

Arterial blood supply of hepatocellular carcinoma is associated with efficacy of sorafenib therapy

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ABSTRACT

Aim: There are some previous reports concerning the relationship between prognosis of patients treated with sorafenib and parameters of computed tomography (CT) and magnetic resonance imaging (MRI). This study presents monocentric experience with sorafenib in the treatment of hepatocellular carcinoma (HCC) patients and will try to identify predictive factors for survival based on the correlation of results from imaging and survival. **Methods:** A total of 38 HCC patients treated from April 2009 to December 2010 with sorafenib were included in this study. HCCs were classified as good arterial supply and poor arterial supply according to the enhancement intensity on CT scan or MRI. Clinical data were collected and survival time was analyzed by Kaplan-Meier method. A Cox's regression model was performed to reveal predictive factors for survival. **Results:** Among the 38 patients treated with sorafenib, mean age was 53.3 ± 11.1 years and 35 (92.1%) were males. Tumors in 17 patients were classified as good arterial supply, while the remaining 21 patients belonged to poor arterial supply. The median survival time (MST) was 10.7 months [95% confidence interval (CI), 8.7-12.7] and the 1-year overall survival (OS) was 41.0%. The MST and 1-year OS in patients with a good arterial supply of tumors were 12 months (range: 4-20 months) and 52.9%, compared with that of 7 months (range: 1-16 months) and 23.8% in patients with a poor arterial supply of tumors ($P = 0.002$). Patients who had tumors at Barcelona Clinic Liver Cancer (BCLC) stage B had longer MST and higher OS than those who had tumors at BCLC stage C, but there was no statistical difference between these two stages. On multivariate analysis, only arterial supply of the tumors remained statistically predictive for OS (hazard ratios 0.22, 95% CI, 0.07-0.67, $P = 0.008$). **Conclusion:** Arterial blood supply is an independent predictor for survival in patients treated with sorafenib, and patients with a good arterial supply of tumors benefit more than those with a poor arterial supply of tumors.

Key words: Arterial blood supply; hepatocellular carcinoma; sorafenib

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Received: 09-07-2015, **Accepted:** 09-11-2015

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most frequent cause of cancer-related death.^[1] Only about 15% patients with HCC are suitable for curative treatment, such as

surgical therapy (resection and liver transplantation) and locoregional therapy (radiofrequency ablation). For patients with advanced HCC, curative therapies cannot be applied, and only systemic therapy is

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How to cite this article: Zhang XH, Zhu Q, Li J, Huang L, Yan JJ, Xu F, Li J, Yan YQ. Arterial blood supply of hepatocellular carcinoma is associated with efficacy of sorafenib therapy. *Hepatoma Res* 2016;2:87-91.

Access this article online	
Website: http://hrjournal.net	Quick Response Code 
DOI: 10.4103/2394-5079.170542	

available.^[2]

Sorafenib is a multikinase inhibitor which inhibits angiogenesis by targeting the vascular endothelial growth factor (VEGF) receptor 2 and platelet-derived growth factor receptor pathway and blocks cell proliferation by targeting the Ras/mitogen-activated protein kinase signaling pathway. Two global phase III trials (SHARP^[3] and Asia-Pacific trial)^[4] showed that sorafenib prolonged the survival of patients with advanced HCC. Following that, multiple studies have been conducted to determine the predictor for survival in patients treated with sorafenib. There are some previous reports concerning the relationship between prognosis of patients treated with sorafenib and parameters of computed tomography (CT) scan and magnetic resonance imaging (MRI).^[5-8] Hahn *et al.*^[6] showed that the area under the contrast concentration vs. time curve 90 s after contrast injection (IAUC90) and volume transfer constant of contrast agent [K (trans)] measured by MRI were prognostic pharmacodynamic biomarkers for metastatic renal carcinoma treated with sorafenib. In addition, Hsu *et al.*^[7] found K (trans) correlated well with tumor response and survival in HCC patients who received sorafenib plus metronomic tegafur/uracil therapy. Sorafenib significantly suppressed tumor per fusion, tumor vascularity, and endothelial permeability-surface area product quantified by CT scan in experimental prostate carcinoma in rats.^[5,9,10] It seems that CT scan or MRI may be applicable for imaging biomarkers of therapy response to antiangiogenic therapy.

