng/ml, and 8 (19%) patients had normal levels of AFP.

At the time of the diagnosis, 16 (38%) patients presented with portal vein thrombosis and 29 (69%) patients presented with extrahepatic disease. The most common site of metastatic spread was the peritoneum (5 patients - 12%), followed by the lung (three patients - 7.14%), bone (two patients - 4.86%) and one (2.38%) patient had adrenal metastases (see Table 1).

Twenty-seven (64%) patients received other treatment prior to sorafenib**.** Nine (21.42%) patients underwent at least one transarterial chemoembolization (TACE) session, eight (19%) patients underwent hepatectomy, four (9.5%) patients received radiofrequency ablation (RFA) and one (2.38%) patient underwent liver transplantation.

Table 1. Clinical characteristics of patients included in the study

Patients and disease characteristics		Number	PERCENTAGE
Gender	Male	33	78.57%
	Female	9	21.42%
Etiology	HCV	17	40.47%
	HBV	14	33.33%

	HBV+HDV NASH	11	26.2%
BCLC Stage	B	13	31%
	C	29	69%
ECOG PS	0-1	28	66.66%
	2	14	33.33%
Child pugh	A	32	76.2%
	B	10	23.8%
AFP LEVEL	<400 ng/ml	24	57.14%
	>400 ng/ml	18	42.86%
Portal vein thrombosis		16	38%
Metastatic sites	peritoneum	5	12%
	lung	3	7.14%
	bone	2	4.76%
	adrenal	1	2.38%

Overall survival

Of the 42 patients, 16 who were alive at the time were censored when the database closed in June 2018. Fourteen were still receiving sorafenib at the time. The median OS for the study group was 11.6 months (95% CI: 9.2-14.1 months) (Figure 1).

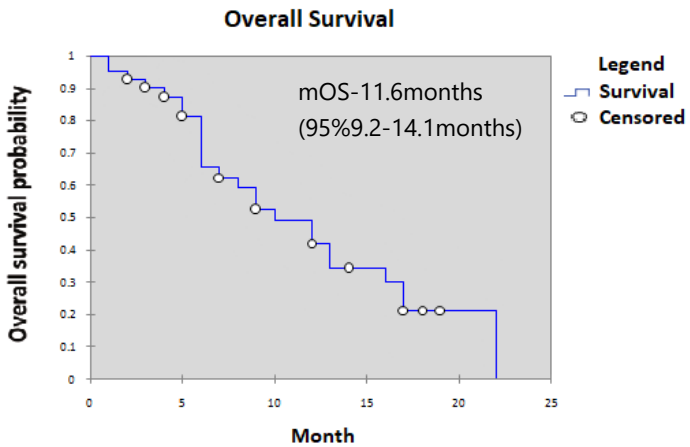

Figure 1. Kaplan Maier Survival Curve for all patients

Univariate analysis showed that reduced survival was associated with 2 ECOG performance status ($p < 0.001$). The median OS of patients with ECOG 1 was 13.8 months (95% CI: 11.3–16.4 months), while the median OS of patients with ECOG 2 was 4.5 months (95% CI: 3.4–5.5 months) (Figure 2).

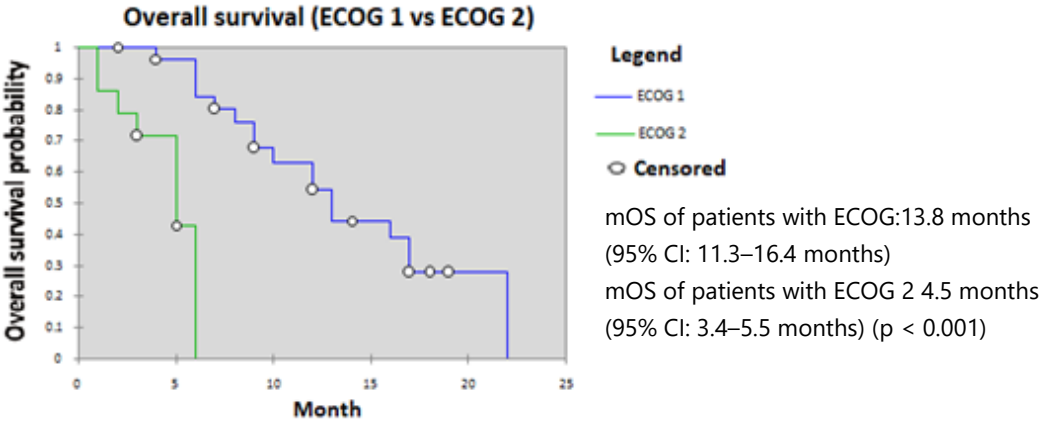

Figure 2. Kaplan Maier Survival Curve; Overall Survival according to ECOG Performance Status.

