Original Article

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Adjuvant sorafenib reduced mortality and prolonged overall survival and post-recurrence survival in hepatocellular carcinoma patients after curative resection: A single-center experience

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Summary **Adjuvant therapy after resection of hepatocellular carcinoma (HCC) is limited. Here, we evaluated the effects of postoperative sorafenib on recurrence and survival in HCC patients. Recurrence-free survival and overall survival were analyzed as the main endpoint, recurrence rate, and mortality rate were analyzed as second endpoint. Furthermore, post-recurrence survival was also analyzed. Clinicopathological factors were compared between sorafenib and control groups. Seventy-eight patients were eligible for final data analysis (46 in control group; 32 in sorafenib group). Sorafenib did not significantly prolong recurrence-free survival (11.0 months in the control group *vs*. 11.7 months in the sorafenib group, $p = 0.702$), but significantly prolonged overall survival (32.4 *vs*. 25.0 months, $p = 0.046$). Sorafenib did not reduce recurrence rate (67.7% *vs*. 78.3%, $p = 0.737$), but significantly reduced mortality rate (28.1% *vs*. 60.9%, $p = 0.004$). The increased post-recurrence survival (22.2 *vs*. 4.4 months, $p = 0.003$) may have contributed to the survival benefit after recurrence in the sorafenib group. Adjuvant sorafenib did not decrease tumor recurrence, but significantly reduced mortality and prolonged overall survival of HCC patients after curative resection, probably by inhibiting tumor growth after tumor recurrence.**

Keywords: Hepatocellular carcinoma, resection, sorafenib

1. Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide and the most deadly cancer in China (*1*), and its incidence continues to increase, especially in North America (*2,3*). Surgery, tumor ablation, and liver transplantation are the main potentially curative treatments for HCC. However, tumor recurrence rate is very high after liver resection and tumor ablation, which is a major problem affecting long term survival (*4,5*). Various postoperative interventions, such as adjuvant therapy with interferon, Vitamin E or K2, or I^{131}, are used to reduce the incidence of tumor recurrence after curative treatment (*6,7*). The adjuvant application of interferon (*7-10*) and antiviral treatment (*11,12*) seems promising but should be confirmed in further multi-center phase III clinical trials.

Sorafenib is an oral, multitargeted inhibitor of tyrosine kinases (such as the vascular endothelial growth factor receptor, Raf kinase, and the platelet-derived growth factor receptor), and it has been shown to inhibit tumor angiogenesis and to induce apoptosis of HCC tumor cells (*13*). Two independent randomized Phase III clinical trials showed that sorafenib was the only effective systemic drug to improve survival in patients with advanced HCC (*14,15*). Furthermore, sorafenib is reported to be well tolerated and safe in patients who received liver transplantation and is associated with a survival benefit (*16-18*). In a

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randomised controlled phase III clinical trial (STORM), sorafenib was administrated to patients with a median-high risk of recurrence, the clinical trial is still ongoing and waiting for final results (*19*). Recently, a retrospective study with 31 patients using sorafenib as an adjuvant therapy after liver resection for HCC showed that time to recurrence in the sorafenib arm was significantly prolonged (by 8 months) compared to that in the control arm (*20*). However, because of the small sample size in this study, the effects of sorafenib in the adjuvant setting remain unclear.

Here, we describe our preliminary results regarding the efficacy of adjuvant sorafenib after liver resection for patients with hepatocellular carcinoma.

2. Materials and Methods

2.1. *Patients and follow-up*

This study was a single-institutional retrospective analysis of the effects of sorafenib in patients with HCC after curative resection. Between August 1, 2009, and December 31, 2011, 248 cases of HCC received liver resection. HCC was diagnosed by two independent pathologists (Cao WF and Zhan ZL). Curative resection was defined as complete removal of tumor without residual tumor by microscopy and free of tumor within one month after operation. One hundred and sixty-two patients without microvessel invasion were regarded as low-risk for recurrence and were excluded; and 8 patients with tumor thrombosis in the main trunk of the portal vein were regarded as un-curative resection and were also excluded. Among 78 patients who were eligible for the final analysis, 32 patients received sorafenib treatment after hepatectomy within one month after hepatectomy and 46 patients who did not receive adjuvant sorafenib treatment were included in the control group. The protocol for adjuvant sorafenib treatment has been approved by the Ethics Committee of Tianjin Medical University Cancer Hospital.

