test was performed to test for homogeneity of variances. Homogeneous variances were indicated as a mean plus or minus SD (mean ± 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, 8.7-12.7) 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.

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

Variable	*n* = 38
Sex (male/female)	35/3
Age (years)	53.3 ± 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 ± 3.1
AFP (ng/mL)	205.1 (2-2,483,000)
Total bilirubin (umol/L)	15.0 ± 7.6
Albumin (g/L)	39.3 ± 4.6
Pre-albumin (mg/L)	144.0 ± 46.0
ALT (IU/L)	48.3 ± 65.9
AST (IU/L)	55.3 ± 49.3
PT (s)	12.5 ± 1.1
BUN (mmol/L)	5.43 ± 0.69
Cr (umol/L)	69.18 ± 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

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

	n	Median survival time (months)	1-year survival rate (%)	Log-rank test *P*
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	*P*
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.[1] 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 formatted 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