

Efficacy and Safety of Sorafenib versus Supportive Care in Egyptian Advanced Hepatocellular Carcinoma Patients

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ABSTRACT

Sorafenib is the standard first-line treatment for HCC. No sufficient data exists regarding its efficacy in the Egyptian population being a costly medication that is not endorsed by insurance and hence is not used in most institutions. This study aimed to evaluate the overall survival (OS), progression-free survival (PFS), and quality of life (QOL) of Egyptian HCC patients receiving sorafenib versus supportive care. A Prospective cohort observational study design was conducted. The study setting was in the Electricity Hospital, Medical Oncology Department-Ain Shams University, and Nasser Institute for Research and Treatment, Egypt. Fifty-five patients with HCC were eligible for enrolment in the trial. Eligible HCC patients were stratified into one of two groups based on institutions' protocols for HCC treatment. Group (1) received supportive care (n=20) and Group (2) received sorafenib (n=35); the patients follow-up was continued for one year after diagnosis. The main outcome measures were the patients' survival, PFS, and QOL. The one-year survival rates were 0.0% and 75.5% (P=0.008) for group (1) versus group (2), respectively. The median PFS was 5 months and 12 months for the group (1) versus group (2), respectively (P=0.008). The QOL of the sorafenib group was better than the supportive care group (P=0.047). The most common side effects of sorafenib were diarrhea (42.8%) and hand-foot syndrome (34.2%). In the sorafenib group, 48.57% of the patients were requiring dose reduction. In conclusion, Sorafenib was an effective first-line therapy in Egyptian HCC patients with a superior QOL, OS, and PFS than those receiving supportive care.

Keywords: Hepatocellular carcinoma; Supportive care; Sorafenib; Safety; Efficacy; Quality of life.

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1. INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the highest widespread cancers [1]. HCC is the second foremost cause of mortality in cancer patients worldwide and the most common

primary liver malignancy [2].

In Egypt, HCC is the reason for approximately 4.7% of all cases of chronic hepatic disorders. The relative frequency of HCC has almost doubled in Egypt from 1993 to 2003.

In 2018, liver cancer had the highest incidence and mortality of all cancers in Egyptians according to the GLOBOCAN 2018 (Global burden of cancer study) database [3–5].

Globally, 80 million hepatitis C virus (HCV) infections have been estimated. The Middle East and North Africa have a large population with genotype 4 (G4) (71%), which was attributed to the high prevalence of G4 in Egypt [6]. Although HCV G4 represents approximately 20% of all HCV infections worldwide, the prevalence of HCV G4 in Egypt is higher than 90% [7]. The high prevalence of HCV and the associated complications in Egypt may be the major cause of the increase in the incidence of HCC [8].

The staging classification of Barcelona Clinic Liver Cancer (BCLC) is the most universally applied staging classification for HCC and comprises 5 stages. Advanced-stage © patients have symptomatic tumors, vascular invasion, and/or extrahepatic spread [9–14].

Sorafenib is a tyrosine kinase inhibitor (TKI) with anti-proliferative and anti-angiogenic effects [15]. This drug has shown a positive impact on survival for patients with BCLC-C disease and vascular invasion, extrahepatic spread, and/or constitutional symptoms [16].

The efficacy of sorafenib greatly varies in different geographic areas, as observed in the SHARP and Asia-Pacific trials. In the SHARP trial, the overall survival (OS) of patients taking sorafenib and OS of those taking a placebo were 10.7 and 7.9, respectively ($P < 0.001$) in advanced HCC patients from Europe, Australasia, North America, Central and South America [16]. Moreover, for advanced HCC patients from the Asia-Pacific region, the OS of patients taking sorafenib and OS of those taking a placebo were 6.5 and 4.2 months, respectively ($P = 0.014$) [17].

Up to now, no controlled studies have assessed the efficacy of sorafenib in contrast to

supportive care in HCC patients [18]. Hence, evaluating the efficacy and safety of sorafenib as an important therapeutic option in the HCC Egyptian population has potential importance.