Relevant clinical data, including medical history, demographic data, laboratory results, tumor characteristics, and follow-up data were recorded prospectively. The primary end points were recurrence-free survival (RFS) and overall survival (OS); the secondary end points were recurrence rate and mortality rate; and another end point was post-recurrence survival. After operation, patients were followed up in our clinic every 1-2 months for routine blood tests, liver function tests, tumor markers including AFP and ultrasound for the first year, and every 3 months one year after operation. If recurrence was suspected, enhanced magnetic resonance imaging or computed tomography scan was performed immediately. If recurrence was confirmed, surgical resection, radiofrequency ablation or trans-arterial remobilization were given to the patients accordingly.

2.2. *Clinicopathological factors*

Clinicopathological factors in this study were selected for their potential relationship to the prognosis on the basis of the previous studies, including age (< 54 or ≥ 54 years, mean age = 54 years), gender (male or female), tumor size (< 5 cm or ≥ 5 cm), number of tumor nodules (single or multiple), microvascular invasion (yes or no), intrahepatic metastasis (yes or no), tumor differentiation (Edmondson's classification I or II was classified into the high-differentiation group, and classification III or IV was classified into the low-differentiation group), portal vein thrombosis (PVTT) is defined as direct invasion of a second branch of portal vein. Invasion of main portal vein or main trunks of portal vein were excluded.

2.3. *Sorafenib treatment and evaluation*

All the patients in the sorafenib (Bayer Healthcare, Leverkusen, Germany) group received an initial dosage of 400 mg twice daily continuously, except in cases in which the drug was discontinued owing to death, tumor progression, or adverse effects such as deterioration of liver function. Blood pressure, coagulation function, hematological parameters and CT scan were monitored every month. If adverse events classified as CTCAE-3 or higher occurred, the dosage of sorafenib was reduced or administration of sorafenib was withdrawn.

2.4. *Statistical analysis*

Survival analysis was computed by the Kaplan-Meier method and the log-rank test for univariate analysis, and Cox regression was used for multivariate analysis. Overall survival (OS) was calculated from the date of surgery to the date of death or the last follow-up. Recurrence-free survival (RFS) was calculated from the date of surgery to the date of recurrence or the last follow-up. Post-recurrence survival was calculated from the date of first recurrence to the date of death or the last follow-up. The χ^2 test, Fisher's exact probability, and Student's *t* test were used for comparisons between groups. Statistical analyses were performed with SPSS 16.0 for Windows (SPSS Inc., Chicago, IL). Two-tailed $p < 0.05$ was considered to indicate a statistically significant difference.

3. Results

3.1. *Patient demographics and tumor characteristics*

Table 1 shows the demographic data and tumor characteristics for all the patients. Median age was 54 years (range 21 to 81 years), and the age of patients in the sorafenib group were similar to that of patients in the control group (54.5 ± 1.6 *vs*. 51.7 ± 1.4, $p = 0.224$).

The male/female ratio was 42:4 in the control group versus 25:7 in the sorafenib group. All the patients had good Eastern Cooperative Oncology Group performance status scores (0-1) before commencement of sorafenib therapy, and the liver function of all the patients was classified as Child-Pugh A. Patients in the sorafenib group have similar tumor size compared to than of patients in the control group (5.7 ± 0.6 cm *vs*. 7.7 ± 0.8, $p = 0.064$). Multiple tumors were present in 18 of 46 patients in the control group and in 11 of 32 patients in the sorafenib group ($p = 0.669$). Portal vein thrombosis was present in 12 of 46 patents in the control group, whereas 8 of 32 patients in the sorafenib group had portal vein thrombosis ($p = 0.914$). Tumor differentiation was low (Edmondson III or IV) in 16 patients in the control group and 7 patients in the sorafenib group ($p = 0.536$) (Table 1). Major resection (≥ 3 segments) was performed in 16 of 46 patients in control group and in 11 of 32 patients in sorafenib group (34.8% *vs*. 34.4%, $p = 0.97$).

