Transarterial chemoembolization with/without cryotherapy is associated with improved clinical outcomes of sorafenib for the treatment of advanced hepatocellular carcinoma

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Abstract. Sorafenib may prolong survival in patients with advanced hepatocellular carcinoma (HCC), but with limited efficacy. The present study aimed to prospectively investigate the efficacy and analyze the prognostic factors for survival in sorafenib-treated patients with advanced HCC. The baseline characteristics and clinical outcomes of 110 patients with advanced hepatitis B virus-related HCC treated with sorafenib with/without local therapy (transarterial chemoembolization with/without cryoablation) at a single liver cancer center were recorded. Predictors of progression-free survival (PFS) and overall survival (OS) were determined by multivariate analysis. A total of 14 (12.7%) patients achieved complete response (CR), 16 (14.5%) achieved partial response (PR) and 40 (36.4%) achieved stable disease (SD) lasting longer than 8 weeks. The median OS and PFS for the whole cohort were 10.5 [95% confidence interval (CI), 8.7-12.3] and 5.0 months (95% CI, 3.7-6.3), respectively. Sorafenib in combination with local therapy was an independent predictor for longer PFS, whereas Eastern Cooperative Group (ECOG) performance status (PS) and Child-Pugh class were associated with reduced PFS. Local therapy was associated with longer OS while ECOG PS and α-fetoprotein were associated with reduced OS. In a subset of patients with radiological progressive disease, a significant difference was found in OS between patients who continued taking sorafenib and those who discontinued therapy (11 vs. 7.5 months, P<0.001). In conclusion, sorafenib in combination with local therapy (transarterial chemoembolization with/without cryoablation) was independently associated with longer OS and PFS in advanced HCC patients. Poor ECOG PS was associated with shorter OS and PFS and is thus a marker of poor outcomes in sorafenib-treated HCC patients.

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Introduction

Hepatocellular carcinoma (HCC) is the most common malignant tumor of the liver and its incidence is particularly high in China relative to other countries (1,2). The development of standardized surveillance strategies and the introduction of the Barcelona Clinic Liver Cancer (BCLC) classification for the clinical management of HCC have significantly improved the outcomes of patients with early or intermediate-stage HCC (3). As local ablative therapies, including transarterial chemoembolization (TACE), have limited efficacy against large HCC and yield incomplete necrosis, the tumors often progress following local therapy (4) and the prognosis may be extremely poor. Meanwhile, there is a lack of convincing evidence showing that systemic chemotherapy lengthens overall survival (OS) for advanced HCC (5).

A fuller understanding of the molecular pathogenesis of HCC has led to the development of molecular-targeted therapies. The oral multikinase inhibitor sorafenib (Nexavar®) has been reported to block angiogenesis and cell proliferation in HCC (6). Two international randomized controlled trials of sorafenib conducted in Caucasian and Asian patients with advanced HCC revealed beneficial effects of sorafenib on the time to tumor progression (TTP) and OS (7,8). Thus, sorafenib is now well-established as a standard of care for HCC. Nevertheless, the efficacy of sorafenib alone for advanced HCC remains moderate and certain patients have extremely short survival (9). The mechanisms underlying tumor resistance to sorafenib therapy are not well known and prognostic factors have not been clearly defined. In a phase II trial conducted by Abou-Alfa *et al* (10), it was found that pretreatment tumor phosphorylated ERK levels were correlated with TTP. However, in patients with advanced HCC who are amenable only to systemic therapy, tumor tissue is generally not available as needle tract metastases may arise from biopsy, hindering further attempts to understand the molecular biology of tumor resistance to therapy. A more recent phase II open-label study

conducted by Yau *et al* (11) revealed that the presence of lung metastasis was a poor prognostic factor and implied that a high tumor load may render the patients refractory to sorafenib treatment. Meanwhile, Vincenzi *et al* (12) reported that early skin toxicity may be a predictive factor for tumor control in HCC patients treated with sorafenib. Despite these reports, it remains unclear whether the established prognostic factors, including Child-Pugh classification, α-fetoprotein (AFP), portal vein thrombosis (PVT), hepatitis B virus (HBV) DNA and tumor differentiation and size, are relevant to patients treated with sorafenib.

Therefore, the aim of this study was to prospectively investigate the efficacy and determine the prognostic factors for progression-free survival (PFS) and OS in patients with advanced HBV-related HCC treated with sorafenib as first-line therapy.

