RESEARCH ARTICLE

Efficiency and Side Effects of Sorafenib Therapy for Advanced Hepatocellular Carcinoma: A Retrospective Study by the Anatolian Society of Medical Oncology

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Abstract

Background: Inoperable and metastatic hepatocellular carcinoma (HCC) is associated with a poor prognosis and low chemotherapeutic efficiency. Sorafenib is an oral multi-kinase inhibitor exerting its effects via the RAF/MEK/ERK pathway, vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor beta (PDGFR-β) tyrosine kinases. Randomized studies have shown a significant contribution of sorafenib to life expectancy and quality of life of cancer patients. The aim of the present study is to evaluate the efficacy and side effects of sorafenib therapy in Turkey. Materials and Methods: Data for 103 patients (82 males, 21 females) receiving sorafenib therapy in 13 centers from February 2008 to December 2012 were evaluated. Median age was 61 years and median ECOG performance status was 1 (range: 0-2). 60 patients (58%) had hepatitis B, 15 patients (15%) had hepatitis C infection and 12 patients (12%) had a history of alcohol consumption. All of the patients had Child scores meeting the utilization permit of the drug in our country (Child A). Results: A total of 571 cycles of sorafenib therapy were administered with a median of four per patient. Among the evaluable cases, there was partial response in 15 (15%), stable disease in 52 (50%), and progressive disease in 36 (35%). Median progression-free survival was 18 weeks and median overall survival was 48 weeks. The dose was reduced only in 6 patients and discontinued in 2 patients due to grade 3-4 toxicity, 18 patients (17%) suffering hand-foot syndrome, 7 (7%) diarrhea, and 2 (2%) vomiting. Conclusions: This retrospective study demonstrated better efficacy of sorafenib therapy in patients with advanced HCC compared to the literature while progression-free survival and overall survival findings were comparable. The side effect rates indicate that the drug was tolerated well. In conclusion, among the available treatment options, sorafenib is an efficient and tolerable agent in patients with inoperable or metastatic HCC.

Keywords: Hepatocellular carcinoma - sorafenib - Turkey

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Introduction

In primary liver cancer, the estimated number of annual new cases is 28,720 and the estimated number of deaths is 20,550 per year in USA. It is the 5th leading cause of death regarding cancer related death among men and 9th leading cause of death regarding cancer related death among women (Siegel et al., 2012). Although hepatocellular carcinoma (HCC) due to chronic hepatitis B infection is more common in Asia and Africa, HCC rates have decreased in some areas due to the hepatitis B vaccination programs in recent years (Chang et al., 1997). An increase in HCC rates is seen in western countries due to hepatitis C infection and alcohol consumption.

The curative approach in early HCC consists of surgery, local ablative therapies or transplantation. Despite these treatments, median survival is 60 months with a 5-year survival rate of 40-70% (EASL-EORTC

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clinical practice guidelines, 2012). However, many patients are diagnosed with advanced disease, resulting in limited treatment options. Sorafenib is an oral multi-kinase inhibitor exerting its effects via RAF/MEK/ERK pathway, vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor beta (PDGFR-β) tyrosine kinases. Increased angiogenesis via VEGFR and PFGFR through the activation of RAF/MEK/ERK pathway -which is particularly responsible from intracellular signal transduction-, play a role in the pathogenesis of HCC (Huynh et al., 2003; Schmitt et al., 2004; Stock et al., 2007). In a phase III study by Llovlet et al. sorafenib has increased median survival by approximately 3 months in HCC patients without previous systemic treatment (Llovet et al., 2008). Subsequently, the second phase III study conducted in Asia-Pacific region confirmed the contribution of sorafenib regarding life expectancy (Cheng et al., 2009).

The aim of this multicenter retrospective study was to evaluate the efficacy and tolerability of sorafenib in patients with advanced HCC.

Materials and Methods

Data were evaluated for 103 patients with advanced HCC who were receiving treatment in a total of 13 centers from February 2008 to December 2012. The data regarding sorafenib therapy were retrospectively recorded for patients who progressed or could not tolerate treatment following first line chemotherapy. Inclusion criteria included histologically confirmed HCC diagnosis, measurable lesion, ineligibility for or progression after locoregional treatment, Child-Pugh hepatic function classification A, Eastern Cooperative Oncology Group (ECOG) performance status 0-2, adequate hematologic function (white blood cells >$3x10^9$/L or absolute neutrophil count >$1.5x10^9$/L, platelets >$100x10^9$/L, hemoglobin >10 g/dL) and adequate renal functions (serum creatinine level <1.5 mg/dL, blood urea nitrogen <30 mg/dL).

