

Original Research Article**Efficacy and Safety of Sorafenib in Patients with Advanced
Hepatocellular Carcinoma****ABSTRACT**

Aims: Advanced Hepatocellular carcinoma (HCC) is a clinical challenge with limited treatment options. The multikinase inhibitor Sorafenib is the first and only agent showing a survival benefit in these patients. In this study, we evaluate the efficacy and tolerability of Sorafenib in advanced and metastatic HCC patients.

Methodology: Twenty patients with advanced HCC (between Jan. 2011 and Dec. 2013), 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: All patients had a performance status of 2 to 3 (Eastern Cooperative Oncology Group 2/3.13/7) and Child-Pugh class A or B (A/B. 8/12). Six patients had stage IV A tumors, whereas 14 had stage IV B tumors. Four patients had (PVTt). Following Sorafenib monotherapy, Five patients (25.0%) had a partial response, and eight (40.0%) had a stable disease, with a disease control rate of 65%. The median overall survival was 12 months and the median progression-free survival

was 0 months. Diarrhea and hand-foot skin reactions were the most troublesome side effects.

Conclusions: A limited proportion of patients with advanced HCC exhibited a remarkable outcome after Sorafenib monotherapy, although the treatment results in this type of patient are extremely poor. Further studies to predict good responders to personalized therapy are recommended.

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 surgical therapies (resection and liver transplantation) and loco regional procedures (radiofrequency ablation). Five-year survival rates of up to 60 to 70% can be achieved in well-selected patients [2]. However, disease that is diagnosed at an advanced stage or with progression after loco regional therapy has a dismal prognosis, owing to the underlying liver disease and lack of effective treatment options [2-4].

Until recently, treatment options for advanced or unresectable hepatocellular carcinoma (HCC) have been limited as chemotherapy in general is ineffective [5].

Significant progress in the treatment of HCC was therefore made with the approval of the multikinase inhibitor Sorafenib for this indication [6]. Sorafenib (Nexavar) is a small molecule that inhibits tumor-cell proliferation and tumor angiogenesis and increases the rate of apoptosis in a wide range of tumor models. It acts by 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]. Cellular signaling that is mediated by the Raf-1 and vascular endothelial growth factor pathways has been implicated 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]. However, in clinical practice the majority of patients with advanced HCC have severe liver cirrhosis and substantial comorbidity, compromising their general medical condition and liver function [6].

Since the prognosis for HCC is dependent upon tumor stage, Performance status (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].

Results of an uncontrolled phase 2 study involving 137 patients with advanced hepatocellular carcinoma and Child–Pugh class A or B status indicated

that single-agent Sorafenib might have a beneficial therapeutic effect. Sorafenib treatment resulted 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) [14].

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

2. MATERIALS AND METHODS

2.1 Patients:

A prospectively study was conducted between January 2011 and December 2013 in Saudi- German Hospitals group at K.S.A. 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) performance status 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 $\geq 60 \times 10^9/L$; hemoglobin ≥ 8.5 gm/dl and prothrombin time international normalized ratio ≤ 2.3 or prothrombin time ≤ 6 seconds above control), adequate hepatic function (albumin ≥ 2.8 gm/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 performed at baseline as well as an electrocardiogram (ECG), blood pressure measurement, blood samples including hematological values, liver biochemistry, serum alpha-Feto Protein (α FP) and tissue biopsy. Patients were required to have at least one untreated target lesion that could be measured in one dimension, according to the modified Response Evaluation Criteria in Solid Tumors (modified RECIST) [18].

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

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.

100 2. 3 Assessment:

101 Dynamic spiral computed tomography (CT) or contrast-enhanced dynamic
102 magnetic resonance imaging (MRI) and determination of AFP level were
103 performed at baseline. The response to treatment was evaluated every 2 months by
104 means of a CT or earlier with clinical signs of progression. Tumor response was
105 assessed until disease progression. The tumor response was evaluated according to
106 the modified RECIST [18]. Patients who died before their first radiographic
107 evaluation were assessed as having progressive disease. Patients with a serum α FP
108 of ≥ 200 ng/L at baseline and with a decline in α FP of $\geq 20\%$ after 4 weeks of
109 Sorafenib therapy were classified as α FP responders. Toxicity was assessed based
110 on information noted in the medical records and graded according to NCI-CTCAE
111 v3.0 [19].