Materials and methods

Patients. Based on the BCLC staging classification, 326 consecutive patients with HBV-related advanced HCC were screened between August 2008 and May 2010 at the Center of Therapeutic Research for Hepatocellular Carcinoma, Beijing 302nd Hospital (Beijing, China). A total of 67 patients were Child-Pugh C, 58 patients were Child-Pugh B8 or B9 with serum bilirubin level >51.3 μmol/l. A total of 91 patients had a history of either hepatectomy (14), preoperative chemotherapy (11), prior TACE or local ablation (47) or radiotherapy (19). As a result, 216 patients were excluded from the analyses and 110 patients were included in the present study (Table I). HCC was diagnosed based on a serum AFP level >400 ng/ml and typical imaging findings consistent with the criteria of the European Association for the Study of the Liver (13). Liver biopsies were obtained in 58 patients with uncertain diagnosis and assessed histologically to confirm diagnosis. The BCLC classification was used to identify tumor stages (14). The presence of PVT, representing macroscopic vascular invasion and extrahepatic spread, was used to define advanced HCC. Performance status (PS) was evaluated according to the Eastern Cooperative Oncology Group criteria. Patients who met the following criteria were included in the study: diagnosis of advanced HCC, first-line treatment with sorafenib, ECOG PS ≤2, Child-Pugh class A or B and total serum bilirubin level <51.3 μmol/l, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels less than five times the normal upper limit, adequate hematological function (platelet count greater than $50x10^9$/l and hemoglobin level more than 80 g/l) and adequate renal function (serum creatinine level less than 1.5 times the normal upper limit). Baseline demographic, clinical and laboratory data were collected for all patients using a uniform database template to ensure consistent data collection. Outcomes, including PFS and OS, were collected from patient charts. All treatments were approved by the Beijing 302nd Hospital Research Ethics Committee, and written informed consent was obtained from the patients who met the inclusive criteria prior to the collection of data and blood and tumor specimens and analysis being performed.

Sorafenib administration. All the patients received sorafenib. The dosage was 400 mg twice daily (the standard dose); treatment interruptions and dose reductions (first 400 mg twice daily, then 200 mg twice daily) were permitted for adverse drug reactions (ADRs) according to the National Cancer Institute Common Toxicity Criteria (15). For ADRs of grade 3-4, sorafenib was reduced to 200 mg twice daily until the ADRs improved to grade 2 or below, then increased to 400 mg twice daily if well tolerated. The criteria for the discontinuation of therapy were as follows: ADRs that required termination of medication, deterioration of ECOG PS score to 4 and withdrawal of consent. If disease progression was observed, sorafenib was continued if the patient was considered to have a good clinical status (e.g., PS, liver function and tolerable side effects) and wished to continue the treatment. Following sorafenib treatment, TACE or cryoablation were conducted in those without absolute contraindications to TACE or cryoablation, based on the potential clinical benefits expected from the treatment and the patient's consent. Sorafenib therapy was continued without interruption during local therapies.

TACE. Patients were eligible for TACE if their tumor burden was <50% of the total liver volume. Hepatic angiography was routinely performed to determine tumor location, size or number and blood vessels using the Seldinger method. Super-selective catheterization was performed to the arteries supplying the tumor where possible. Then 40 mg of cisplatin, 1,000 mg of 5-fluorouracil and 20 mg of doxorubicin were infused via the arteries for chemotherapy, after which the blood vessels supplying the tumor were filled with a suspension of 10-20 ml of 40% ultra-fluid lipiodol and 10 mg of ADM. TACE was carried out with an interval of 4-6 weeks between cycles. Total course of TACE was terminated if more than 75% of the tumor volume was occupied by iodine oil on computed tomography (CT) scans 1 month after 1, 2 or 3 cycles of TACE. In our experience, if three cycles of TACE do not achieve adequate iodine deposition, the likelihood of increasing iodine accumulation is low with further TACE cycles. Therefore, at our institution, we limit TACE to a maximum of three cycles.

Argon-helium cryoablation. Argon-helium cryoablation was performed as previously described (16). Briefly, an argon-helium gas-based CRYOcare system (EndoCare, Irvine, CA, USA) and cryoprobes were used to freeze the tumor with a dual freeze-thaw cycle under ultrasound (US) guidance. After sonographically determining the most favorable percutaneous approach, we inserted the cryoprobes into the tumor under US guidance and advanced the tip to reach the distal margin of the targeted lesion. The number of probes used depended on the location and size of the lesions to be ablated. The dual freeze-thaw cycle consisted of a 20-min freeze, followed by a 10-min thaw and a 15-min freeze. The dimensions of the frozen tissue were monitored by US. The cryoprobe temperatures were reduced with 1 min to -135±2˚C. Upon removal of the probes, all tracts were packed with Surgicel (Johnson & Johnson, Inc., Arlington, TX, USA), to control bleeding. We aimed to ablate all the tumors with a curative intent in a single or repeated cryoablation, especially for tumors less than 5 cm in diameter. For large tumors, complete ablation using percutaneous modality is not possible, so in these cases we reduced tumor load larger than 50% as much as possible. We limited cryoablation to a maximum of three procedures.

Table I. Patient characteristics (n=110).