This research aimed to evaluate the efficacy and safety of sorafenib versus supportive care in Egyptian HCC patients. The primary endpoint was OS, and the secondary endpoints were progression-free survival (PFS), quality of life (QOL), and the safety profile of sorafenib.

2. METHODS

Design: This is a multicentre, prospective, cohort observational trial conducted in three different Egyptian cancer centers, (Electricity Hospital, Medical Oncology Department-Ain Shams University, and Nasser Institute for Research and Treatment, Egypt)

The HCC patients who presented to these centers were screened for enrolment in this trial, and the eligibility criteria included the following: age ≥ 18 years, advanced HCC (BCLC-C), not appropriate for or progressed after surgery or locoregional therapy, HCV etiology, Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2 , Child-Pugh class A or early B (score 7), a life expectancy ≥ 12 weeks, adequate hematologic function, adequate hepatic function, and normal renal function. At least one untreated lesion could be measured in one dimension, according to the Modified Response Evaluation Criteria in Solid Tumors (mRECIST). The exclusion criteria included previous therapy with any systemic treatment, concomitant systemic antiviral therapy, or any comorbid diseases that could affect the QOL assessment.

The dose of sorafenib (Bayer - Leverkusen, Germany) was 400 mg twice daily (two 200-mg tablets). If adverse drug events (ADEs) of grade 3–4 occurred, then treatment was temporarily interrupted or the dose was reduced to 400 mg once according to the manufacturer's guidelines

while waiting for the symptoms resolved to grade 1 or 2, after that dose to increase again to the full dose. If toxicity persisted, the patients were instructed to stop the treatment and were withdrawn from the trial. The dose was also reduced for patients who showed unmanageable grade 2 toxicity, based on the clinical status of the patient [19].

The control group received only the best supportive care (BSC), which included hepatic support medications, analgesics, and gastrointestinal medication, (silymarin, pantoprazole, and NSAIDs when required).

Symptom progression and clinical assessments were evaluated every 4 weeks. Response assessments were performed every 2 months by imaging, hepatic function, and alpha-fetoprotein (α fp) levels. Toxicity assessments were performed every 4 weeks according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. QoL assessments were performed using the Functional Assessment of Cancer Therapy (FACT) - Hepatobiliary Symptom Index (FHSI-8) questionnaire, which was applied initially and then every 6 months.

Patients in both groups were regularly followed up until the occurrence of one of the following endpoints: radiological and symptomatic progression, as defined by the FACT (FHSI-8) Version 4 questionnaire; the occurrence of unacceptable ADEs; or death.

2.1. Ethical considerations

The study was approved by the ethical committee of Ain shams University, Faculty of Pharmacy on 16th November 2016 approval number 40.

2.2. Statistical Analysis

Data collected was analyzed with a statistical package for social sciences (SPSS) version 20.0

for windows (SPSS Inc., Chicago, IL). Categorical data were described by frequencies and percentages, while quantitative variables were stated as the means and standard deviations.

Categorical data of the 2 groups were compared by Chi-square tests/Fisher's exact test. Student T-tests/Mann-Whitney U tests according to normality were used to compare the numerical data.

Survival analysis was conducted by Kaplan-Meier curves for OS and PFS. A log-rank test was used to compare the survival probabilities between the two groups. All borderline significant variables were entered into a Cox regression model and Hazard ratios (HRs) were stated. The level of significance was set at a P-value <0.05.

3. RESULTS

From November 2016 to November 2018, 110 patients were screened for the trial; 10 patients did not meet the eligibility criteria and thus, 100 patients were recruited. Of these 100 patients, 45 patients were lost to follow -up, so only 55 patients completed the trial (**Fig. 1**).

The sorafenib arm included 35 patients, and the control arm included 20 patients. At baseline, the two study groups were evaluated regarding patient demographics, clinical characteristics, and laboratory parameters (**Table 1**).

Twenty-five out of the 55 patients previously received direct-acting antiviral (DAA) or interferon therapy as HCV treatment. Previous HCC treatment (embolization, radiofrequency, and radiotherapy) was reported in 48.5% and 25% of the sorafenib and control groups, respectively.

