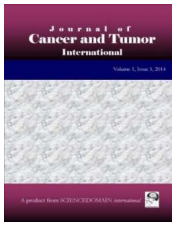

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Efficacy and Safety of Sorafenib in Patients with Advanced Hepatocellular Carcinoma

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Authors' contributions

This work was carried out in collaboration between both authors. Author WH designed the study, wrote the protocol and wrote the first draft of the manuscript. Author YMS managed the literature searches, analyses of the study performed the spectroscopy analysis, managed the experimental process and identified the species of plant. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: Advanced Hepatocellular carcinoma (HCC) is a major health problem with limited treatment options. The Sorafenib monothearpy is the only efficacious systemic treatment agent showing a survival benefit in these patients. In our study, we evaluated the efficacy and tolerability of Sorafenib in advanced and metastatic HCC patients.
Methodology: Twenty patients with advanced HCC (between Jan. 2011 and Dec. 2013), and not eligible for loco regional therapy were treated prospectively with Sorafenib monotherapy with assessment of survival and toxicity. Follow up was until Oct. 2014.
Results: According to Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 was found in the most of patients 13/20 while Ps 3 in 7/20 and Child-Pugh class A in (40.0%) of cases and B (60.0%) of patients. Six patients had stage IV-A tumors, whereas 14 had stage IV-B tumors. Four patients had portal vein tumor thrombosis (PVTT). Following Sorafenib monotherapy, the disease control rate was(65.0)% with 5 patients (25.0%) had a parial response while stable

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disease in 8 patients (40.0%) with a median overall survival of 12 months and the median progression-free survival was 0 months. Diarrhea and hand-foot skin reactions were the major side effects.

Conclusions: In our study, the use of Sorafenib monotherapy in the patients with advanced HCC showed a reasonable outcome and was well tolerated. Further study with a larger number of patients and treated with a long duration is warranted.

Keywords: Advanced HCC; sorafenib; overall survival; toxicity.

1. INTRODUCTION

Hepatocellular carcinoma is a major health problem, accounting for more than 626,000 new cases per year worldwide [1]. In the West, the disease is diagnosed in 30 to 40% of all patients at early stages and is amenable to potentially curative treatments, such as loco regional procedures (radiofrequency ablation) and surgical therapies (resection and liver transplantation) achieving 5-year survival rates of 60 - 70% in well-selected patients [2]. However, the disease with an advanced stage or with progression after loco regional therapy has a poor prognosis owing to the underlying liver disease and lack of effective lines of treatment [2-4].

Until recently, treatment options for locally advanced or metastatic (HCC) have been limited as chemotherapy in general is ineffective [5]. However, a great progress in the treatment of HCC was made with the use of the multikinase inhibitor Sorafenib for this indication [6]. Sorafenib (Nexavar) is a small molecule that inhibits tumor-cell proliferation, has anti tumor angiogenesis and increases the induction of apoptosis in many of tumors. It acts through inhibiting the serine–threonine kinases Raf-1 and B-Raf and the receptor tyrosine kinase activity of vascular endothelial growth factor receptors 1, 2, and 3 and platelet-derived growth factor receptor β [7,8]. These pathways have been included in the molecular pathogenesis of hepatocellular carcinoma, [9-12] providing a rationale for investigating Sorafenib for this indication.

Sorafenib is the only efficacious systemic treatment and is well tolerated in patients with advanced HCC [2]. Clinically however, in clinical practice the most of patients with advanced HCC have underlying hepatic cirrhosis and subclinical comorbidity, affecting their general medical condition and liver functions [6].

Since the prognosis for HCC is dependent upon tumor stage, PS, severity of underlying liver disease, and the availability of appropriate therapies, the unavailability of Sorafenib may have a significantly adverse effect on the prognosis of patients with advanced HCC [13].

Abou-Alfa et al. [14] had studied 137 patients with advanced (HCC) and their Child–Pugh class A or B status indicated that the use of Sorafenib monotherapy might have a beneficial therapeutic effect resulting in a median overall survival of 9.2 months and a median time to progression of 5.5 months (as assessed by independent radiologic evaluation.

The aim of this study was to assess the efficacy (response and time to progression), overall survival (OAS) from the start of treatment until death or last follow up and the side effects (skin rash and diarrhea) of Sorafenib in advanced and metastatic HCC patients.