Clinical features	Values
Gender, n (%)	
Male	100 (90.9)
Female	10 (9.1)
Age (years), median (range)	54 (31-76)
ECOG PS, n (%)	
0	22 (20.0)
1	46 (41.8)
2	42 (38.2)
Tumor differentiation, n	
Medium	29
Low	29
Tumor diameter (cm), median (range)	8 (2.2-19.3)
No. of tumors, n (%)	
1	34 (30.9)
2	16 (14.5)
3	16 (14.5)
4	44 (40.1)
Invasion of portal vein, n (%)	
Branch	84 (76.4)
Trunk	26 (23.6)
Extrahepatic metastasis, n (%)	
Lung	36 (32.7)
Adrenal	2 (1.8)
Bone	2 (1.8)
HBV DNA (IU/ml), n (%)	
0-9,999	70 (63.6)
10,000-99,999	14 (12.7)
≥100,000	26 (23.7)
Combined treatment, n (%)	
Sorafenib alone	32 (29.1)
TACE	38 (34.5)
TACE and cryoablation	40 (36.4)
Child-Pugh class, n (%)	
A	87 (79.1)
B	23 (20.9)
Platelet count ($x10^9$/l), median (range)	110 (27-351)
AFP (ng/ml), median (range)	1019 (7-20000)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; HBV, hepatitis B virus; TACE, transarterial chemoembolization; AFP, α-fetoprotein.

Disease assessment. Disease status was assessed using CT scans or magnetic resonance imaging (MRI) performed approximately every 8 weeks. The response was classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) according to Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma (17). Patients who achieved CR, PR or SD were defined as achieving clinical benefits (CB). PFS was calculated from the date of starting sorafenib treatment to the date of disease progression or mortality. OS was calculated from the date of starting sorafenib to the date of mortality or last follow-up.

Statistical analysis. Continuous data are expressed as medians and range. All continuous data were classified into subgroups according to the median value. Univariate associations between OS, PFS and potential prognostic factors were assessed using the Kaplan-Meier method with the log-rank test. Cox's proportional hazards model was used for multivariate analyses with a step-wise procedure and a significance level of 0.10 to enter and remove variables. All statistical analyses were performed using SPSS software version 16.0 for Windows (SPSS Inc., Chicago, IL, USA). $P<0.05$ was considered to indicate a statistically significant result.

Results

Patient characteristics and clinical outcomes. The baseline characteristics of the patients are presented in Table I. The median follow-up was 9 months (range, 3-18) and the median duration of sorafenib treatment was 6.5 months (range, 1.5-18). A total of 15 patients discontinued sorafenib at 6-24 weeks due to liver function deterioration (10 cases) and esophagogastric variceal bleeding (5 cases). A total of 27 (24.5%) patients reduced sorafenib dosage to 200 mg twice daily due to grade 3-4 ADRs, but all these patients were restored to 400 mg twice daily after 1-2 weeks. Overall, 14 (12.7%) patients achieved CR, 16 (14.5%) achieved PR and 40 (36.4%) achieved SD lasting >8 weeks. Therefore, the overall clinical benefit rate (CBR) was 63.6% (70/110). The median OS and PFS for the whole cohort were 10.5 [95% confidence interval (CI), 8.7-12.3] and 5.0 months (95% CI, 3.7-6.3), respectively (Fig. 1). Disease progression occurred in 100 (90.9%) patients. Furthermore, a total of 58 (52.7%) patients died during the study; 25 (22.7%) succumbed to recurrence/metastasis, 14 (12.7%) to liver failure, 10 (9.1%) to esophagogastric variceal bleeding, 6 (5.5%) to refractory ascites-induced renal failure and 3 (2.7%) to tumor rupture/hemorrhage.

Treatment-related adverse effects. Hand-foot skin reaction (65.5%) was the most common adverse event, followed by rash (63.6%), hypertension (55.5%), alopecia (50.9%), fatigue (46.3%), weight loss (45.5%), diarrhea (40.0%) and liver toxicity (elevated bilirubin levels, 39.1%). Hematological toxicities occurred in 38 (34.5%) patients, including leucopenia (14.5%), hemorrhage (12.7%), anemia (3.6%) and thrombocytopenia (3.6%) and were the most frequently encountered grade 3-4 toxicities (16.4%). The most common grade 3 toxicities were hand-foot skin reaction (15.5%), liver toxicity (8.2%), diarrhea (4.5%), hypertension (3.6%) and hemorrhage (2.7%). Liver toxicity (6.4%), hemorrhage (4.5%), leucopenia (3.6%), anemia (1.8%) and diarrhea (1.8%) were the most common grade 4 toxicities. Liver toxicity occurred in 43 (39.1%) patients and grade 3-4 toxicity was observed in 16 (14.5%), 10 of whom succumbed to liver failure.