After a follow-up of one year for all patients, the median OS and 6-month and 1-year survival rates were significantly better in the sorafenib arm than in the control arm, and the median OS

in the control patients was 6 months. In the sorafenib group, the median OS was not reached since more than 50% of the patients were still alive at the end of the study. The 6-month survival rates were 97.1% and 54.2% in the

sorafenib and control groups, respectively (P=0.008). The survival rate at 1 year was 75.7% in the sorafenib group, and no patients survived beyond 1 year in the control group (**Fig. 2A**).

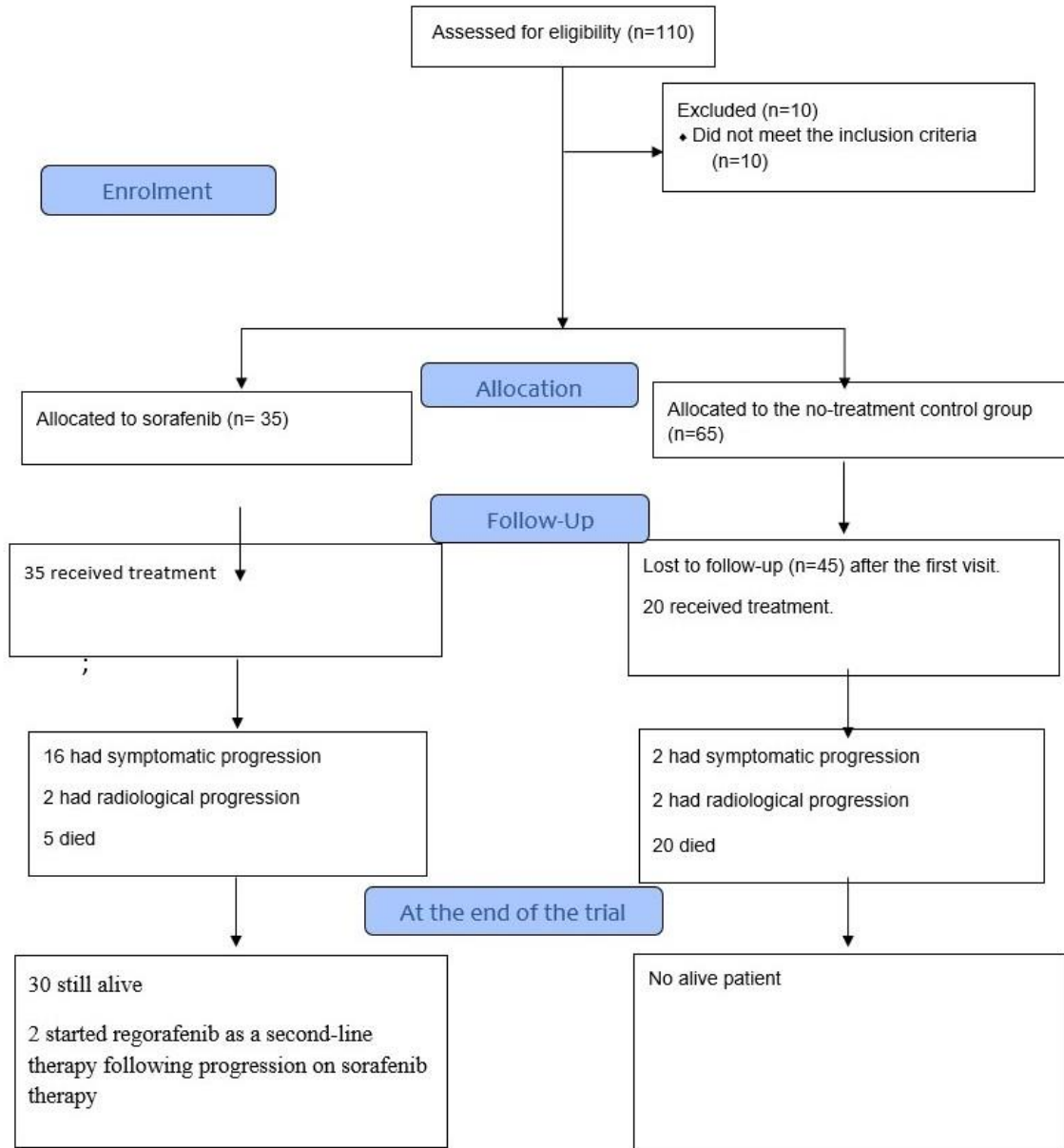


Fig. 1. Trial flow chart

Table 1. Baseline demographic and baseline characteristics of the patients

		Supportive care (n=20)	Sorafenib (n=35)	p-value
Sex no. (%)		Female 8 (40.0%)	0 (0.0%)	<0.001
		Male 12 (60.0%)	35 (100.0%)	
Age (years) ± SD		62.90±7.90	61.46±6.67	0.474
ECOG* no. (%)	0	2 (10.0%)	22 (62.9%)	<0.001
	1	8 (40.0%)	13 (37.1%)	
	2	10 (50.0%)	0 (0.0%)	