For patients with HCC and Child-Pugh A liver cirrhosis, the median OS was 12.6 months (95% CI: 10.0-15.2 months). For patients with Child-Pugh B, the median OS decreased to 5.3 months (95% CI: 3.8-6.7 months), but the difference was not statistically significant (p = 0.104) (Figure 3).

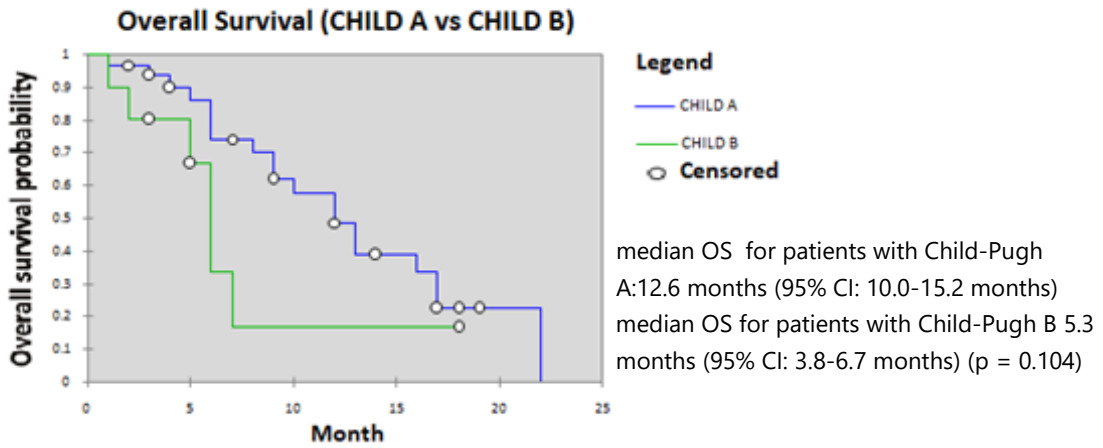

Figure 3. Kaplan Maier Survival Curve Median Overall Survival according to Child-Pugh classification of cirrhosis.

The median OS was calculated according to BCLC stage: the median OS of BCLC B patients was 15.4 months (95% CI: 12.4-19.4 months) and the median OS for BCLC C was 8.8 months (95% CI: 6.7-10.9 months) (Figure 4). Median OS by AFP value was calculated; for patients with AFP < 20 ng/ml, median OS was 8.3 months (95% CI: 4.6-12.0); for patients with AFP levels between 20-400 ng/ml, median OS was 12.3 months (95% CI: 8.9-15.7); and for patients with AFP levels > 400 ng/ml, median OS was 10 months (95% CI: 6.9-13.1). The comparative difference between these variables was not statistically significant.

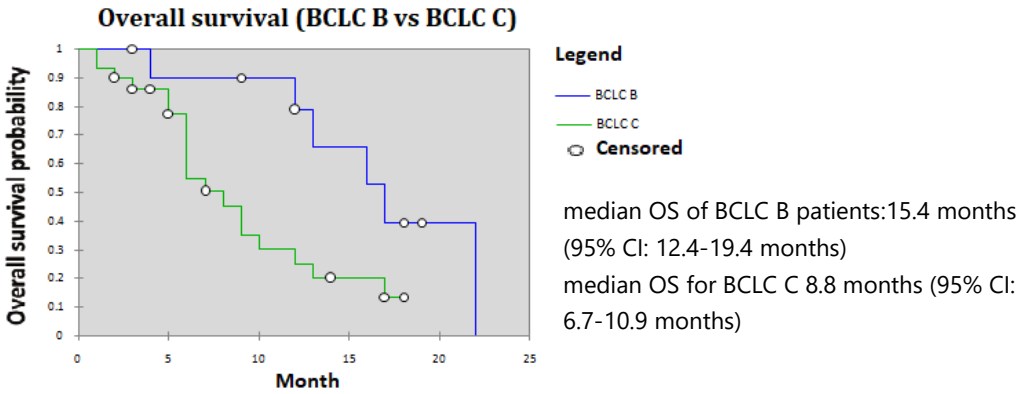

Figure 4. Kaplan Maier Survival Curve Median Overall Survival according to BCLC classification.