Univariate analysis of factors associated with PFS and OS. Univariate analysis (Table II) revealed that ECOG PS ≥1, extrahepatic metastasis, high HBV DNA level, Child-Pugh

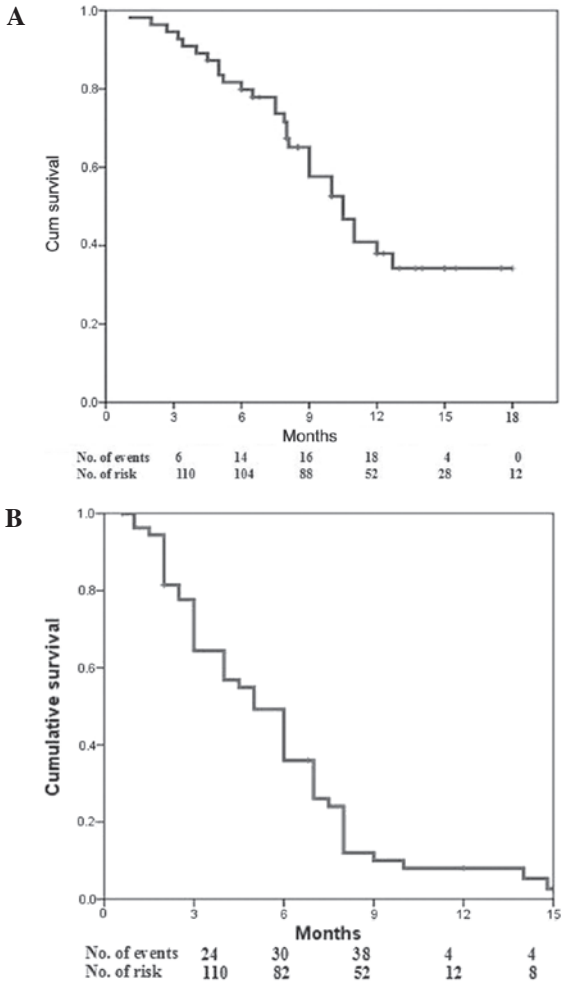

Figure 1. Kaplan-Meier curves for (A) overall survival and (B) progression-free survival in patients receiving sorafenib for the treatment of advanced hepatocellular carcinoma.

class B and AFP >1019 ng/ml were significantly associated with reduced PFS. Meanwhile, ECOG PS ≥1, tumor diameter, extrahepatic metastasis, high HBV DNA level and AFP >1019 ng/ml were associated with reduced OS. Use of local therapy was associated with longer PFS and OS.

Multivariate analysis of factors associated with PFS and OS. Cox proportional hazards model analyses revealed that local therapy was independently associated with improved PFS [odds ratio (OR), 0.576; 95% CI, 0.399-0.831; P=0.003] whereas ECOG PS (OR, 5.705; 95% CI, 3.352-9.709; P=0.000) and Child-Pugh class (OR, 2.628; 95% CI, 1.416-4.878; P=0.002) were independently associated with reduced PFS (Fig. 2). Moreover, local therapy (OR, 0.245; 95% CI, 0.071-0.846; P=0.026) was independently associated with improved OS while ECOG PS (OR, 8.998; 95% CI, 4.275-18.938; P=0.000) and AFP (OR, 2.260; 95% CI, 1.174-4.352; P=0.015) were independently associated with reduced OS (Fig. 3).

Effects of local therapy on PFS, OS and safety. In terms of clinical efficacy, local treatment in combination with sorafenib was superior to sorafenib alone. Indeed, comparing sorafenib plus TACE plus cryoablation versus sorafenib plus TACE versus sorafenib alone, we found significant differences in CBR (80.0 vs. 73.7 vs. 31.3%; P=0.000), PFS (6.0 vs. 6.0 vs. 3.0 months; P=0.000) and OS (12.7 vs. 12.0 vs. 8.0 months; P=0.000) among the three groups. However, the use of cryoablation yielded only slight numerical increases in CBR and OS compared with sorafenib plus TACE.

