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

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Background: To explore the efficacy of sorafenib in treating hepatocellular carcinoma (HCC) and its relationship with the computed tomography (CT) and magnetic resonance imaging (MRI) features of HCC, analyze the prognostic factors of HCC patients treated with sorafenib, and investigate the relationship between imaging findings and outcomes.

Methods: A total of 38 HCC patients who were treated with sorafenib from April 2009 to December 2010 were included in this study. HCCs were classified as good arterial supply and poor arterial supply according to the intensity enhancement on CT scan or MRI. Clinical data were collected and the survival time was calculated by Kaplan-Meier method.

Results: Among these 38 patients [35 (92.1%) were males] treated with sorafenib, the median age was (53.3±11.1) years. Tumors in 17 patients had good arterial supply while those in the remained 21 patients had poor arterial supply. The median survival time (MST) was 10.7 months (95% CI, 8.7-12.7) and the 1-year overall survival (OS) was 41.0%. The MST and 1-year OS in patients with tumors with good arterial supply were 12 months (range, 4-20 months) and 52.9%, respectively, compared with those of 7 months (range, 1-16 months) and 23.8% in patients with tumors with poor arterial supply (P=0.002). Patients with BCLC stage B tumors had longer MST and higher OS than those with BCLC stage C tumors, although the differences were not statistically significant. Multivariate analysis showed that arterial supply of tumors remained statistically predictive for OS (HR =0.22; 95% CI, 0.07-0.67; P=0.008).

Conclusions: Arterial blood supply is an independent predictor for survival in HCC patients treated with sorafenib, and patients with tumors with good arterial supply benefit more than those with tumors with poor arterial supply.

Keywords: Hepatocellular carcinoma (HCC); sorafenib; arterial blood supply

Introduction

Hepatocellular carcinoma (HCC) is a clinically common disease. As the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections increases worldwide, the incidence of HCC also gradually rise. HCC is now the third leading cause of cancer deaths (1). Only about 15% of HCC have a chance to be cured by surgery (e.g., liver resection or transplantation) or minimally invasive local treatment

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(e.g., radiofrequency ablation). For HCC at advanced stages, radical treatment is impossible and multidisciplinary treatment may be more feasible (2).

As a multiple kinase inhibitor, sorafenib can selectively inhibit the vascular endothelial growth factor 2/platelet-derived growth factor receptor pathway to prevent tumor angiogenesis and meanwhile suppress cell proliferation by targeting the mitogen-activated protein kinase signaling pathway. Two global phase III clinical trials [SHARP (3) and Asia-Pacific trial (4)] have demonstrated that sorafenib can improve the prognosis of patients with advanced HCC. Among studies focusing on the prognostic factors of HCC patients treated with sorafenib, many of them found that the prognosis of these patients may be associated with the computed tomography (CT) and magnetic resonance imaging (MRI) features (5-10). Hahn *et al.* (6) found that the area under the contrast concentration *vs.* time curve 90 s after contrast injection (IAUC90) and the volume transfer constant of contrast agent (Ktrans) are pharmacodynamic biomarkers for sorafenib. Hsu *et al.* (7) also found that, among the prognostic factors of HCC patients receiving sorafenib and tegafur/uracil treatment, Ktrans was closely correlated with tumor response. In an experimental prostate cancer study in mice, sorafenib significantly suppressed tumor perfusion, vascular growth, and CT-visible endothelial permeability region (5). Therefore, CT and MRI identified biomarkers that may be feasible for detecting the possible response to antiangiogenic therapy in HCC patients.

In our current study, we explored the predictive factors on the efficacy of sorafenib in treating HCC, with a particular focus on the relationship between imaging findings and efficacy.

Materials and methods

Materials

A total of 38 consecutive HCC patients who were treated with sorafenib from April 2009 to December 2010 were included in this study. The diagnosis of HCC with good blood supply depends on at least two imaging approaches and featured by the remarkably enhanced lesion density in the arterial phase and decreased density in the venous phase; or, one imaging mode shows characteristic liver cancer lesion, along with an α-fetoprotein (AFP) level of ≥400 ng/mL. In contrast, the confirmation of HCC with poor blood supply is highly dependent on molecular biological approaches and histopathology. The inclusion

criteria also included an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1 and a Child-Pugh grade of A. The enrolled patients were orally administered with 400 mg sorafenib (Bayer Healthcare, 200 mg × 2 tablets; twice daily). HCC was graded according to Barcelona clinic liver cancer (BCLC) staging system (11). Based on the results of enhanced CT or MRI scans, the HCC patients were divided into rich blood supply group and poor blood supply group. The imaging diagnoses were performed by specialists with rich experiences (without referring to the clinical features of the patients). Lesions with a hyperenhancement area of ≥60% were defined as with good blood supply, and those with a hyperenhancement area of ≤40% as poor blood supply.