Table 1. Patient demographics and tumor characteristics at baseline

Demographic or characteristic	Control ($n = 46$)	Sorafenib ($n = 32$)	p-value
Gender (male/female)	42/4	25/7	0.100
Age, years (mean ± S.D.)	54.5 ± 1.6	51.7 ± 1.4	0.224
Age (< 54 years/ ≥ 54 years)	21/25	15/17	0.915
Hepatitis status (HBV/non-HBV)	38/8	28/4	0.912
Tumor size (cm, mean ± S.D.)	7.7 ± 0.8	5.7 ± 0.6	0.064
Tumor size (< 5 cm/ ≥ 5 cm)	17/29	15/17	0.381
AFP (< 20/ ≥ 20 ng/mL)	22/24	16/16	0.850
No. of tumors (single/multiple)	28/18	21/11	0.669
Portal vein thrombosis (yes/no)	12/34	8/24	0.914
Tumor differentiation (high/low)	30/16	25/7	0.536
Intrahepatic metastasis (yes/no)	26/20	17/15	0.767
TNM stage (II/III)	26/20	22/10	0.275
Recurrence (yes/no)	36/10	24/8	0.737
Death (yes/no)	28/18	9/23	0.004

Abbreviations: HBV, hepatitis B virus; SD, standard deviation; TNM, tumor-node-metastasis.

3.2. *Treatment efficacy*

Sorafenib significantly prolonged OS: the 1-, 2-, and 3-year OS rates were 79.8%, 68.1%, and 45.4% for the sorafenib group and 60.9%, 52.2%, and 38.0% for the control group. Median OS was 25.0 months (95% CI: 7.3-42.7 months) in the control group and 32.4 months (95% CI: 24.3-40.5 months) in the sorafenib group, and the difference was statistically significant ($p = 0.046$, Figure 1A).

Sorafenib did not prolong RFS: the 1-, 2-, and 3-year RFS percentages were 46.9%, 25.2%, and 18.9% for the