Child-Pugh class no. (%)	A	10 (50.0%)	29 (82.9%)	0.01
	B	10 (50.0%)	6 (17.1%)	
Chronic Diseases no. (%)				
Diabetes mellitus	No	16 (80.0%)	29 (82.9%)	1
	Yes	4 (20.0%)	6 (17.1%)	
Hypertension	No	16 (80.0%)	32 (91.4%)	0.242
	Yes	4 (20.0%)	3 (8.6%)	
HCV treatment no. (%)	Yes (DAAs/Interferon)	10 (50.0%)	15 (42.9%)	0.609
	NO	10 (50.0%)	20 (57.1%)	
Previous HCC treatment no. (%)	Embolization (TACE/TARE)	No 16 (80.0%)	24 (68.6%)	0.360
		Yes 4 (20.0%)	11 (31.4%)	
	Radiofrequency/Radiotherapy	No 19 (95.0%)	29 (82.9%)	
	Yes 1 (5.0%)	6 (17.1%)		
Albumin 1 (g/dL) ± SD		3.20±0.30	3.38±0.50	0.155
Total bilirubin 1 (mg/dL) ± SD		1.74 ±1.31	1.32 ±0.44	0.667
Alpha-fetoprotein 1 (ng/mL) ± SD		5365.95±11758.47	7172.64±16994.63	0.018
Platelets (x 10⁹/L) ± SD		234.38±63.26	164.63±67.66	0.131

ECOG, Eastern Cooperative Oncology Group Performance Status; HCV, Hepatitis C virus; DAA, direct-acting antiviral; RF, Radiofrequency; RTH, Radiotherapy; TACE, Transarterial chemoembolization; TARE, Transarterial radioembolization.