112 2. 4 Treatment outcome and statistical analysis:

113 The primary study objective was to assess OAS. Secondary objectives were to
114 evaluate overall response rate, progression-free survival (PFS), and toxicity. OAS
115 was defined as the time interval between the initiation of Sorafenib and death. PFS
116 was defined as the time interval from the first cycle of Sorafenib to the date when
117 disease progression or any cause of death was first observed. Survival curves were
118 calculated by the Kaplan-Meier method and compared with the log-rank test. A

119 Cox-regression hazard model was used for multivariate Cox proportional analysis.
 120 Qualitative variables were expressed as number and percentage. Quantitative
 121 variables were expressed as mean $\pm$ standard deviation. $P = .05$ was considered
 122 statistically significant. All statistical analyses were performed using the SPSS
 123 software package version 17.0 (SPSS Inc., Chicago, IL, USA).

124 **3. RESULTS**

125 *3.1 Patients:*

126 The study involved 20 patients with advanced HCC (14 males and 6
 127 females) with age ranged from 45 to 70 years (mean of age; 58.30 years). The most
 128 common underlying cause of liver disease was NAD; No Abnormality Detected
 129 (55 %) while hepatitis C virus (40.0 %). The ECOG performance status score was
 130 2 (65 %) and 3 (35 %). Patients with Child-Pugh class B represent 60%. Portal
 131 vein invasion occurred in 20 % of cases. Eleven patients (55.0 %) showed extra
 132 hepatic involvement (i.e., nodal invasion and/or distant metastases; 40.0 % and
 133 30.0 %, respectively) (Table 1).

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

Characters	Value
Age (years): Mean $\pm$ SD (Minimum.- Maximum)	58.3 $\pm$ 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)
Portal vein invasion: -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)

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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; LN, lymph node.

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3. 2 Efficacy and Survival:

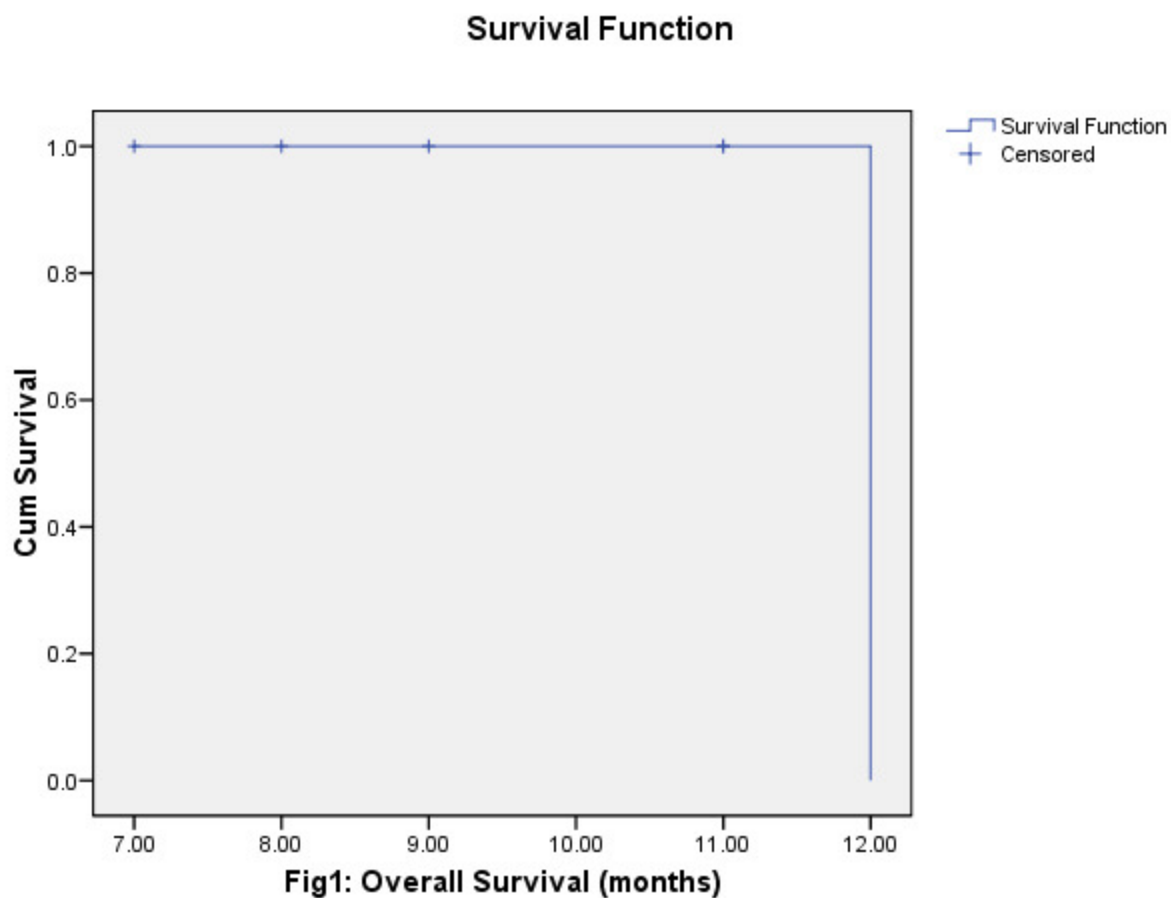
Median duration of Sorafenib therapy was 12 months in both Child A and Child B patients. Five patients (25 %) died at their last follow-up from hepatic failure, hepato-renal syndrome and pneumonia (15 %, 5 % & 5 %, respectively). The median OAS was 12 months (Fig. 1). The median PFS was 0 month. Five 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).