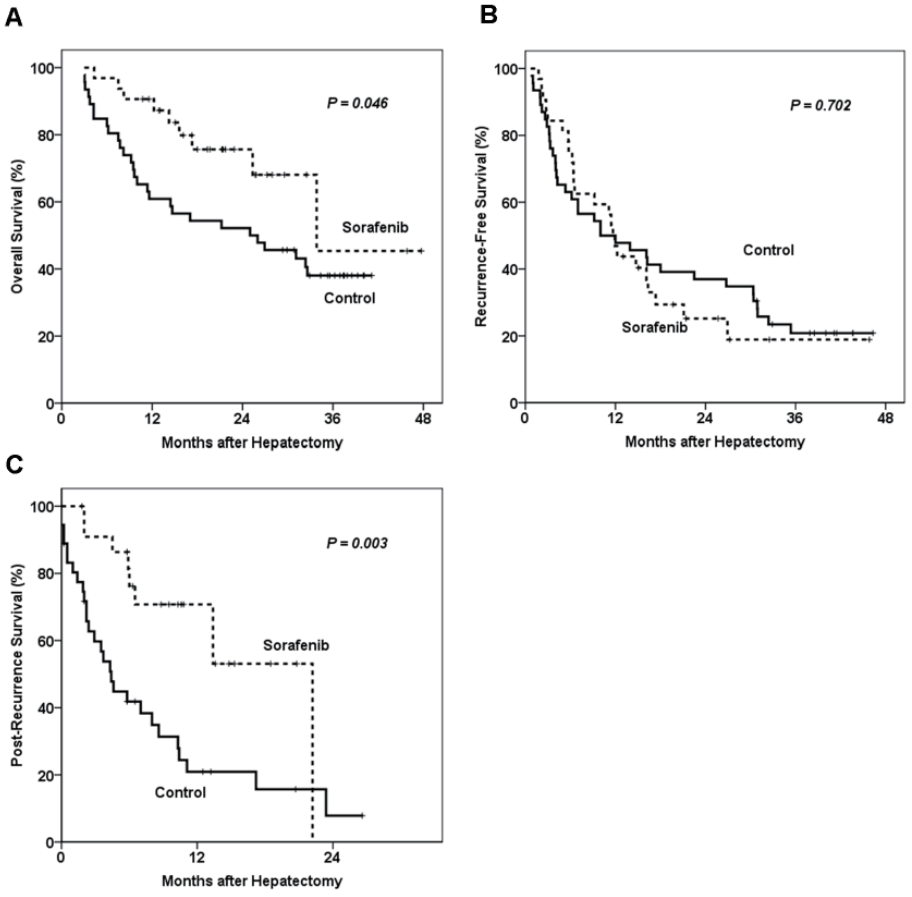

Figure 1. The effects of adjuvant sorafenib on RFS, OS and post-recurrence survival. (A) Overall survival, **(B)** Recurrence-free survival, and **(C)** Post-Recurrence Survival of HCC patients treated with adjuvant sorafenib after curative resection.

Table 2. Univariate and multivariate analysis for Overall Survival (OS) and Recurrence-Free Survival (RFS)

Factors	OS				RFS			
	Univariate *p*	Multivariate			Univariate *p*	Multivariate		
		HR	95% CI	*p*		HR	95% CI	*p*
Sorafenib	0.046	0.490	0.224-1.071	0.074*	0.702			
Gender (male/female)	0.432				0.816			
Age (< 54 years/ ≥ 54 years)	0.722				0.823			
Tumor size (< 5 cm/ > 5 cm)	0.576				0.734			
AFP (< 20 *vs*. ≥ 20)	0.631				0.604			
No. of tumors (single/multiple)	0.173	1.358	0.637-2.893	0.428	0.063	1.871	1.045-3.349	0.035
Portal vein thrombosis (yes/no)	0.106	1.533	0.561-4.193	0.405	0.022	2.601	1.119-6.049	0.026
Tumor differentiation (high/low)	0.284				0.628			
Intrahepatic metastasis (yes/no)	0.071	1.550	0.761-3.154	0.227	0.209			
TNM stage (II/III)	0.051	1.037	0.371-2.895	0.945	0.155	0.655	0.287-1.492	0.314

HR, hazard ratio; TNM, tumor-node-metastasis; CI, confidence interval; *, $p = 0.040$ if forward stepwise (likelihood ration) is used in the COX analysis.

sorafenib group and 47.8%, 37.0%, and 20.8% for the control group. Median RFS was 11.0 months (95% CI: 1.5-20.1 months) in the control group and 11.7 months (95% CI: 10.1-13.2 months) in the sorafenib group ($p = 0.702$, Figure 1B).

Tumor recurrence occurred in 36 patients (78.3%) in the control group and 24 patients (67.7%) in the sorafenib group ($p = 0.737$); 28 patients (60.9%) died in the control group, compared to 9 patients (28.1%) in the sorafenib group ($p = 0.004$) (Table 1). Recurrent tumor was not significantly different in location, for liver recurrence occurred in 33 of 46 in control group and 22 of 32 in the sorafenib group (71.7% *vs*. 68.8%, $p > 0.05$), and lung metastasis occurred in 3 of 46 in control group and 2 of 32 in sorafenib group (28.3% *vs*. 31.2%, $p > 0.05$).

Post-recurrence survival was significantly longer in the sorafenib group than that in the control group; in the control group, the median post-recurrence survival was 4.4 months (95% CI: 2.9-5.9 months), and in the sorafenib group, the median post-recurrence survival was 22.2 months (95% CI: not reached) ($p = 0.003$, Figure 1C).

Univariate analysis showed that adjuvant sorafenib, multiple tumors, portal vein thrombosis, intrahepatic metastasis and TNM stage III were risk factors for OS, while only adjuvant sorafenib was an independent risk factor of overall survival (HR: 0.490, 95% CI: 0.224-1.071, $p = 0.040$). As for Recurrence Free Survival, univariate analysis showed that multiple tumors, portal vein thrombosis and TNM stage III were risk factors, however, only multiple tumors (HR = 1.871, 96% CI: 1.045-3.349, $p = 0.035$) and portal vein thrombosis (HR = 2.601, 95% CI: 1.119-6.049, $p = 0.026$) were independent risk factors (Table 2).