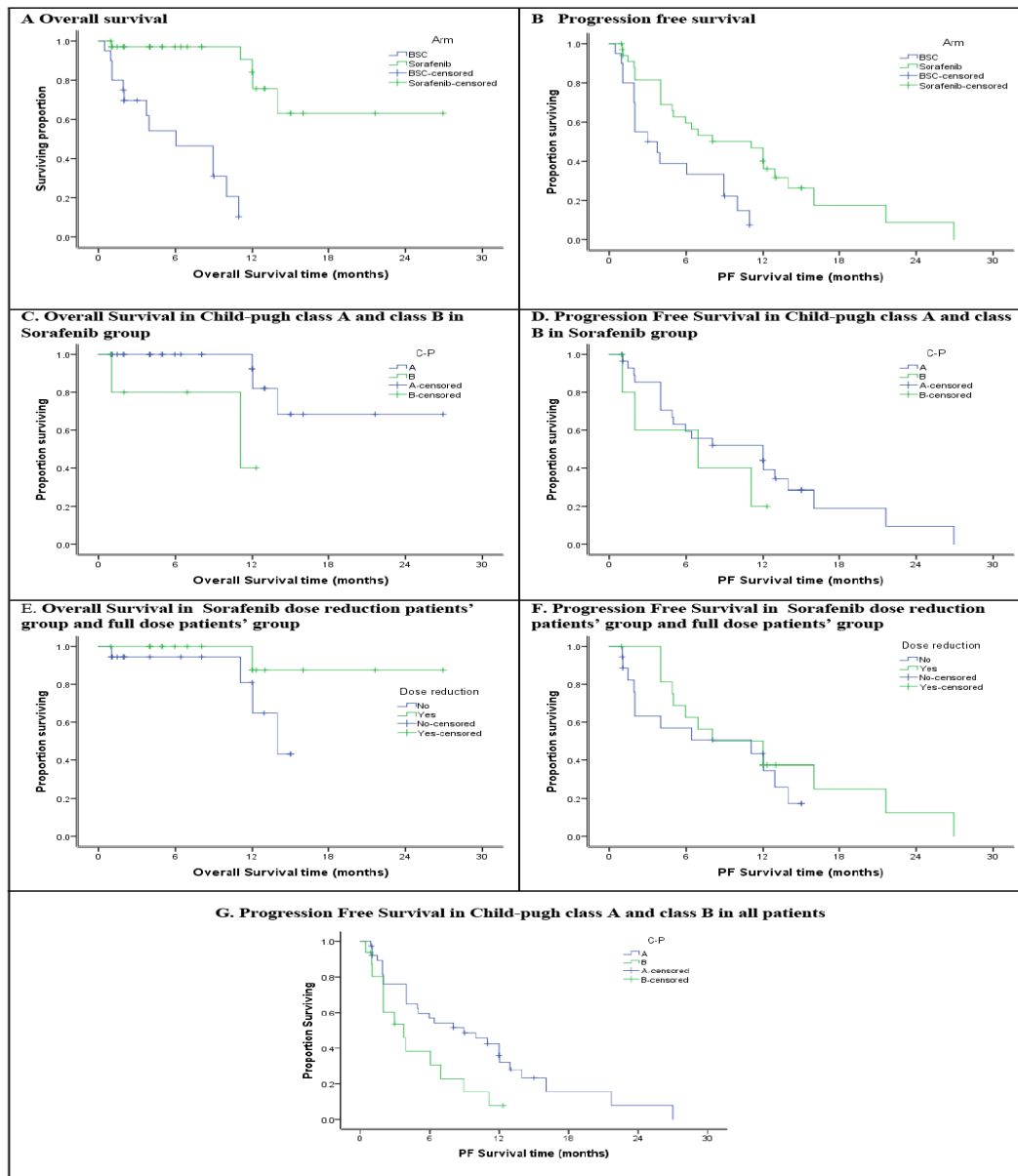


Fig 2. Kaplan-Meier analysis of overall survival and event-free survival

Among 55 patients, 35 received sorafenib and 20 received the placebo; the one-year OS of the supportive care group was 0.0% while that for the sorafenib group was 75.7% (P=0.008) (Panel A).

The one-year PFS was 0.0% in the supportive care group and 40.2% in the sorafenib group (P=0.008). The HR for the risk of progression in the supportive care group was 2.35 higher than that in the sorafenib group (95CI, 1.19 to 4.62; P=0.014) (Panel B). In the sorafenib arm, the one-year OS rate of Child-Pugh class A patients (n=29) was 81.0% while that for Child-Pugh class B patients (n=6) was 87.5% (P=0.158) (panel C). The one-year PFS of Child-Pugh class A patients (n=29) was 43.3% while that for Child-Pugh class B patients (n=6) was 20.0% (P=0.317). The 6-month PFS was 59.3% and 60.0% for Child-Pugh class A and class B patients, respectively (Panel D).

The 1-year OS of patients who received a full dose of sorafenib was 92.3% while that for those with a dose reduction was 40.0% (P=0.014) (Panel E). The 1-year PFS of patients who received full dose was 43.4% while that of those with a dose reduction was 37.5% (P=0.345) (Panel F). The 6 months PFS of class A (n=39) was 89.6% While class B group (n=16) 6 months PFS was 62.5%. Twelve months PFS in class A was 74.0% while in class B (30.3%) with a median time to progression longer in class A patients than in class B group (10 VS. 5 months) (P=0.036)(Panel G).

The one-year PFS was 0.0% in the control group and 40.2% in the sorafenib group. The 6-month PFS rates were 62.9% in the sorafenib group and 49.1% in the control group ($P=0.008$). The HR for the risk of progression among control patients was 2.35 higher than that among the sorafenib patients (95% confidence interval (CI), 1.19 to 4.62; $P=0.014$) (**Fig. 2B**).