We present our monocentric experience with sorafenib in the treatment of HCC patients and will attempt to identify predictive factors for survival, by placing emphasis on the correlation of the results from imaging and survival.

METHODS

Patients

A total of 38 HCC patients treated from April 2009 to December 2010 with sorafenib were included in this study. Hypervascular HCCs were diagnosed by at least 2 radiologic imaging showing characteristic features of HCC (contrast enhancement on the arterial phase with venous washout), or 1 radiologic imaging showing characteristic features of HCC associated with alpha-fetoprotein (AFP) ≥ 400 ng/mL, while hypovascular HCCs were diagnosed by biopsy with cytological or histological confirmation. Eligibility

criteria also included Eastern Cooperative Oncology Group Performance Status of 0 or 1; Child-Pugh liver function class A. All eligible patients received continuous oral treatment with 400 mg of sorafenib (consisting of two 200-mg tablets, provided by Bayer HealthCare Pharmaceuticals) twice daily. HCC is staged according to the Barcelona Clinic Liver Cancer (BCLC) classification.^[11] HCCs were divided into good arterial supply and poor arterial supply according to the enhancement intensity on CT scan or MRI and were assessed by an experienced radiologist who was blind to clinical information. Good arterial supply is defined as enhancement in $\geq 60\%$ lesions while poor arterial supply is defined as enhancement in $\leq 40\%$ lesions.

Study design

Our null hypothesis was that patients with a good arterial supply of tumors and those with a poor arterial supply of tumors benefitted similar outcomes. The primary endpoint of the trial was the 12-month overall survival (OS) rate. The secondary endpoints were the recurrence-free survival rate and the overall recurrence rate. Data were collected and stored in the liver cancer database management system by a designated clinical study center assistant chosen by the Research Ethics Committee.

This study met the requirements of the Declaration of Helsinki and was approved by the Research Ethics Committee of the Eastern Hepatobiliary Surgery Hospital, which is affiliated with the Second Military Medical University. Informed consent was obtained from all recruited patients.

Follow-up

Clinical examinations were performed for each patient, with laboratory assessment (routine tests of liver and kidney function and AFP) every month and imaging exams (chest X-ray and abdominal CT scan or MRI) every other month. A systemic nuclide scan was carried out when metastasis was suspected. Additional treatments, such as transarterial chemoembolization (TACE), were applied when necessary. Adverse events were under surveillance, and proper managements were provided when necessary.

Statistical analysis

Quantitative data were expressed as a mean \pm standard deviation (SD) or median (range) where appropriate and compared using the independent sample *t*-test. For quantitative data, the gaussianity

test was performed to test for homogeneity of variances. Homogeneous variances were indicated as a mean plus or minus SD (mean \pm SD) and the Student's *t*-test was used for statistical analysis. If the variances were not homogeneous, they were presented as median in combination with the range. Categorical variables were compared using the Chi-square test with Yates correction or the Fisher exact test where appropriate. $P < 0.05$ was considered significantly. Hazard ratios (HRs) and their corresponding 95% confidence interval (CI) were calculated using simple logistic-regression analysis.

Survival rates were obtained by the Kaplan-Meier method and were compared using the log-rank test. Cox regression model was used to analyze the prognostic predictors for survival. Survival time started from the date of treatment with sorafenib until death or the closing date. The closing date of this study was August 31, 2011.

RESULTS

Baseline characteristics

Among the 38 patients treated with sorafenib, mean age was 53.3 ± 11.1 years and 35 (92.1%) were males. All the patients had viral hepatitis background, with a hepatitis B prevalence of 94.7%. The baseline characteristics of the 38 patients are shown in Table 1. Tumors in 17 patients were classified as good arterial supply while the other patients belonged to poor arterial supply according to the judgment of the radiologist. A total of 30 patients received 1 time additional therapy of TACE during the period of follow-up, of which 13 patients with a good arterial supply of the tumors and 17 with poor arterial supply.

Safety and adverse events

Each patient experienced at least one adverse event in the duration of sorafenib administration. Hand-foot skin reaction and diarrhea were the most common discomforts complained by the patients. Less common adverse effects included fatigue, alopecia, hypertension, and diabetes. A total of 6 patients had dose reduction due to severe adverse events, of which 3 for diarrhea and 3 for hand-foot skin reaction. None of the patients had drug discontinuation.