3.3. *Patients' adherence and tolerability for sorafenib treatment*

All the patients had good adherence in both the sorafenib group and control group. Grade 3 adverse effects occurred in 6 patients with sorafenib treatment but with a reduction to half dosage, all the patients recovered and 4 patients received full dose again. None of the patients withdrew sorafenib treatment

4. Discussion

The results of the current study showed that sorafenib neither reduced recurrence rate nor prolonged RFS. However, sorafenib reduced mortality rate and prolonged overall survival; furthermore, sorafenib prolonged post-recurrence survival, perhaps because the recurrent tumors that developed after sorafenib treatment progressed more slowly.

Sorafenib has two main types of effects: an anti-angiogenic and a direct antitumoral effect (*13*). Tumor angiogenesis occurs only after a tumor grows to a certain minimum size (*e.g.*, 1 cm) (*21*), and anti-angiogenic agents are mostly tumor-static agents, that is, they retard tumor growth rather than reduce tumor size (*22*). Therefore, the anti-angiogenic effect of sorafenib can be expected to play a role only when a tumor is sufficiently large, and sorafenib is unlikely to decrease tumor growth before tumor recurrence. It has been reported that sorafenib delays the progression of recurrent tumors following liver transplantation, and this delay is associated with a survival benefit (*6*). Wang *et al*. found that in two cohorts of patients ($n = 39$ patients, 24 of whom received best supportive care and 15 of whom received sorafenib) who presented with HCC recurrence after liver transplantation, patients' outcome in the sorafenib group was significantly better than that in the other group, with a median survival from recurrence of 21.3 vs. 11.8 months (HR = 5.2, $p = 0.0009$), and a median survival from untreatable presentation/progression of 10.6 vs. 2.2 months (HR = 21.1, $p < 0.0001$).

Resistance to anti-angiogenic therapy is common, and some tumors possess intrinsic mechanisms of resistance to sorafenib (*23*). Despite the success of sorafenib in the treatment of some patients with

advanced HCC (*24*), most such patients do not respond to sorafenib, and some patients who initially respond subsequently develop resistance and experience tumor progression (*25*). Sorafenib also directly targets tumor cells, but perhaps only tumor cells with a specific activated signaling pathway and the drug may thus exert its direct effects only in patients whose tumors exhibit that specific molecular pathway. Molecular markers may be useful for predicting the efficacy of sorafenib. Specifically, mitogen-activated protein kinase and signal transducer and activator of transcription 3 are known targets of sorafenib in HCC (*26*), but the prognostic value of these markers has not yet been confirmed. Results obtained in a mouse model indicate that the efficacy of sorafenib against HCC may depend on the level of expression of HIV-1 Tat interactive protein 2 (HTATIP2) in tumors (*27*).

Meanwhile, factors in the tumor and host microenvironment should also have been considered in the resistance of sorafenib, for studies have shown that progression-free survival under sorafenib treatment is significantly shorter in patients with high levels of angiogenin-2 (Ang-2) and granulocyte colony-stimulating factor (G-CSF), and that as the number of cytokines present at high concentrations increases, the treatment response deteriorates (*28*). Short-term and high-dose sorafenib treatment is associated with decreased survival in multiple preclinical animal models (*29,30*). Thus, molecular markers in serum and in tumor tissue will be of prognostic value and may permit prediction of the efficacy of sorafenib.

The current study has several limitations. First, it was a retrospective study, and the cases included in the control and treatment groups were not randomized. Second, the sample size was small. Randomized controlled clinical trials should be carried out to confirm the present findings in a larger population. Finally, molecular prediction of efficacy of sorafenib should be emphasized, and a molecular classification of HCC based on genome-wide investigations and identification of patient subclasses according to drug responsiveness will lead to a more personalized medicine.

In conclusion, adjuvant sorafenib did not decrease tumor recurrence, but significantly reduced mortality and prolonged overall survival of HCC patients after curative resection, probably by inhibiting tumor growth and prolonging post-recurrence survival after tumor recurrence. Randomized controlled clinical trials with specific emphasis on molecular markers are needed for selecting optimal candidates for sorafenib treatment and prediction of its efficacy.

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