Methods

The follow-up data included the monthly laboratory test results (liver and kidney functions and AFP) and imaging findings (chest radiography, and abdominal CT or MRI). PET-CT was immediately performed if tumor metastasis was suspected. Transcatheter arterial chemoembolization (TACE) was performed if necessary. The adverse reactions following drug administration were monitored and properly managed.

Statistical analysis

The count data are presented using mean ± standard deviation, and their differences were compared using t-test. Measurement data were compared using Chi-square test or Fisher's exact probability test, and a P value of <0.05 was regarded as statistically significant. HR and 95% CI were calculated using the logistic regression formula. Factors found to be statistically significant (P<0.05) during univariate analysis were further analyzed using Logistic multivariate regression analysis, so as to identify the relatively independent risk factors. Survivals were analyzed using the Kaplan-Meier estimator with log-rank testing. Prognostic analysis was performed using Cox regression model. The overall survival (OS) and tumor-free survival (TFS) were calculated from the initiation of treatment to death and from the initiation of treatment to the deadline for follow-up, respectively. The follow-up deadline was August 31, 2011.

Results

Among these 38 patients, there were 35 men and 3 women, with a mean age of (53.3±11.1) years. All of them had a

Table 1 Clinical features of patients

Variables	Number (n=38)
Gender (male/female)	35/3
Age (years)	53.3±11.1
ECOG PS (0/1)	32/6
SCLC stage (B/C)	18/20
Arterial supply of tumors (good/poor)	17/21
Vascular involvement (yes/no)	14/24
Extrahepatic metastasis (yes/no)	9/29
Adjuvant therapy (TACE/none)	30/8
Hepatitis (B/C)	36/2
AFP (ng/mL)	205.1
	(2.0-2,483,000.0)
Total bilirubin (µmol/L)	15.0±7.6
Plasma albumin (g/L)	39.3±4.6
Prealbumin (mg/L)	144.0±46.0
Alanine aminotransferase (IU/L)	48.3±65.9
Aspartate aminotransferase (IU/L)	55.3±49.3
Prothrombin time (s)	12.5±1.1
Urea nitrogen (mmol/L)	5.43±0.69
Creatinine (µmol/L)	69.18±11.61

ECOG PS, Eastern Cooperative Oncology Group performance status; TACE, transcatheter arterial chemoembolization; AFP, α-fetoprotein.

history of hepatitis, among which hepatitis B accounted for 94.7%. The clinical data of these patients are summarized in *Table 1*. HCC with good blood supply was seen in 17 cases, and those with poor blood supply in 21 cases. Up to 30 patients (13 from the good blood supply group and 17 from poor blood supply group) received TACE during the follow-up.

Adverse reactions

During the sorafenib treatment, each patient had experienced at least one adverse event, among which hand/foot rashes and diarrhea were most common, whereas fatigue, alopecia, hypertension, and diabetes were relatively rare. The dose of sorafenib was tapered due to severe adverse reactions in 6 patients (3 due to severe diarrhea and 3 due to severe rashes). No drug withdrawal was noted during the follow-up.

Survival analysis

Up to 29 patients (76.3%) died during the follow-up, yielding a median survival time (MST) of 10.7 months (95% CI, 8.7-12.7) and a 1-year OS of 41%. The MST and 1-year OS in patients with tumors with good arterial supply were 12 months (range, 4-20 months) and 52.9%, respectively, compared with those of 7 months (range, 1-16 months) and 23.8% in patients with tumors with poor arterial supply (P=0.002). The MST and 1-year OS were better in patients with BCLC stage B HCC than those with BCLC stage C HCC, although the differences were not statistically significant.

The results of multivariate analysis and Cox regression analysis are shown in *Tables 2,3*. It was found that the arterial blood supply of tumor is a prognostic factor for OS in HCC patients (HR =0.22; 95% CI, 0.07-0.67; P=0.008).