Survival analysis

At the closing date of this study, 29 (76.3%) patients died and 9 patients were still alive. The median survival time (MST) was 10.7 months (95% CI, 8.7-

Table 1: Baseline characteristics of 38 patients included in the study

Variable	n = 38
Sex (male/female)	35/3
Age (years)	53.3 \pm 11.1
ECOG PS	
0	32
1	6
BCLC stage	
B	18
C	20
Arterial supply of the tumor	
Good	17
Poor	21
Portal invasion	
Yes	14
No	24
Extrahepatic metastasis	
Yes	9
No	29
Collaborative treatment	
TACE	30
None	8
Hepatitis background	
Hepatitis B	36
Hepatitis C	2
Vascular thrombus	
Presence	12
Absence	26
Tumor size	8.1 \pm 3.1
AFP (ng/mL)	205.1 (2-2,483,000)
Total bilirubin (umol/L)	15.0 \pm 7.6
Albumin (g/L)	39.3 \pm 4.6
Pre-albumin (mg/L)	144.0 \pm 46.0
ALT (IU/L)	48.3 \pm 65.9
AST (IU/L)	55.3 \pm 49.3
PT (s)	12.5 \pm 1.1
BUN (mmol/L)	5.43 \pm 0.69
Cr (umol/L)	69.18 \pm 11.61

ECOG PS: Eastern Cooperative Oncology Group Performance Status; BCLC: Barcelona Clinic Liver Cancer; TACE: transarterial chemoembolization; AFP: alpha-fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; PT: prothrombin time; BUN: blood urea nitrogen; Cr: creatinine

12.7) and the 1-year OS was 41.0%. On univariate analysis [Table 2], the MST and 1-year OS in patients with good arterial supply of tumors were 12 months (range: 4-20 months) and 52.9%, compared with that of 7 months (range: 1-16 months) and 23.8% in patients with poor arterial supply of tumors ($P = 0.002$). Similarly, patients who had tumors at BCLC stage B had longer MST and higher OS than those who had tumors at BCLC stage C. However, there was no statistically significant difference between these two stages.

Eight variables were selected on multivariate analysis to determine the prognostic predictors for survival in patients treated with sorafenib [Table 3]. Only arterial supply of the tumors remained statistically predictive for OS (HR: 0.22, 95% CI, 0.07-0.67, $P = 0.008$).

DISCUSSION

As a highly vascularized neoplasm, most HCCs exert imaging characteristics of intense contrast uptake in the arterial phase, followed by contrast washout in the delayed venous phase at dynamic imaging by

Table 2: Univariate analysis of factors associated with survival of patients included in the study

	<i>n</i>	Median survival time (months)	1-year survival rate (%)	Log-rank test <i>P</i>
BCLC stage				
B	18	12.5 (2-18)	61.1	0.067
C	20	7.5 (1-20)	15.0	
Arterial supply of the tumors				
Good	17	12 (4-20)	52.9	0.002
Poor	21	7 (1-16)	23.8	
Portal invasion				
Yes	14	8.5 (1-19)	21.4	0.206
No	24	11.5 (2-20)	50.0	
Extrahepatic metastasis				
Yes	9	9 (2-20)	22.2	0.591
No	29	10 (1-18)	41.4	
Collaborative treatment				
TACE	30	10 (1-19)	40.0	0.504
None	8	8 (2-20)	25.0	
AFP				
≥ 400 ng/mL	15	8.5 (2-18)	20.0	0.347
< 400 ng/mL	23	11 (1-20)	47.8	
Albumin				
> ULN	12	9.5 (4-19)	41.7	0.159
≤ ULN	26	9 (1-20)	34.6	
ALT				
> ULN	12	13 (1-20)	58.3	0.063
≤ ULN	26	9 (2-19)	35.0	
AST				
> ULN	18	9 (2-18)	38.9	0.881
≤ ULN	20	10 (1-20)	35.0	

BCLC: Barcelona Clinic Liver Cancer; TACE: transarterial chemoembolization; AFP: alpha-fetoprotein; ULN: upper limit of normal; ALT: alanine aminotransferase; AST: aspartate aminotransferase