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.



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By univariate and multivariate 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 ($p = .01$) (Table 3).

Table 3: Univariate analyses for overall survival.

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Variables	Number (n-20)	Median Survival (month)	<i>P value</i>
Age < 63	14	12.0	.07
≥ 63	6	11.5	
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	.01*
3	7	11.0	
Child-Pugh class: A	8	12.0	.04*
B	12	12.0	
Diarrhea: +ve	6	11.5	.12
-ve	14	12.0	
Skin rash: +ve	13	12.0	.27
-ve	7	12.0	
PR or SD Yes	13	12.0	.003*
No	7	11.0	

161 *: Significant

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3.3 Toxicity:

The overall incidence of treatment-related adverse events was 75.0%. The reported adverse events were predominantly grades 1 or 2 in severity and, dermatological, or gastrointestinal in nature. Four patients (20%) showed several adverse events together. Skin rash were the most troublesome side effects (13 patients, 65%). Other frequent toxicities were diarrhea (six patients, 30.0%) (Table 4).

Table 4: Incidence of adverse events.

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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 (%).

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The percentage of, diarrhea, skin rash or desquamation of Child B patients were higher than Child A. The OAS of patients with skin rash and diarrhea showed no better survival ($p = .27$ & $p = .12$, respectively). Four patients (20%) required a dose reduction of Sorafinib due to severe diarrhea and five patients (25%) from

skin rash. Besides adverse events, seven patients (35%) stopped the Sorafenib by disease progression.

4. DISCUSSION

The present study aimed to analyze the effect of Sorafenib monotherapy in patients with advanced HCC. Although Sorafenib has been recommended for patients with HCC, the clinical data of Sorafenib in those patients was rare. In this study, 25% of patients showed PR and 40% of patients showed SD (DCR 65%). The median OS duration was 12 months which was better than the SHARP trial (10.7 months) in the Sorafenib group, and the median PFS was 0 month and responsive patients showed a significant prolongation in OAS compared with that in nonresponsive patients.

SD population in this study was (40%) lower than SHARP trial (SD, 71%) and Asia-Pacific population study (SD, 54%). This difference may be due to different methods of evaluation (modified RECIST vs. RECIST). Also, the percentage of patients with Child-Pugh A in this study was 40%, lower than SHARP trial (95%) and Asia-Pacific population study (97.3%). However, DCR in our study was better (65%) than SHARP trial and Asia-Pacific population study (DCR 43% and 35.3% respectively). The low SD may reflect the abysmal prognosis of patients in this study rather than lack of effect of the Sorafenib.

197 SHARP trial showed a significant effect with a DCR of 43% in the Sorafenib
198 group compared with 32% in its placebo group.

199 The benefit of Sorafenib was also consistent among all prespecified
200 stratification groups, including patients with the worst prognosis, such as those
201 with an ECOG performance status of 2 or 3 or extra-hepatic spread .In this study,
202 we also analyzed prognostic factors impacting survival. Child-Pugh A and tumor
203 response (PR or SD) were favorable parameters relative to PFS and OS. These
204 findings are similar to those in other reports [20-22]. The adverse events in this
205 study were similar to those in previous clinical trials, [2, 23] with dermatological
206 and gastrointestinal symptoms being common adverse events. Four patients
207 required a dose reduction because of diarrhea, and it was the most frequent adverse
208 event leading to Sorafenib discontinuation. From the clinical results of advanced
209 HCC treated with Sorafenib, we can get three important points; first is the
210 chemosensitivity of Sorafenib, second is the resistance, and the final point is
211 individualized therapy. HCC is a complex and heterogeneous disease at the
212 molecular level and different pathways can be aberrantly activated in distinct
213 patient subgroups. With such heterogeneity of pathway activation, an
214 individualized approach based on detecting predictive markers for sensitivity and
215 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 an in vitro study.