The median PFS was 7.7 months (95% CI: 5.8-9.6 months) for the whole study group. Baseline performance status had a effect on PFS. Thus, the median PFS for patients with ECOG 1 was 9.1 months (95% CI: 7.9-11.2 months), while the median PFS for patients with ECOG 2 was 3.9 months (95% CI: 2.9-4.7 months), p<0.001. Child-Pugh score and BCLC stage had no statistically significant impact on PFS for the patients included in the study.

All 42 patients enrolled in the study received an initial dose of 800 mg/day sorafenib, with dose adjustments based on toxicity. Most adverse events occurred within 30 days of beginning sorafenib. Approximately 59% of patients had at least one adverse event and 9% had grade 3–4 adverse events. Drug-related adverse events were experienced by 40% of patients and 7% had grade 3–4 drug-related adverse events. Overall, 23,8% of patients (*n* = 10) experienced serious adverse events, among which only 1 event was drug-related (0.2%). No differences in overall adverse events, serious adverse events or deaths were observed between Child-Pugh A and Child-Pugh B patients. The most common adverse event was fatigue (76%), followed by diarrhea (51%), hypertension (33%), weight loss (30%) and hand-foot skin reaction (14.3%).

Serious adverse events requiring discontinuation of sorafenib were reported in four patients and included diarrhea, uncontrolled arterial hypertension, and hand-foot skin reaction.

4. Discussions

This study aimed to evaluate the effectiveness and safety profile of sorafenib in patients with advanced HCC. The median OS of the whole study group was 11.6 months (95% CI: 9.2-14.1). The patients included in the SHARP trial had a median OS of 10.7 months, followed by the Italian SOFIA study (SOraFenib Italian Assessment) with a median OS of 10.5 months and the Asia-Pacific study with a median OS of 6.5 months (6,7,12). Other studies conducted around the world had the following results: the Egyptian study reported a median OS of 6.25 months, while the median OS in the Danish study was 6.2 months (13,14). The GIDEON study (Global Investigation of therapeutic DEcisions in HCC and Of its treatment with SorafeNib) reported different results between the ethnic and regional groups treated with sorafenib for unresectable HCC (15). Patients from Japan had the longest median OS of 14.7 months (16). The use of sorafenib in our patients with advanced stage HCC is superior compared to other studies regarding the median OS, mainly because sorafenib has been administered to patients with clinical benefit after radiological progression.

According to our results, the median PFS was 7.7 months (95% CI: 5.8-9.6), longer compared to the SHARP trial (4.1 months) and also compared to the Asia-Pacific trial (5.5 months) (6,7). Our data suggested a higher median OS for women (12.6 months) than for men (11.2 months), without finding a statistical

significance (p=0.533). However, CT or MRI evaluated treatment response to sorafenib for the patients included in our study every 6 months, and this could be a possible explanation for the longer PFS.

According to the BCLC staging system, most patients (29/42) were BCLC stage C, while the remaining 13 were BCLC stage. The median OS of patients with BCLC stage B was higher than the median OS of patients with BCLC stage C (15.4 months vs. 8.8 months), but the difference was not statistically significant. The median PFS was 10.7 months (95% CI: 7.2–13.2) for BCLC stage B and 6.2 months (95% CI: 4.1–8.4) for BCLC stage C HCC.

Median OS of patients with ECOG 1 was significantly ($p < 0.001$) higher than patients with ECOG 2 (13.8 months vs. 4.5 months). In the Asia-Pacific study, patients with ECOG 1 and ECOG 2 had a median OS of 6.1 months (6). In the Egyptian study, median PFS was 7 months in patients with ECOG 1 and 3 months in patients with ECOG 2 (13). In our study, median PFS was 9.1 months (95% CI: 7.9-11.2) for ECOG 1 and 3.9 months (95% CI: 2.9-4.7) for ECOG 2 ($p = 0.001$). ECOG performance status reflects how the disease affects patients' daily lives, thus being a strong prognostic factor.