2. MATERIALS AND METHODS

2.1 Patients

A prospectivily study was conducted between January 2011 and December 2013 in Saudi-German Hospitals group at KSA. The study enrolled 20 patients with advanced HCC as confirmed by pathological analysis. Patients were classified as having advanced disease if they were not eligible for/or had disease progression after surgical or locoregional therapies. The eligibility criteria also included an Eastern Cooperative Oncology Group (ECOG) PS score of 3 or less [15], Child–Pugh liver function class A or B [16,17], a life expectancy of 12 weeks or more, adequate hematologic function (platelet count ≥ 60 × 10^9/L; hemoglobin ≥8.5 g/dL and prothrombin time international normalized ratio ≤2.3 or prothrombin time ≤6 seconds above control), adequate hepatic function (albumin ≥2.8 g/dL; total bilirubin ≤3 mg/dL; and alanine aminotransferase & aspartate aminotransferase ≤5 times the upper limit of the normal range) and adequate renal function (serum creatinine 1.5 times the upper limit of the normal range).

All patients had a dynamic three-phase CT scan of liver performed at baseline as well as an

electrocardiogram (ECG), blood pressure measurement, blood samples including hematological values, liver biochemistry, serum Alpha-Feto Protein (AFP) and tissue biopsy. Patients were required to have at least one untreated target lesion that could be measured in one dimension, according to the modefied Response Evaluation Criteria in Solid Tumors (modefied RECIST) [18].

Patients were excluded if they had other primary malignancies, had any other concurrent serious medical condition(s), or had undergone systemic chemo-therapy previously. All patients provided informed written consent before enrollment in the study. The study was approved by Local Ethical Commitee.

2.2 Treatment

An initial dose of 400 mg Sorafenib was administered twice daily. The dose was reduced to 400 mg/day (200 mg twice daily) if there were drug-related grade 3/4 toxicities until recovery from the adverse effects. If symptoms did not improve although the dose reduction was continued, Sorafenib was discontinued until the patient recovered from the adverse event. Treatment continued until disease progression or intolerable toxicities appeared, or until a patient refused further treatment or death.

2.3 Assessment

Dynamic spiral computed tomography (CT) of liver and determination of AFP level were performed at baseline. The response to treatment was evaluated every 2 months by means of a CT liver or earlier with clinical signs of progression. Tumor response was assessed until disease progression. The tumor response was evaluated according to the modified RECIST [18]. Patients who died before their first radio-graphic evaluation were assessed as having progressive disease. Patients with a serum AFP of ≥ 200 ng/L at baseline and with a decline in AFP of ≥ 20% after 4 weeks of Sorafenib therapy were classified as AFP responders. Toxicity was assessed based on information noted in the medical records and graded according to NCI-CTCAE v3.0 [19].

2.4 Treatment Outcome and Statistical Analysis

The primary study objective was to assess OAS. Secondary objectives were to evaluate overall response rate, progression-free survival (PFS), and toxicity. OAS was defined as the time interval between the initiation of Sorafenib and death or last follow up. PFS was defined as the time interval from the first cycle of Sorafenib to the date when disease progression or any cause of death was first observed. Survival curve was calculated by the Kaplan-Meier method and compared with the log-rank test. Qualitative variables were expressed as number and percentage. Quantitative variables were expressed as mean ± standard deviation. $P = .05$ was considered statistically significant. All statistical analyses were performed using the SPSS software package version 17.0 (SPSS Inc., Chicago, IL, USA).

3. RESULTS

3.1 Patients

The study involved 20 patients with advanced HCC (14 males and 6 females) with age ranged from 45 to 70 years (mean of age; 58.30 years). Pre-existing no abnormality detected (NAD) was found in most of cases (55.0%) followed by hepatitis (C) in (40.0%). The most of patients had (ECOG) performance status score 2 (65.0%) while 3 in (35.0%). Patients with Child-Pugh class B represented (60.0%). PVTT occurred in (20.0%) of cases. Eleven patients (55.0%) showed extra hepatic involvement (i.e., nodal invasion and/or distant metastases; 40.0% and 30.0%, respectively) (Table 1).

Data (other than age) are presented as number (%). HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; NAD; No Abnormality Detected, ECOG, Eastern Cooperative Oncology Group; PVTT, Portal Vein Tumor Thrombosis; LN, lymph node.

3.2 Efficacy and Survival

Median duration of Sorafenib therapy was 12 months in both Child A and Child B patients. Five patients (25%) died at their last follow-up from hepatic failure, hepato-renal syndrome and pneumonia (15%, 5% & 5%, respectively). The median OAS was 12 months (Fig. 1). The median PFS was 0 month. Five patients (25.0%) had a partial response (PR) and eight patients (40.0%) had stable disease, making the disease control rate (DCR) (65%) (Table 2).