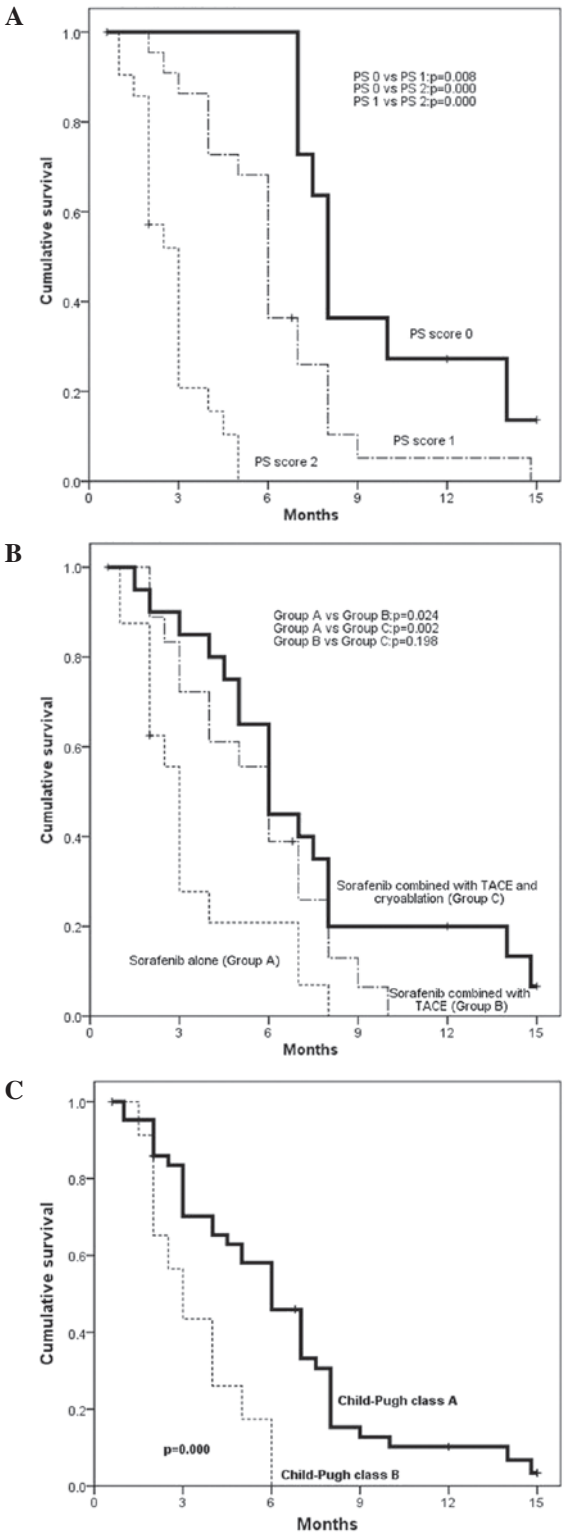

Figure 2. Kaplan-Meier curves showing the effects of (A) Eastern Cooperative Oncology Group performance status (PS), (B) combination with local therapy and (C) Child-Pugh class on progression-free survival. TACE, transarterial chemoembolization.

Table II. Univariate analysis of factors associated with PFS and OS.

		PFS (months)		OS (months)	
Parameter	No. of mortalities	Median	P-value	Median	P-value
Gender			0.214		0.898
Male	53	6.0		10.5	
Female	5	3.0		9.0	
Age (years)			0.668		0.228
≤54	33	5.0		9.0	
>54	25	6.0		10.5	
ECOG PS			<0.001		<0.001
0	2	8.0		17.2	
1	20	6.0		11.0	
2	36	3.0		7.5	
Tumor differentiation			0.255		0.401
Medium	21	3.0		8.0	
Low	21	4.5		9.0	
Tumor diameter (cm)			0.125		0.007
≤8	22	6.0		12.0	
>8	36	5.0		8.1	
Tumor number			0.165		0.995
1	15	6.0		12.7	
2	11	6.0		11.0	
3	11	5.0		10.0	
4	21	4.0		10.0	
Invasion of portal vein			0.856		0.399
Branch	43	5.0		11.0	
Trunk	15	6.0		10.0	
Extrahepatic metastasis			0.019		0.040
No	34	6.0		11.0	
Yes	24	4.0		9.0	
HBV DNA (IU/ml)			<0.001		<0.001
0-9,999	26	6.0		12.7	
10,000-99,999	10	4.0		10.0	
≥100,000	22	3.0		8.0	
Combined treatment			<0.001		<0.001
Sorafenib alone	24	3.0		8.0	
TACE	18	6.0		12.0	
TACE and cryoablation	16	6.0		12.7	
Child-Pugh class			<0.001		0.246
A	47	6.0		11.0	
B	11	3.0		9.0	
Platelet count ($x10^9$/l)			0.555		0.427
≤110	26	6.0		10.5	
>110	32	5.0		10.0	
AFP (ng/ml)			0.005		0.001
≤1019	24	6.0		12.7	
>1019	34	4.0		9.0	

Analyses were conducted using the Kaplan-Meier method with log-rank tests. ECOG, Eastern Cooperative Oncology Group; PS, performance status; HBV, hepatitis B virus; TACE, transarterial chemoembolization; AFP, α-fetoprotein; PFS, progression-free survival; OS, overall survival.