Most patients in our study (32 patients) were Child-Pugh A. The median OS in Child-Pugh A patients was higher than in Child-Pugh B patients (12.6 months vs. 5.3 months), but the difference did not reach statistical significance. Patients enrolled in the Egyptian study were similar, with a median OS of 12 months in patients with Child-Pugh A and a median OS of 5.2 months in patients with Child-Pugh B (13). According to our results, the median PFS was 8.3 months (95% CI: 6.2-10.5) for Child-Pugh A patients and four months (95% CI: 3.1-4.9) for Child-Pugh B patients.

Interestingly, patients with AFP levels < 20 ng/ml had a median OS of 8.3 months (95% CI: 4.6-12), which was lower than those with AFP between 20-400 ng/ml who showed a median OS of 12.3 months (95% CI: 8.9-15.7). Also, 18 patients had AFP levels > 400 ng/ml and they had a better OS (10 months, 95% CI: 6.9-13.1) than those with normal AFP levels, but without statistical significance ($p = 0.257$). The median duration of sorafenib treatment in our study was 8.2 months (95% CI: 6.9-10.4 months). Some patients received sorafenib beyond radiological progression, which could explain why OS is higher than PFS in our study. Apostolodis et al. published similar results, showing that patients who continue sorafenib for three months beyond progression have higher OS compared to patients that discontinue sorafenib in under three months or immediately after radiological progression (17).

Therefore, we can say that sorafenib is a treatment that brings a clinical benefit to Romanian patients if it is administered to patients with a good performance status (ECOG 0,1) and with compensated liver function (Child-Pugh class A). The outcomes of patients with impaired performance status and impaired liver function are measurably worse.The use of sorafenib in patients with advanced stage HCC has been shown to be superior in terms of overall survival when compared to other studies (Sharp: 10.7 months; Asia-Pacific study: 6.5 months; Egyptian study: 6.25 months) (6,7,13). This can be explained by the fact that sorafenib was administered to patients after radiologic confirmation of progressive disease, based only on clinical benefit and the dose was reduced or the treatment was discontinued if unacceptable toxicity occurred.

Several limitations of the current study must be acknowledged. This was a retrospective single-center study with a small sample size. Tumor response to sorafenib therapy was evaluated after at least 5 months of treatment, which could explain the longer median OS and PFS of patients included in the study compared to sorafenib registration trials.

5. Conclusions

Hepatocellular carcinoma continues to be a significant public health problem in Romania. Its incidence and mortality rate continue to increase, and the disease has significant socio-economic consequences. This retrospective single-center study confirmed the benefit of

sorafenib in treatment of advanced HCC, particularly in patients with well-preserved liver function and performance status. The median OS of the entire study group was 11.6 months, which was significantly longer than the median OS in phase III trials. Patients with ECOG 1, Child-Pugh A, or BCLC stage B HCC had an improved survival rate.

Abbreviations:

AFP - alpha-fetoprotein
BCLC - Barcelona Clinic Liver Cancer
ECOG - Eastern Cooperative Oncology Group
CT - Computer Tomography
HBV - hepatitis B virus
HCV - hepatitis C virus
HDV - hepatitis D virus
HCC - Hepatocellular Carcinoma
NASH - nonalcoholic steatohepatitis
MR - magnetic resonance imaging
OS - overall survival
PDGFR - platelet-derived growth factor receptor
PFS - progression-free survival
RFA - radiofrequency ablation
RECIST - Response Evaluation Criteria in Solid Tumors
TACE - transarterial chemoembolization
VEGFR - vascular endothelial growth factor receptor
WHO - World Health Organization

Statements:

Authors' contributions: CSG: study design, research, wrote the paper, conceived the analysis, statistical analysis SD: study design, review of the manuscript and consent for publication: LMN, MM, LCA, GC review of the manuscript. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Patients' consent: Study included retrospective data and the patients` information was de-identified.

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