By univariate analysis, the median OAS was better in Child-Pugh A ($p = .04$) and with tumor

response (PR and SD; *p* = .003). The median OAS of patients with PS 2 was better than PS 3 (*p* = .01). The OAS of patients with skin rash and diarrhea showed no better survival (p = .27 & p = .12, respectively) (Table 3).

3.3 Toxicity

Treatment-related adverse events had occurred in the majority of cases with overall incidence (75.0%) with mainly grades 1 and 2 in severity.

Table 1. Baseline characteristics of the patients (n = 20)

Characters			Value
Age (years):			
Mean ± SD (Minimum.- Maximum)			58.3 ± 7.76 (45-70)
Gender:	Male		14 (70.0)
	Female		6 (30.0)
Cause of disease:	HCV only		8 (40.0)
	HBV only		1 (5.0)
	NAD		11 (55.0)
ECOG performance status:		2	13(65.0)
		3	7 (35.0)
Child-Pugh class:	A		8 (40.0)
	B		12 (60.0)
PVTT:	-ve		16 (80.0)
	+ve		4 (20.0)
Extra hepatic distant spread:		No	6 (30.0)
		Yes	14 (70.0)
LN metastases:		No	12 (60.0)
		Yes	8 (40.0)

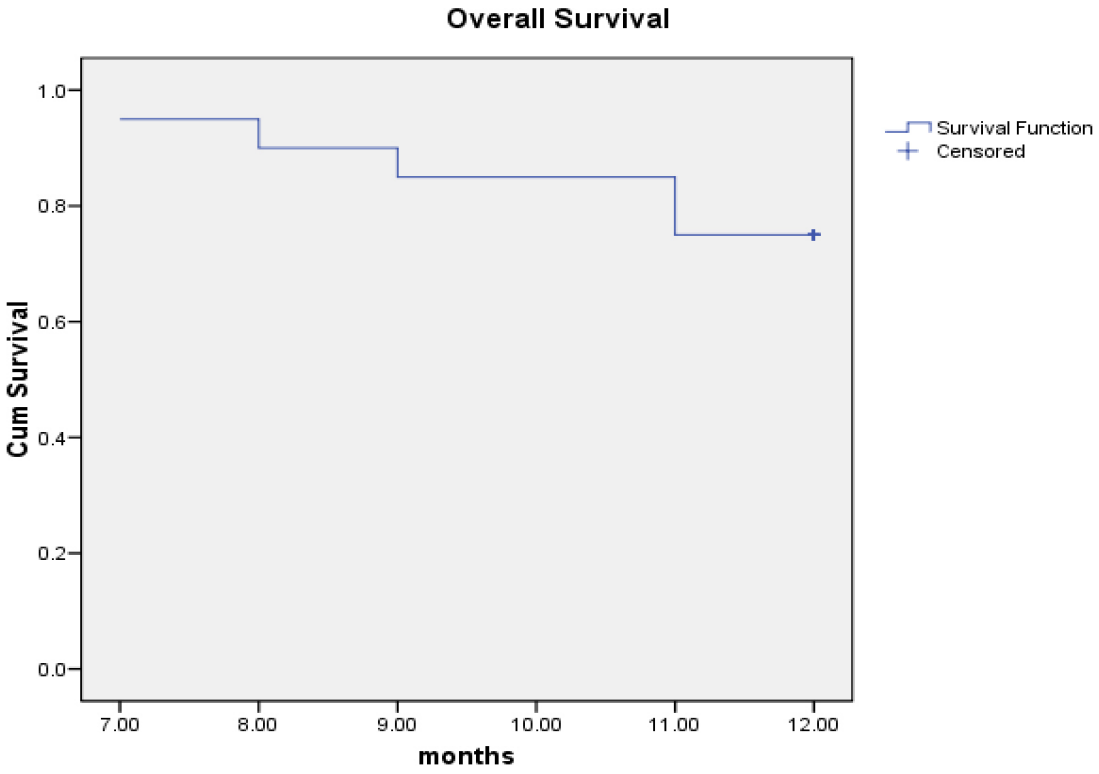

Fig. 1. Kaplan-Meier curve of overall survival. The median overall survival was 12 months

Several adverse events had occurred together in 4 patients (20.0%) only. The most common side effect was Skin rash (13 patients, 65.0%). while diarrhea had occurred in (6patients, 30.0%) (Table 4).