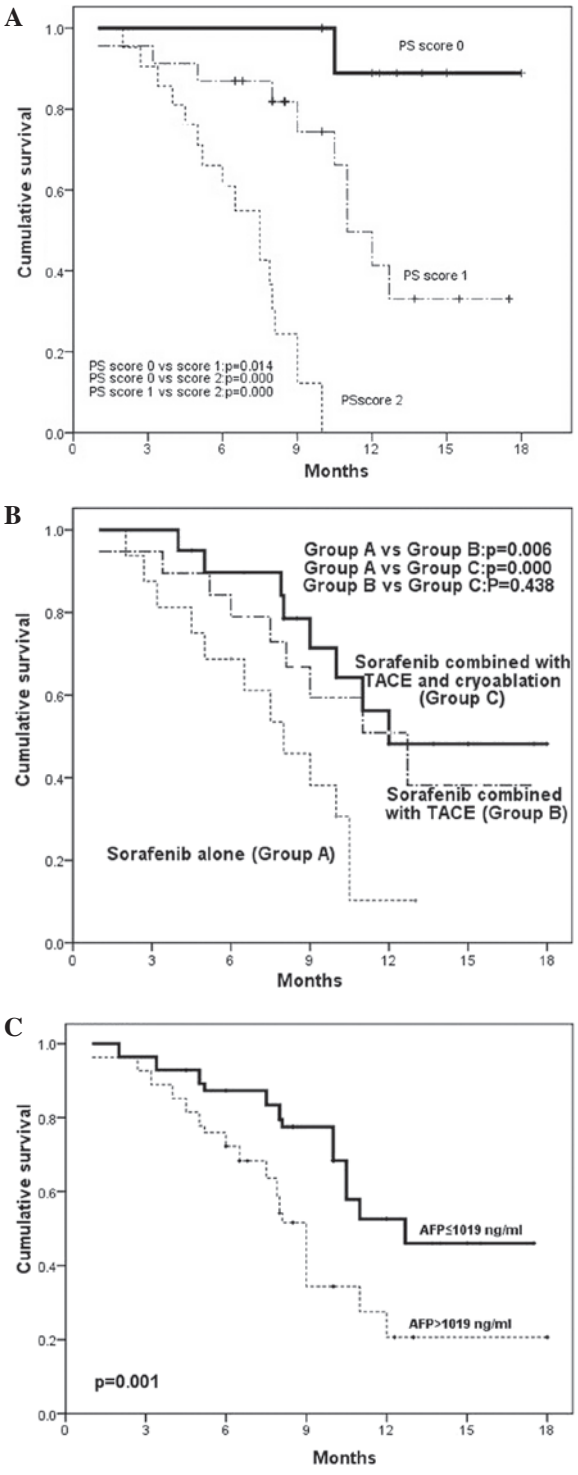

Figure 3. Kaplan-Meier curves showing the effects of (A) Eastern Cooperative Oncology Group performance status (PS), (B) combination with local therapy and (C) AFP on overall survival. TACE, transarterial chemoembolization; AFP, α-fetoprotein.

Continuation of sorafenib in a subset of patients with radiological PD improves OS. At the end of follow-up, disease progression occurred in 100 patients. In 42 patients, therapy of sorafenib was discontinued due to new lesions or concomitant clinical deterioration, but 58 patients with continuing clinically stable presentation continued to receive sorafenib despite disease progression. There was a marked difference in OS between the patients who continued to take sorafenib and those who discontinued therapy (11 vs. 7.5 months, P<0.001; Fig. 4).

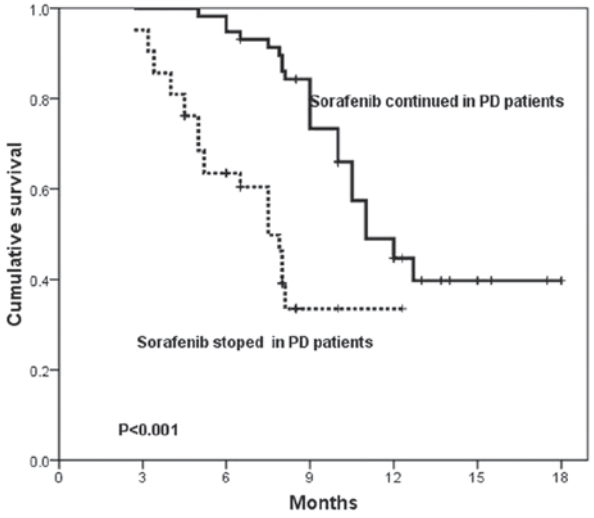

Figure 4. Kaplan-Meier curves showing the effect of continuing sorafenib therapy in patients with radiological progressive disease (PD) on overall survival.

Discussion

Sorafenib has created a new era for advanced HCC therapy. In the present study, 14 (12.7%) patients achieved CR (Fig. 5), 16 (14.5%) achieved PR (Fig. 6) and 54 (49.1%) had SD, according to Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma. The median OS and PFS were 10.5 and 5.0 months, respectively. These findings are encouraging and similar to those of other studies (7,10,18), although our patients had a poorer prognosis than those of the aforementioned studies due to the presence of advanced tumors (including PVT). For comparison, in two previous studies the median OS of patients with similar advanced tumors was 4 months (19,20). Notably, compared with studies with similar populations of patients, our results are superior to those of other studies (8,11). For example, in the Asia-Pacific study, the median OS and PFS were 6.5 and 2.8 months, respectively, although this is unsurprising as patients in that study had poorer PS, with 74% having ECOG PS ≥1, and more advanced cancer, with 96% at BCLC stage C (8). In the study by Yau *et al* (11), the median OS and PFS were 5 and 3 months, respectively; in their cohort, 47% of patients had major vessel invasion, 39% had lung metastasis and 29% were Child-Pugh class B or C. Nevertheless, the 10.5-month OS and 5-month PFS achieved in patients with PVT in the current study are impressive. These encouraging results are at least partly due to the use of local therapy, as 70.9% (78/110) of patients received sorafenib in combination with local therapy (TACE or cryoablation).