For the 29 Child-Pugh class A patients in the sorafenib group, the median OS duration was 14 months. The expected 6-month OS was 94.4%, and the 12-month OS was 81.0%. In the 6 Child-Pugh class B patients, the 6-month and 12-month expected OS was 100.0% and 87.5%, respectively ($P=0.158$) (**Fig. 2C**). The PFS was not significantly different between the 2 groups (Child-Pugh A vs B). The one-year PFS of the class A group ($n=29$) was 43.3% while that for the class B group ($n=6$) was 20.0%. The 6-month PFS was 59.3% and 60.0% for the class A and B groups, respectively ($P=0.317$) (**Fig. 2D**).

Dose reductions due to adverse events were necessary for 17 of the 35 patients (48.57%) treated with sorafenib. The PFS was not significantly different between the dose reduction patients and the full dose of patients. The 6-

month PFS was 56.9% in the full-dose group and 62.5% in the dose reduction group. The 12-month PFS was 43.4% and 37.5% in the full dose and dose reduction groups, respectively, with a longer median time to PFS in the full-dose group than in the dose reduction group (11.1 vs. 8.1 months, $P=0.345$) (**Fig. 2F**). The difference was significant between the 2 groups in terms of OS; the one-year OS was 92.3% in the full dose patient group and 40.0% in the dose reduction patient group. The 6-month OS was 100% in the full-dose group and 80.0% in the reduced-dose group. The median OS was 11.1 months in the dose reduction group ($P=0.014$) (**Fig. 2E**).

The 2 arms were not significantly different in terms of the QOL scores at the first time point according to the FACT FHSI-8 questionnaire. The mean QOL score in the control patients at the first time point was 20.6 (± 6.0). In the sorafenib group, the mean score was 20.8 (± 6.3) ($P=0.071$). At the second time point, the scores were considerably different between the two groups. The QOL score dropped to 11.5 (± 4.2) in the control patients, while in the sorafenib group, the score remained almost the same at 20.6 (± 20.6) ($P=0.006$) (**Fig. 3**).

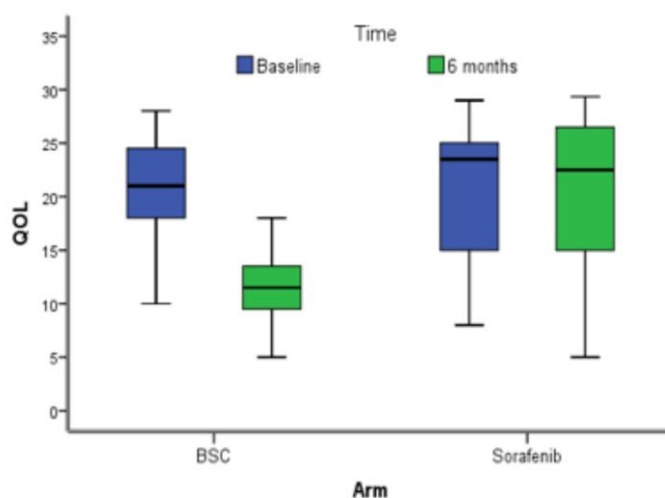


Fig. 3. Quality of life assessment at baseline and after 6 months

Table 2. Drug-related adverse events* (all grades)

Drug-related adverse events, n	Supportive care (n=20)	Supportive care Grade 3/4	Sorafenib (n=35)	Sorafenib Grade 3 / 4
Abdominal pain	1	0	2	0
Constipation	0	0	1	0
Diarrhoea	0	0	15	3
Epistaxis	0	0	1	0
Fatigue	1	0	1	0
HFS	0	0	12	5
Hypoglycaemic coma	0	0	1	0
Infection	1	0	0	0
Low platelet count	0	0	2	0
Bleeding	0	0	1	0
Melena	1	0	0	0
Hypertension	0	0	1	0
Gastritis	0	0	1	0
Pain	6	4	0	0
Nausea	2	0	0	0
Ascites	0	0	4	0
Rash	0	0	1	0
Mucositis	0	0	2	0

*The adverse events, as defined by the National Cancer Institute Common Terminology Criteria (version 4.03), are listed. HFS= Hand, Foot Syndrome.