Abdominal and/or thoracic computed tomography was performed after every 2 cycles of sorafenib administration to evaluate response to treatment. Progression-free survival (PFS) was calculated as the time from initiation of sorafenib therapy to progression demonstrated with an imaging method or to death from any cause. Overall survival (OS) was calculated as the time from initiation of sorafenib therapy to the date of last follow-up or to death from any cause. Response to treatment was assessed according to the modified RECIST criteria (Eisenhauer et al., 2009). National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0 was used for the evaluation of side effects.

Sorafenib was administered at dose of 400 mg twice daily. The dose was reduced or delayed in accordance with the updated guidelines and according to the type and severity of side effects that occurred during treatment.

Statistical analysis

The Kaplan-Meier method was used for the survival analysis. Statistically significance was set at $p<0.05$ level.

Table 1. Demographic and Clinical Charactertics of Patients

Characteristic		n (%)
Age, years (median)		61
Gender	Male	82 (80)
	Female	21 (20)
Alcohol	No	91 (88)
	Yes	12 (12)
Viral etiology	Hepatitis B	60 (58)
	Hepatitis C	15 (15)
Performance Status (ECOG)	0	33 (32)
	1	50 (49)
	2	20 (19)
Albumin-g/dl (median)		3.6
Total Bilirubin-mg/dl (median)		1

Table 2. Summary of Adverse Events

	Patients (n=103)			
	All events		Grade ¾	
	n	%	n	%
Anemia	3	3	-	
Neutropenia	3	3	-	
Asthenia	12	12	-	
Nausea	6	6	-	
Vomiting	9	9	2	2
Diarrhea	15	15	7	7
Hand-foot syndrome	29	28	18	17

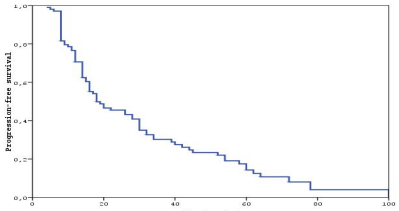

Figure 1. Progression-free Survival Median PFS was 18 Weeks

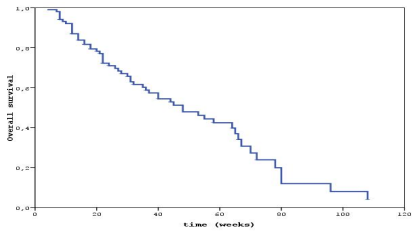

Figure 2. Overall Survival Median OS was 48 Weeks

Results

A total of 103 patients with advanced HCC who had progressed after first-line chemotherapy were included in this retrospective multicenter study. Response to treatment, toxicity and life expectancy were evaluated for all patients. The demographic characteristics and clinical data of the patients are presented in Table 1. A total of 571 cycles of sorafenib therapy were administered with a median of 4 sorafenib cycles.

The dose was reduced only in 6 patients and discontinued in 2 patients due to grade 3-4 toxicity. The most common grade 3-4 side effects were hand-foot syndrome (17%). The other side effects are summarized in Table 2.

Regarding the response to treatment, partial response was observed in 15 patients (15%), stable disease in 52 patients (50%), and progressive disease in 36 patients (35%). Median PFS was 18 weeks while median OS was 48 weeks (Figures 1 and 2).

OS was found to be better in patients with a good PS compared to those without a good PS. Median OS was 67 weeks in patients with PS=0, 48 weeks in those with P=1, and 26 weeks in those with PS=2. These differences were statistically significant ($p<0.0001$). Age and gender had no predictive value regarding OS. Clinical and demographic characteristics also had no predictive value regarding PFS.

Discussion

The efficacy of sorafenib is well known in first line treatment of advanced HCC. However, a more effective treatment than sorafenib has not been discovered yet and patients die in a short period of time following progression. SHARP and Asia-Pacific studies have previously shown the advantage regarding life expectancy with an OS of 10.7 months and 6.5 months, respectively (Llovet et al., 2008; Cheng et al., 2009). In the present multicenter retrospective study, sorafenib therapy resulted in an OS of 48 weeks in patients with advanced HCC.

Overall survival was found to be better in patients with a good PS in this study. These findings have not been clearly shown in randomized studies but have been demonstrated in some retrospective studies. In a retrospective study, Køstner AH et al. found the median OS as 6.2 months in patients with an ECOG performance status of 0-1, and 1.8 months in those with a PS of 2-3 (Køstner et al., 2013). OS was 67 weeks in patients with PS 0 in the present study. Although long-term response may be achieved in some patients, currently there is no biomarker available to predict the response to sorafenib in advanced HCC (Oliveri et al., 2011).