There is a strong theoretical rationale for combining sorafenib with local therapy. Sorafenib is able to prolong survival in advanced HCC patients, but sorafenib monotherapy rarely elicits HCC shrinkage (18). Furthermore, a high tumor load may render the patients refractory to sorafenib (11). TACE has been widely used for non-surgical HCC patients (21), but residual tissue at the margin of treatment and tumor progression

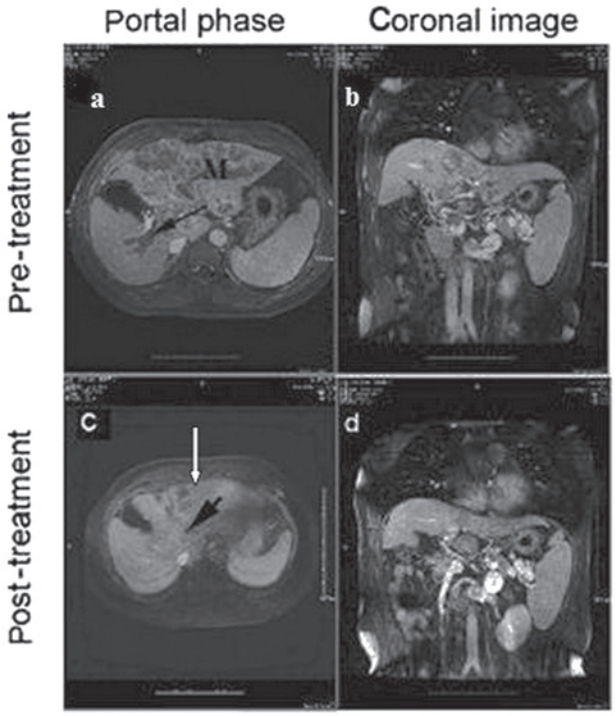

Figure 5. Overall response consisted of a complete response to the combined sorafenib and cryotherapy for advanced HCC in a 55-year-old male over an 18-month period at end-point. (a) MRI scan reveals a huge mass (M) at the dome of the left hepatic lobe (upper section); histopathological diagnosis was HCC, moderately differentiated (Edmondson classification). The black arrow indicates portal vein thrombosis. (b) Portal vein thrombosis is shown on coronal image of MRI. (c) Following continuation of sorafenib treatment, concurrent administration of 2-times percutaneous cryoablation reduced the tumor burden by up to 60% in two weeks. After 10 months, the treated tumor had shrunk and the non-treated tumor also decreased. The long white arrow indicates necrosis in the treated tumor. The short black arrow indicates the portal vein tumor thrombus, which was almost invisible. (d) Coronal image of MRI shows that the portal vein tumor thrombus was almost invisible. HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging.

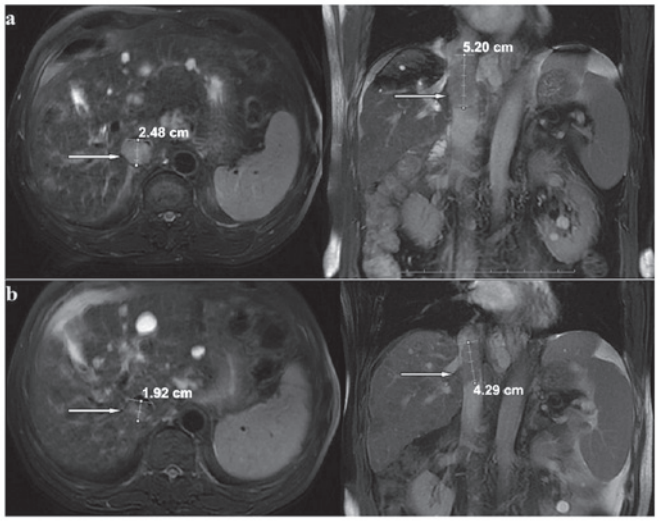

Figure 6. A partial response was achieved in a 61-year-old male with advanced HCC 4 months after receiving a combination of sorafenib and local therapy [transarterial chemoembolization (TACE) and cryoablation]. (a) MR image showing vena cava tumor thrombus prior to sorafenib treatment (maximal diameter, 2.48 cm; maximal length, 5.20 cm). By TACE and cryoablation, two tumor nodules in the liver exhibited coagulation necrosis and the patient began to receive sorafenib. (b) Follow-up MR images obtained 4 months after receiving a combination of sorafenib and local therapy showing the decrease of the vena cava tumor thrombus (maximal diameter, 1.92 cm; maximal length, 4.29 cm). No tumor recurrence in the liver occurred. HCC, hepatocellular carcinoma; MR, magnetic resonance.