Four patients (20.0%) required a dose reduction of Sorafinib due to severe diarrhea and five patients (25.0%) from skin rash. Besides adverse events, seven patients (35.0%) stopped the Sorafenib by disease progression.

4. DISCUSSION

The aime of our study was to evaluate the efficacy and tolerability of Sorafenib in patients with advanced HCC. Although Sorafenib as a monotherapy has been used in many trials for patients with HCC, the clinical data of this drug in those patients was not enough. In our study, (25.0%) of patients showed PR and (40.0) % of patients showed SD with (DCR 65.0%). The median OAS duration was 12 months which was better than the SHARP trial (10.7 months) in the Sorafenib group. Also, the median PFS in our study was 0 month and the patients with disease controlled (PR + SD) showed a significant increase in OAS compared with that in nonresponsive patients with disease progression (PD).

Table 2. Summary of efficacy values

Characters	Value
OAS (months)	12.0 (7.00- 12.00)
Tumor progression (months)	0.0 (0.00-12.00)
Tumor response:	
Complete response	0 (0.00)
Partial response	5 (25.00)
Stable disease	8 (40.00)
Disease progression	7 (35.00)
Disease-control rate *	13 (65.00)

Data are presented as median (95% confidence interval) or number (%). OAS; Overall Survival. :The proportion of patients who had a best response rating of a complete response, partial response or stable disease that was maintained ≥4 weeks from the first manifestation of that rating*

SD population in our study was (40%) lower than the SHARP trial and Asia-Pacific population study (SD, 71% and 54% respectively). This difference may be due to the use of different methods for evaluation (modified RECIST vs. RECIST) and the lower percentage of patients with Child-Pugh A in our study (40%) than in SHARP trial and Asia-Pacific population study (95.0% and 97.3%) respectively. Although, the DCR in our study was better (65.0%) than SHARP trial and Asia-Pacific population study (DCR 43.0% and 35.3% respectively). The low SD in our study may reflect the more advanced state of patients rather than lack of effect of Sorafenib. In SHARP trial the use of sorafenib showed a significant benefit with a DCR of 43.0% compared with 32.0% in its placebo group.

In this study, we also analyzed the prognostic factors affecting survival. We found that Child-Pugh A and tumor responsiveness (PR or SD) were favorable parameters as regard PFS and OAS which are constant with those in other reports [20-22]. Also, we found that skin rash and diarrhea symptoms are the most common adverse events and similar to those in previous clinical studies, [2,23]. Four patients (20.0%) required a dose reduction of sorafenib because of diarrhea, and it was the most frequent adverse event leading to its discontinuation. HCC is a complex and heterogeneous disease at the molecular level and different pathways can be aberrantly activated in distinct patient subgroups. With such heterogeneity, different approaches based on detecting predictive markers for sensitivity and resistance will improve treatment efficacy. Zhang et al. [24] reported that phosphorylated extracellular signal-regulated kinase could be a useful biomarker predicting sensitivity to Sorafenib in HCC tumor cells *in vitro* study.

However, there are no clear predictive factors, are available on resistance. Hoshida et al. [25] suggested that a new class of genomic information, micro-RNA dysregulation and epigenetic alterations, will provide insight for more understanding of HCC mechanism. Our study has several limitations, including the small number of patients and a single arm study without a control group. Most patients had advanced HCC and/or extra hepatic metastases, so they could not maintain long-term Sorafenib treatment. Therefore, a pre-protocol evaluation in an adequate number of assessable patients could not be achieved and treatment duration was too short to assess the efficacy of Sorafenib.

The effect of Sorafenib in this advanced disease also gives the chance in patients who will have or have already undergone resection, ablation chemoembolization or liver transplantation. Also, this success encourages us to test other targeted therapies and their combinations in HCC.

Table 3. Univariate analyses for overall survival

Variables		Number (n-20)	Median OAS (months)	*P value*
Age	< 63	14	12.0	
	≥ 63	6	11.5	.07
Cause of disease:				
HCV only		8	12.0	.20
HBV only		1	12.0	
NAD		11	12.0	
ECOG performance status:				
2		13	12.0	
3		7	11.0	.01*
Child-Pugh class:	A	8	12.0	
	B	12	12.0	.04*
Diarrhea:	+ve	6	11.5	
	-ve	14	12.0	.12
Skin rash:	+ve	13	12.0	
	-ve	7	12.0	.27
PR or SD	Yes	13	12.0	
	No	7	11.0	.003*

**: Significant*

Table 4. Incidence of adverse events

Adverse events	All Grade	Grade 2	Grade 3	Grade 4
Overall incidence	15(75.0)	10(50.0)	2(10.0)	0
Dermatologic events:				
Rash or Desquamation	13(65.0)	9 (45.0)	1(5.0)	0
Gastrointestinal events:				
Diarrhea	6 (30.0)	4(20.0)	1(5.0)	0

Data are presented as number (%).