In the sorafenib group, the drug-related adverse events incidence of any grade was 100% (35 of 35 patients). Diarrhea (15 of 35 (42.8%)) and hand-foot syndrome (HFS) (12 of 35 patients (34.2%)) were the most frequently reported drug-related adverse events in patients treated with sorafenib. The other reported adverse events were fatigue, rash, hypertension, abdominal pain,

constipation, epistaxis, hypoglycaemic coma, low platelet count, gastritis, ascites, and mucositis. All of these drug-related adverse events happened in patients in the sorafenib group (**Table 2**). The sorafenib-related adverse events stated were mainly classified as grade 1 or 2.

Sorafenib discontinuation due to death occurred in 5 patients (14.2%), while in the

control, death was the cause of discontinuation for 13 patients (65%). At the end of the study, no patients were alive in the control arm, and 30 were alive in the sorafenib treatment group. Two patients from the sorafenib arm started regorafenib as second-line therapy following progression with sorafenib therapy [20] (Fig. 1).

4. DISCUSSION

Based on the observation of the study patients and the assessment of the efficacy of sorafenib versus supportive care. The current study reported significant differences in OS favoring the sorafenib group.

Sorafenib showed a better 1-year survival rate (75.7%) than the control group (0%). In the SHARP trial, the survival rates at 1 year were 44% and 33% in the sorafenib and placebo groups, respectively [16]. In this trial, the 6-month OS rates were 97.1% in the sorafenib group and 54.2% in the control group. In the Asia-Pacific region trial, the 6-month OS rates were 53.3% and 36.7% in the sorafenib and placebo groups, respectively [17].

4.1. Ethnic Variations

Parsons et al. found a significant disparity in sorafenib use by ethnicity [21]. The patients involved in the SHARP trial were mainly from the Caucasian population and predominantly had HCV; conversely, the patients were in the Asia-Pacific study were mainly infected by the hepatitis B virus (HBV). These variations can clarify the differences in OS observed between the two trials (10.7 and 6.5 months); however, the HR for survival was similar between the two trials (0.69 and 0.68) [16, 17].

In the Indian population, after a median follow-up of 4.9 months, the median event-free survival (EFS) was 4.20 months [22]. Hence, ethnic variations are associated with differences in sorafenib-related outcomes. Moreover, various

risk factors for HCC differ among populations, including those for HBV, HCV, cirrhosis, alcohol use, smoking history, aflatoxins, and male sex [23]. In Egypt, HCV is considered the main risk factor for HCC, where 71% of HCC patients are positive for anti-HCV antibodies [24].

4.2. Previous Egyptian Population Studies

In a single-arm study that included 41 patients who were treated with sorafenib, the median PFS was 4 months, and the median OS was 6.25 months. The authors recommended that in Egypt, which is a limited resource country, the use of sorafenib to treat advanced HCC patients should be limited to patients with a good performance status who are classified as Child-Pugh class A [25]. Additionally, in a retrospective cohort study in 2018, the authors recommended limiting the use of sorafenib for patients who are Child-Pugh class A, have a performance status of 0-1, and have a low disease burden [26]. The study included 130 patients and reported a median OS of 5 months (CI: 4.166-5.834) for patients treated with sorafenib and a median PFS of 4 months (CI: 3.479-4.521) [26].

On the other hand, the current study is the first controlled trial that showed a preferable sorafenib outcome compared to supportive care in the Egyptian population who has advanced HCC.

This outcome was different from the previously mentioned Egyptian studies, and the differences may be due to the different study designs and the different sample sizes. Regarding the primary outcome "Survival", the current study showed that the median OS in the BSC patients was 6 months. In the Sorafenib group, the median OS was not reached as more than 50% were still alive at the end of the study. While the two previously mentioned Egyptian studies presented that median OS for patients treated with sorafenib was 6 & 5 months only [25, 26]. Additionally, all the previous studies

were uncontrolled, which leads to limitations. Physician dissatisfaction should be discussed in scientific meetings by displaying these current data to allow Egyptian HCC patients an opportunity for the best treatment.