However, there are no clear predictive factors, and limited data 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 precise understanding of HCC mechanism and expand the opportunity of biomarker/therapeutic target discovery. Further study to investigate predictive factors and resistance to Sorafenib for personalized therapy is recommended. This 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. Further study with a large number of patients treated with long duration will be necessary to assess the efficacy.

In conclusion, Sorafenib is effective for the treatment of advanced hepatocellular carcinoma in our study, and is well tolerated. Taken together with the data from the SHARP trial and the Asia-Pacific region, it seems to be an appropriate option for the treatment of advanced HCC. The activity of Sorafenib in advanced disease also opens the doors for studies in patients who will have or have

236 already undergone resection, ablation chemoembolization or liver transplantation.
 237 Also, this success encourages us to proceed with other targeted therapies and their
 238 combinations in HCC, as well as to search for new biomarkers predictive of
 239 response.

240 **5. REFERENCES**

- 241 1- Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA
 242 Cancer J Clin 2005; 55:74-108.
- 243 2- Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular
 244 carcinoma. N Engl J Med 2008; 359:378-390.
- 245 3- Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology
 246 2005; 42:1208-36.
- 247 4- Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular
 248 carcinoma: conclusions of the Barcelona-2000 EASL Conference. J Hepatol 2001;
 249 35:421-30.
- 250 5- Lau YK. Sorafenib: new reference standard for systemic treatment of
 251 advanced hepatocellular carcinoma. Community Oncology 2007; 4(9): 529–530.
- 252 6- Di Maio MM, Daniele B and Perrone F. Targeted therapies: role of Sorafenib in
 253 HCC patients with compromised liver function. Nature Reviews Clinical
 254 Oncology. 2009; 6 (9): 505–506.

- 255 7- Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum
256 oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor
257 tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res*
258 2004; 64:7099-109.
- 259 8- Chang YS, Adnane J, Trail PA, et al. Sorafenib (BAY 43-9006) inhibits tumor
260 growth and vascularization and induces tumor apoptosis and hypoxia in RCC
261 xenograft models. *Cancer Chemother Pharmacol* 2007; 59: 561-74.
- 262 9- Ito Y, Sasaki Y, Horimoto M, et al. Activation of mitogen-activated protein
263 kinases/extracellular signal-regulated kinases in human hepatocellular carcinoma.
264 *Hepatology* 1998; 27:951-8.
- 265 10- Villanueva A, Newell P, Chiang DY, Friedman SL, Llovet JM. Genomics and
266 Signaling pathways in hepatocellular carcinoma. *Semin Liver Dis* 2007; 27:55-76.
- 267 11- Calvisi DF, Ladu S, Gorden A, et al. Ubiquitous activation of Ras and
268 Jak/Stat pathways in human HCC. *Gastroenterology* 2006; 130: 1117-28.
- 269 12- Semela D, Dufour JF. Angiogenesis and hepatocellular carcinoma. *J Hepatol*
270 2004; 41:864-80.
- 271 13- Palmer DH, Johnson PJ. Prognostic factors in hepatocellular carcinoma. In:
272 *UICC Prognostic Factors in Cancer*. 3rd edn. John Wiley & Sons: Hoboken, NJ,
273 USA. 2006

- 274 14- Abou-Alfa GK, Schwartz L, Ricci S, et al. Phase II study of sorafenib in
275 patients with advanced hepatocellular carcinoma. J Clin Oncol 2006; 24:4293-300.
- 276 15- Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the
277 Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-55.
- 278 16- Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R.
279 Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;
280 60:646-9.
- 281 17- Therasse P, Arbuck SG, Eisenhauer. Child CG III. The liver and portal
282 hypertension. vol. 1 of Major problems in clinical surgery. Philadelphia: W.B.
283 Saunders, 1964:50-64.
- 284 18- Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for
285 hepatocellular carcinoma. Semin Liver Dis 2010; 30:52-60.
- 286 19- Colevas AD, Setser A. "The NCI common terminology criteria for adverse
287 events (CTCAE) v 3. 0 is the new standard for oncology clinical trials," J Clinical
288 Oncology 2004; 22: 6098.
- 289 20- Leung TW, Tang AM, Zee B, et al. Factors predicting response and survival in
290 149 patients with unresectable hepatocellular carcinoma treated by combination
291 cisplatin, interferon-alpha, doxorubicin and 5-fluorouracil chemotherapy. Cancer
292 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.