Recently, local treatments in addition to sorafenib have led to more effective outcomes in treatment of advanced and metastatic HCC. Wei bai et al. compared transarterial chemoembolization (TACE) in combination with sorafenib to sorafenib alone. Time to progression (TTP) was 6.3 months versus 4.3 months, while OS was 7.5 months versus 5.1 months, resulting in a survival advantage. A notable increase was not seen regarding toxicity with sorafenib and TACE combination (Bai et al., 2013). Over-expression of EGFR in HCC has been suggested to result in sorafenib resistance (Ezzoukhry et al. 2012). However, addition of erlotinib to sorafenib therapy in a clinical study did not lead to any benefits (Zhu et al., 2012).

The most common grade 3-4 side effects seen with sorafenib therapy in advanced HCC are hand-foot syndrome and diarrhea. Among side effects of any grade, asthenia is seen is 66% of the patients (Brunocilla et al., 2013). Asthenia is usually at grade 1-2 level. Diarrhea rates were similar in the present study while incidence of hand-foot syndrome was higher compared to other studies. However, side effects related to sorafenib therapy are mostly manageable side effects.

Sorafenib is the standard treatment in advanced HCC. The side effects seen with sorafenib are usually manageable side effects. New treatment options are sought with the understanding of pathways responsible from progression in liver cancer at a molecular level. It also is necessary to identify biologic factors predictive of efficacy for the most appropriate combination drugs in treatment HCC. However it would be reasonable to evaluate the potentially effective agents in combination with sorafenib.

References

Bai W, Wang YJ, Zhao Y, et al (2013). Sorafenib in combination with transarterial chemoembolization improves the survival of patients with unresectable hepatocellular carcinoma: a propensity score matching study. *J Dig Dis*, **14**, 181-90.

Brunocilla PR, Brunello F, Carucci P, et al (2013). Sorafenib in hepatocellular carcinoma: prospective study on adverse events, quality of life, and related feasibility under daily conditions. *Med Oncol*, **30**, 345.

Chang MH, Chen CJ, Lai MS, et al (1997). Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med*, **336**, 1855-9.

Cheng AL, Kang YK, Chen Z, et al (2009). Efficacy and safety of sorafenib in patients in the asia-pacific region with advanced hepatocellular carcinoma: a phase III randomised,double-blind, placebo-controlled trial. *Lancet Oncol*, **10**, 25-34.

Eisenhauer EA, Therasse P, Bogaerts J, et al (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*, **45**, 228-47.

European Association for Study of Liver; European Organisation for Research and Treatment of Cancer (2012). EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *Eur J Cancer*, **48**, 599-641.

Ezzoukhry Z, Louandre C, Trécherel E, et al (2012). EGFR activation is a potential determinant of primary resistance of hepatocellular carcinoma cells to sorafenib. *Int J Cancer*, **131**, 2961-9.

Huynh H, Nguyen TT, Chow KH, et al (2003). Over-expression of the mitogen-activated protein kinase (MAPK) kinase (MEK)-MAPK in hepatocellular carcinoma: its role in tumor progression and apoptosis. *BMC Gastroenterol*, **3**, 19.

Køstner AH, Sorensen M, Olesen RK, et al (2013). Sorafenib in advanced hepatocellular carcinoma: a nationwide retrospective study of efficacy and tolerability. *ScientificWorld Journal*, **2013**, 931972.

Llovet JM, Ricci S, Mazzaferro V, et al (2008); Sharp investigators study group. sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*, **359**, 378-90.

Oliveri RS, Wetterslev J, Gluud C (2011). Transarterial(chemo) embolisation for unresectable hepatocellular carcinoma. *Cochrane Database Syst Rev*, **16**, 4787.

Schmitt M, Horbach A, Kubitz R, et al (2004). Disruption of hepatocellular tight junctions by vascular endothelial growth factor (VEGF): a novel mechanism for tumor invasion. *J Hepatol*, **41**, 274-83

Siegel R, Naishadham D, Jemal A (2012). Cancer statistics, 2012. *CA Cancer J Clin*, **62**, 10-29.

Stock P, Monga D, Tan X, et al (2007). Platelet-derived growth factor receptor-alpha: a novel therapeutic target in human hepatocellular cancer. *Mol Cancer Ther*, **6**, 1932-41.

Zhu AX, Rosmorduc O., Evans J, et al (2012). A phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with hepatocellular carcinoma (HCC). 37th ESMO Congress; Vienna, Austria. European Society Med Oncol.