4.3. Dose Reduction

The data on sorafenib dose reduction are still conflicting. Fucile et al. demonstrated that the sorafenib concentrations of patients who received the full dose were not significantly different from those of patients who received a reduced dose [27]. In Italy, 77 patients treated with a half dose for >70% of the time had a survival of 21.6 months (95% CI 13.6-29.6), and 219 patients treated with a full dose for >70% of the time had a survival of 9.6 months (95% CI 6.9-12.3) [19].

In the current trial, 17 of the 35 patients (48.57%) treated with sorafenib needed a dose reduction due to intolerable side effects. The PFS was not significantly different between the dose reduction patients versus the full dose of patients. The median PFS time was 11.1 months and 8.1 months in the full dose and reduced dose groups, respectively (P=0.345). However, the OS was significantly different between the 2 groups. The 6-month OS rate in the dose reduction group was 80.0% and that in the full-dose group was 100.0%. The one-year OS rate was 40.0% and 92.3% in the reduced group and full-dose group, respectively (P=0.014). These findings are in favor of a full dose for preferable survival outcomes.

4.4. Side Effects

In the Indian population, the most observed side effects were liver dysfunction (38.5%), HFS (grades 2 and 3; 25.6%), fatigue (grades 2 and 3; 10.3%), and diarrhoea (7.7%) [22].

In the SHARP trial, the total incidence of serious adverse events was 52% in the sorafenib group and 54% in the control group. The most

reported adverse events were diarrhea, HFS, and fatigue [16].

In the Asian study, the most common adverse events were classified as grade 1 or 2. The reported adverse events included HFS, diarrhea, skin rash, fatigue, alopecia, and hypertension. Severe adverse events (grade 3/4), most notably HFS and diarrhea, were stated more in the sorafenib group than in the control group [17].

In Egypt, in a previous retrospective study, the most frequent grade 3/4 adverse events reported were HFS, fatigue, and diarrhea in 27.6% of the patients [26]. In the single-arm study, 23% of the patients suffered from fatigue, diarrhea, and HFS (grade 3/4 toxicity) [25].

In the current trial, diarrhea (15 of 35 patients (42.8%)) and HFS (12 of 35 patients (34.2%)) were the most often reported adverse events in the sorafenib group. The other reported adverse events were fatigue, rash, hypertension, abdominal pain, constipation, epistaxis, hypoglycaemic coma, low platelet count, gastritis, ascites, and mucositis. The sorafenib-related adverse events reported were mainly classified as grade 1 or 2.

4.5. Limitations

Despite this study's current strength of being a controlled, prospective trial in Egyptian patients with advanced HCC, the research has limitations. These limitations include the small sample size and the limited follow-up of the supportive care control arm, which was due to lack of medical awareness as the patients lost hope for a cure and considered that the outcomes from BSC were not favorable.

Sorafenib has not been appropriately prescribed in oncology practice since being endorsed as a treatment for advanced HCC. Insurance status is yet one of the most crucial issues that influence the choice of the treatment

protocol for patients in Egypt. Sorafenib is not financially covered by all institutions, and the patients were enrolled in the treatment groups according to the availability of sorafenib and insurance coverage of the institution.

Conclusion

Sorafenib treatment had better OS, PFS, and QOL outcomes than the control in Egyptian patients with advanced HCC. Egyptian patients with advanced HCC should seize the opportunity for favorable treatment outcomes with sorafenib with consistent follow-up, optimum patient counseling, and proper management of the side effects.

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Ethical approval and consent to participate

The study was approved by the Ain Shams University- Faculty of Pharmacy Ethical Committee on 16 November 2016 (Approval number: 40). And written informed consent has been obtained from patients to participate in the study.

Availability of data materials

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interest

The authors declare that they have no competing interests.

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Author's contributions

NS, LM, MA, SM, and NH have contributed to the study conception, design of the work, data interpretation, revision of the work. AM has contributed to the study design and revision of the work. All authors have read and approved the final manuscript.

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