Discussion

As a tumor with good blood supply, HCC showed hyper-enhancement on CT or MRI in most cases; more specifically, it showed obvious hyper-enhancement during arterial phase, and such enhancement gradually decreases during the venous phase and disappears during the delayed phase (1). The arterial-phase enhancement is not obvious in only a small number of HCC cases.

In our current study, we found the prognosis of HCC patients treated with sorafenib was closely associated with the degree of arterial-phase enhancement, and the prognosis of patients with HCC with good blood supply was significantly better than that of patients with HCC with poor blood supply. Li *et al.* (12) and Ippolito *et al.* (13) found that CT could provide sufficient information on tumor-related vessels and thus can be a good tool for evaluating the degree of tumor vascularization. Blood supply from hepatic artery and portal vein can be relatively insufficient during the rapid growth of HCC; as a result, the new vessels continuously form around the tumor, leading to the formation of tumors with good blood supply (14,15). The degree of arterial-phase enhancement on CT or MRI may be an important marker of tumor vascularization. The newly formed vessels are extremely important during the development of tumors (16), whereas the vascular endothelial growth factor play a key role in regulating angiogenesis and endothelial cell proliferation (17). Many studies have found that the expression of vascular endothelial growth factor in HCC is closely related with imaging findings (18-21). Kwak *et al.* (21) found that the obvious arterial-phase enhancement in HCC was due to vascular endothelial growth factor over-expression, which further results in the constant increase of vascular permeability and the proliferation of

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Table 2 Multivariate analysis on the efficacy of sorafenib for liver cancer

Influencing factors	n	Median survival time [range] (months)	1-year survival rate (%)	P value
SCLC stage				0.067
B	18	12.5 [2-18]	61.1	
C	20	7.5 [1-20]	15.0	
Arterial supply of tumors				0.002
Good	17	12 [4-20]	52.9	
Poor	21	7 [1-16]	23.8	
Vein involvement				0.206
Yes	14	8.5 [1-19]	21.4	
No	24	11.5 [2-20]	50.0	
Extrahepatic metastasis				0.591
Yes	9	9 [2-20]	22.2	
No	29	10 [1-18]	41.4	
Adjuvant therapy				0.504
TACE	30	10 [1-19]	40.0	
None	8	8 [2-20]	25.0	
AFP (ng/mL)				0.347
≥400	15	8.5 [2-18]	20.0	
<400	23	11 [1-20]	47.8	
Plasma albumin (g/L)				0.159
>35	12	9.5 [4-19]	41.7	
≤35	26	9 [1-20]	34.6	
Aspartate aminotransferase (IU/L)				0.063
>44	12	13 [1-20]	58.3	
≤44	26	9 [2-19]	35.0	
Aspartate aminotransferase (IU/L)				0.881
>38	18	9 [2-18]	38.9	
≤38	20	10 [1-20]	35.0	

TACE, transcatheter arterial chemoembolization; AFP, α-fetoprotein.

Table 3 Cox regression analysis on the efficacy of sorafenib for liver cancer

Variables	HR	95% CI	P value
BCLC stage (B vs. C)	0.33	1.29-10.53	0.335
Vein involvement (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 tumors (good vs. poor)	0.21	0.07-0.67	0.008
Adjuvant therapy (TACE vs. none)	1.54	0.48-4.91	0.470
AFP (≥400 vs. <400 ng/mL)	1.33	0.50-3.49	0.568
Albumin (>35 vs. ≤35 g/L)	2.13	1.00-6.50	0.064
ALT (>44 vs. ≤44 IU/L)	0.35	0.11-1.08	0.068
AST (>38 vs. ≤38 IU/L)	1.05	0.37-2.98	0.925

TACE, transcatheter arterial chemoembolization; AFP, α-fetoprotein.

vascular endothelial cells. In our current study, the degree of arterial-phase enhancement was positively correlated with the prognosis of HCC patients treated with sorafenib. Although it has been proposed that the vascular endothelial growth factor level may affect the efficacy of sorafenib in treating HCC, more studies are warranted to further demonstrate the relationship between the activation of vascular endothelial growth factor and the efficacy of sorafenib in treating HCC. Also, prospective randomized controlled trials are needed to clarify the relationship between the degree of HCC arterial-phase enhancement and the prognosis of HCC patients treated with sorafenib.

In summary, arterial blood supply is an independent predictor for survival in HCC patients treated with sorafenib, and patients with tumors with good arterial supply benefit more than those with tumors with poor arterial supply.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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