5. CONCLUSION

In conclusion, Sorafenib was effective for the treatment of advanced HCC in our study, and was well tolerated. Consistent with the SHARP trial and the Asia-Pacific population study, it seems to be an appropriate option for treatment of advanced HCC. Further study with a larger number of patients and treated with a long duration is warranted.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74-108.
2. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378-390.
3. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology. 2005;42:1208-36.
4. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma: conclusions of the Barcelona-2000 EASL Conference. J Hepatol. 2001;35:421-30.
5. Lau YK. Sorafenib: New reference standard for systemic treatment of advanced hepatocellular carcinoma. Community Oncology. 2007;4(9):529–530.
6. Di Maio MM, Daniele B, Perrone F. Targeted therapies: Role of Sorafenib in HCC patients with compromised liver function. Nature Reviews Clinical Oncology. 2009;6(9):505–506.
7. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res. 2004;64:7099-109.
8. Chang YS, Adnane J, Trail PA, et al. Sorafenib (BAY 43-9006) inhibits tumor

growth and vascularization and induces tumor apoptosis and hypoxia in RCC xenograft models. Cancer Chemother Pharmacol. 2007;59:561-74.
9. Ito Y, Sasaki Y, Horimoto M, et al. Activation of mitogen-activated protein kinases/extracellular signal-regulated kinases in human hepatocellular carcinoma. Hepatology. 1998;27:951-8.
10. Villanueva A, Newell P, Chiang DY, Friedman SL, Llovet JM. Genomics and Signaling pathways in hepatocellular carcinoma. Semin Liver Dis. 2007;27:55-76.
11. Calvisi DF, Ladu S, Gorden A, et al. Ubiquitous activation of Ras and Jak/Statpathways in human HCC. Gastroenterology. 2006;130:1117-28.
12. Semela D, Dufour JF. Angiogenesis and hepatocellular carcinoma. J Hepatol. 2004;41:864-80.
13. Palmer DH, Johnson PJ. Prognostic factors in hepatocellular carcinoma. In: UICC Prognostic Factors in Cancer. 3rd edn. John Wiley & Sons: Hoboken, NJ, USA; 2006.
14. Abou-Alfa GK, Schwartz L, Ricci S, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol. 2006;24:4293-300.
15. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.
16. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60:646-9.
17. Therasse P, Arbuck SG, Eisenhauer. Child CG III. The liver and portal hypertension. vol. 1 of Major problems in clinical surgery. Philadelphia: W.B. Saunders. 1964;50-64.
18. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30:52-60.
19. Colevas AD, Setser A. The NCI common terminology criteria for adverse events (CTCAE) v 3. 0 is the new standard for oncology clinical trials. J Clinical Oncology. 2004;22:6098.
20. Leung TW, Tang AM, Zee B, et al. Factors predicting response and survival in 149 patients with unresectable hepatocellular carcinoma treated by combination cisplatin, interferon-alpha, doxorubicin and 5-fluorouracil chemotherapy. Cancer. 2002;94:421-427.
21. Stuart KE, Anand AJ, Jenkins RL. Hepatocellular carcinoma in the United States. Prognostic features, treatment outcome, and survival. Cancer. 1996;77: 2217-2222.
22. Vora SR, Zheng H, Stadler ZK, Fuchs CS, Zhu AX. Serum alpha-fetoprotein response as a surrogate for clinical outcome in patients receiving systemic therapy for advanced hepatocellular carcinoma. Oncologist. 2009;14:717-725.
23. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomized, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10:25-34.
24. Zhang Z, Zhou X, Shen H, Wang D, and Wang Y. Phosphorylated ERK is a potential predictor of sensitivity to sorafenib when treating hepatocellular carcinoma: Evidence from an in vitro study. BMC Med. 2009;7:41.
25. Hoshida Y, Toffanin S, Lachenmayer A, Villanueva A, Minguez B, Llovet JM. Molecular classification and novel targets in hepatocellular carcinoma: Recent advancements. Semin Liver Dis. 2010;30: 35-51.

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