or metastasis following TACE remain limiting factors (22,23). The upregulation of angiogenic factors in surviving tumor cells following TACE is associated with tumor growth and invasiveness (24,25). Percutaneous cryoablation offers a promising treatment modality for HCC due to the ability to ablate larger zones than other ablation procedures (16,26,27). In this context, we believe that the combination of sorafenib with local therapies offers several advantages. First, local therapy is able to reduce the tumor load to increase the efficacy of sorafenib. Second, sorafenib-mediated blockade of the Raf/MAPK and VEGFR pathways may enhance the efficacy of local therapy if sorafenib is continued during and following TACE or cryoablation. Third, TACE plus cryoablation promotes necrosis of the treated tumor. In mice with implanted renal tumors, the efficacy of radiofrequency ablation in combination with sorafenib on tumor ablation increased in a sorafenib dose-dependent manner (28). In our study, the combination of sorafenib plus local therapy was an independent predictor of PFS and OS, resulting in marked survival benefits compared with sorafenib alone. Meanwhile, although there were no significant differences between sorafenib plus TACE plus cryoablation versus sorafenib plus TACE in terms of CBR (P=0.639), PFS (P=0.198) or OS (P=0.588), the use of cryoablation did provide slight improvements in these parameters. The clinical benefits may be due to a greater reduction of tumor burden by cryoablation, based on prior studies of local ablation combined with TACE (29). As this study had a relatively small number of subjects, further prospective studies with a larger number of patients are needed to confirm that cryoablation improves the prognosis of patients with HCC when used in combination with sorafenib and TACE.

Other than the benefits of combined therapy, one aspect of this study may also contribute to prolonged survival. In the majority of previous studies, sorafenib was discontinued upon tumor progression. In the SHARP trial (7), the median survival time after disease progression was 5.2 months. By contrast, in a Japanese phase I study (18) of sorafenib, the median TTP was 4.9 months, while median OS was 15.6 months. In the study by Yau *et al* (11), OS was substantially longer compared with their historical cohort, even in patients who did not demonstrate any clinical benefits with sorafenib. Wörns *et al* (30) reported that radiological disease stabilization (PR and SD) was achieved in 50% of patients after a median of 3.2 months, or stable clinical presentation was obtained in a subset of patients with radiological PD leading to the continuation of therapy. These results suggest that even patients lacking demonstrable clinical benefits of sorafenib may gain some survival benefit from the treatment. This is a phenomenon that has also been observed using molecular-targeted agents for the treatment of other types of solid tumors (31). If radiological progression criteria are applied, sorafenib would be discontinued after 3-4 months in a number of patients, possibly denying these patients the opportunity for further clinical benefits and prolonging OS. We believe that continuing sorafenib therapy following radiological progres-

sion is justified in patients with a stable clinical presentation. Therefore, sorafenib was continued in 58 patients despite disease progression. Our results show that continuing sorafenib therapy in patients with PD improved OS. Therefore, we argue that a sudden stop of sorafenib treatment in advanced HCC patients may promote tumor progression to a certain extent. It will be of interest to further investigate the issue in future studies.

Multivariate analysis revealed that poor ECOG PS predicted poor PFS and OS, which is consistent with the results of previous studies (32,33). In the current study, none of the patients had an ECOG PS greater than 2 or a Child-Pugh class worse than B. Ideally, the tumor control rate increases with sorafenib dose and the completion of local treatment. Patients with a better PS had the opportunity for sorafenib maintenance therapy and successful local treatment due to the acceptable adverse effects.

Traditional prognostic factors, including tumor number, tumor differentiation and PVT within the branch or trunk, were not found to be associated with survival. Although tumor size was significantly associated with OS based on the log-rank test, which suggests that tumor load might be a mechanism involved in refraction to sorafenib, it was excluded from multivariate analysis. Similar to the results of previous studies, Child-Pugh class and AFP were independently associated with PFS and OS, respectively. The precise mechanism by which AFP influences prognosis remains unclear. However, several studies have reported that AFP is a novel protein-binding partner for caspase-3, blocks the apoptotic signaling pathway and promotes the growth of human hepatoma cells as a co-repressor in RA-RAR signaling (34,35).

The major limitation of the current study is its nonrandomized design and that patients with a prior history of treatment were excluded. Considering that patients with complete PVT always have poor liver function (Child-Pugh class C) and an expected survival time of less than 3 months, these patients were also excluded.

In conclusion, taking into account the limitations of the study, our results provide further evidence to show that poor ECOG PS is associated with poor prognosis of sorafenib therapy with/without local therapy for HCC. On the other hand, the use of local therapy (TACE with/without cryoablation) improved the prognosis of sorafenib therapy for HCC. The safety and efficacy of sorafenib in combination with local therapies, including TACE or local ablation, should be confirmed in well-designed, prospective clinical studies.

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