Table 3: Multivariate Cox's model for factors associated with survival of patients included in the study

Variable	HR	95% CI for HR	<i>P</i>
BCLC stage (B vs. C)	0.33	1.29-10.53	0.335
Portal invasion (yes vs. no)	1.15	0.19-7.03	0.881
Extrahepatic metastasis (yes vs. no)	0.88	0.13-5.94	0.893
Arterial supply of the tumor (good vs. poor)	0.21	0.07-0.67	0.008
Collaborative treatment (TACE vs. none)	1.54	0.48-4.91	0.470
AFP (≥ 400 ng/m vs. < 400 ng/m)	1.33	0.50-3.49	0.568
Albumin (> ULN vs. ≤ ULN)	2.13	1.00-6.50	0.064
ALT (> ULN vs. ≤ ULN)	0.35	0.11-1.08	0.068
AST (> ULN vs. ≤ ULN)	1.05	0.37-2.98	0.925

HR: hazard ratio; CI: confidence interval; BCLC: Barcelona Clinic Liver Cancer; TACE: transarterial chemoembolization; AFP: alpha-fetoprotein; ULN: upper limit of normal; ALT: alanine aminotransferase; AST: aspartate aminotransferase

contrast-enhanced CT scan or gadolinium-enhanced MRI.^[11] However, there are also many HCCs, which display poor contrast enhancement on CT scan or MRI on the arterial phase.

In this study, when we concentrated on the relationship between the degree of enhancement on the arterial phase of CT scan/MRI and the prognosis of HCC patients treated with sorafenib, the results showed that patients with good arterial supply benefitted more than those with poor arterial supply. Previously, Li *et al.*^[12] and Ippolito *et al.*^[13] found that CT scan could provide quantitative

information about tumor-related angiogenesis, which could be used to assess tumor vascularization. During hepatocarcinogenesis, arterial and portal blood flow would decrease, and then new arterial vessels formed because of the reduced arterial blood flow. And this caused hypervascular lesions to occur.^[14,15] The degree of tumor enhancement on the arterial phase could be an important symbol of vascularization. Neovascularization played a critical role during growth of solid neoplasms,^[16] and VEGF played an important role in regulating angiogenesis and endothelial cell proliferation.^[17] In the past few years, several studies had shown that the VEGF expression in HCC was correlated with imaging findings.^[18-21] Kwak *et al.*^[21] found that the strong arterial enhancement of HCC resulted from a strong VEGF expression which was responsible for an increased vascular permeability and increased proliferation of the endothelial cells. In contrast, sorafenib inhibited the activity of VEGF receptors and other proangiogenic signaling pathways. In mouse xenograft models of HCC, sorafenib significantly reduced tumor microvessel density. These observations, combined with the relatively short half-life of sorafenib, suggest that sorafenib administered during and after TACE treatment may counteract hypoxia-induced angiogenesis and potentially yield synergistic efficacy in decreasing tumor burden. However, these hypothesis generated findings remain speculative until sufficient clinical trial data can be accumulated.

It is reported that there is a significant correlation between efficacy of sorafenib administered combined with TACE treatment and arterial blood supply of HCC. According to our study, the stronger the enhancement intensity of HCCs on the arterial phase, the longer the HCC patients treated with sorafenib survived. Maybe the level of VEGF could indicate the treatment effect of sorafenib, and further research needs to be done to reveal the correlation between the VEGF activity and efficacy of sorafenib.

The major limitations of this study are the non-comparative design and a limited number of patients. A prospective study should be done to investigate the correlation between enhancement intensity of HCCs in the arterial phase and survival of HCC patients treated with sorafenib.

In conclusion, arterial blood supply is an independent predictor for survival in patients treated with sorafenib, and patients with a good arterial supply of

tumors benefit more than those with a poor arterial supply of tumors. Further prospective studies need to be conducted to reveal the relationship between the degree of tumor enhancement in the arterial phase and the prognosis of HCC patients treated with sorafenib therapy.

Financial support and sponsorship

This work is supported by Second Military Medical University Funds for Young Scholar (2011QN23) and National Natural Science Foundation (81301878).

Conflicts of interest

There are no conflicts of interest.

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