Sorafenib Combined with Cryoablation to Treat Unresectable Hepatocellular Carcinoma

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ABSTRACT

Objective: To evaluate the efficacy and tolerability of sorafenib combined with cryoablation in treating unresectable hepatocellular carcinoma (HCC).

Methods: Patients with unresectable advanced HCC received cryoablation and sorafenib at a dose of 400 mg twice daily in 4-week cycles on the same day of the cryoablation. Tumor response, median overall survival and the median time to radiological progression were calculated and the toxicity was evaluated.

Results: Seventy-eight patients with unresectable HCC were involved in this study. The median age was 52 years (range, 22-81 years). The Eastern Cooperative Oncology Group (ECOG) performance status scores were 0 (39.7%), 1 (55.1%), and 2 (5.1%). Nine (11.5%) patients were at Barcelona clinic liver cancer (BCLC) stage A, twenty-four (30.8%) patients were at stage B and 45 (57.7%) patients were at stage C. Five (6.4%) achieved partial responses, and 34 (43.6%) achieved stable disease. The median time to progression (TTP) for all enrolled patients was 6.6 months and the median overall survival (OS) was 12.2 months.

Conclusion: Cryoablation combined with sorafenib demonstrates good efficacy and acceptable tolerability in treating unresectable advanced HCC patients.

Key words: Hepatocellular carcinoma; Sorafenib; Cryoablation; Unresectable

INTRODUCTION

The prognosis of patients with unresectable hepatocellular carcinoma (HCC) is poor, with a median survival of <1 year[1]. Patients with advanced-stage disease who are left untreated have a median survival of only 6–7 months[2].

Cryoablation is a revolutionary treatment for renal or hepatic tumors. Cryoablation has been reported to be effective, compared with best supportive care[3, 4]. But patients frequently develop recurrence or disease progression after the regional treatments[5]. Among patients with advanced disease who do not qualify for surgical or liver transplantation therapies, the only non-chemotherapeutic treatment that has been shown to increase survival is sorafenib[6]. A phase III, double-blind, and placebo-controlled trial of sorafenib showed survival benefit in patients with advanced HCC in 2007[7]. It can also be used in combination with local therapies, such as cryoablation. Rather than gross advanced tumors, tiny residual tumors after cryoablation may be more effectively treated by cytostatic agents like sorafenib. Thus, the combination of sorafenib and cryoablation may deliver a better treatment outcome in unresectable advanced HCC. Although interest has been focused on the use of the drug as adjuvant treatment after cryoablation, no such data have been established to date in HCC. In this paper, we report the results of our prospective study conducted to evaluate the efficacy and acceptable tolerability of sorafenib as adjuvant treatment after cryoablation in the treatment of unresectable HCC.

MATERIALS AND METHODS

This was a single-center, open-label, and single-arm prospective study. It was approved by the Ethic Committee of Tianjin Medical University Cancer Institute & Hospital and informed consent was obtained from all patients before the treatment.

Patients' Eligibility

HCC diagnosis was based on increased serum α-fetoprotein (α-FP) level >400 ng/ml and typical imaging appearance according to the criteria of the European Association of Study of the Liver[8]. Fine-needle aspiration or biopsy was conducted in the case of diagnostic uncertainty. The unresectable was defined as being not treatable by surgical resection due to the presence of portal hypertension or by liver transplant due to the patient’s disease severity being outside UNOS/Milan criteria (http://www.unos.org/) or due to comorbid conditions prohibiting a surgical procedure. The Barcelona clinic liver
cancer (BCLC) classification was used to identify tumor stage\(^6\). Inclusion criteria included BCLC stage A, B or C; Eastern Cooperative Oncology Group (ECOG) performance status scores of 0, 1 or 2; Child-Pugh (CP) score of A or B; life expectancy of at least three months. Before the treatment, all patients had at least one unidimensionally measurable lesion by computed tomography (CT) scan. The largest is limited to less than 6 cm and no more than 5 lesions. Portal thrombosis and the prior treatment such as transarterial chemoembolization (TACE) and chemotherapy were not exclusion criteria.

**Percutaneous Cryoablation**

The cryoablation system we used is Cryocare System (Endocare, Irvine, CA). After CT scan determining the most favorable percutaneous approach, cryoprobes (1.7 mm, 2 mm, 3 mm, 3.8 mm; 12-15 cm long) were inserted into the tumor and the probe tip was advanced to the distal margin of the targeted lesion by a modified Seldinger technique. CT was used to verify placement of the multiple cryoprobes. The tumors were frozen at maximum flow rate for about 15 min, thawed for 5 min and then refrozen. Two cycles (consisting of freezing-heating-freezing) were used for each procedure. Duration of the freezing time was based on growth of the iceball relative to the tumor (mean, 15 min; range, 10-20 min). Limited unenhanced CT scans were obtained approximately every 3 min during the freezing time using 1.25 mm collimation to accurately monitor growth of the iceball. The probes were removed after thawing with helium and the inserting sites were pressed for several minutes. CT scan was performed to determine the effect of cryoablation.

**Sorafenib Administration and Dose Modification**

All patients received sorafenib orally 400 mg twice daily (bid, approximately 12 h apart) on a continuous dosing schedule with 4 weeks counting as a single cycle started at the day of first percutaneous cryoablation. Discontinuation and dose reduction were based on tolerance. Side effects of sorafenib were determined via the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 3.0. For grade 3 of 4 toxicities, sorafenib was withdrawn until the toxicities changed to grade 2 or lower. Afterward, sorafenib was reintroduced at a dose of 200 mg twice daily and escalated back to 400 mg twice daily if well tolerated. Treatments continued until disease progression or intolerable toxicities appeared, or until a patient refused further treatment.

**Assessment of Tumor Response**

Patients were observed regularly every 2 weeks when they were receiving sorafenib. During the follow-up period after they were discontinued from sorafenib, assessment was performed every 4 weeks. Tumor response was assessed every 2 cycles (8 weeks) according to the new Response Evaluation Criteria in Solid Tumor (RECIST)\(^8\) by an independent radiologist, with a hepatologist as co-investigator, until disease progression was confirmed by comparison of pre- and post-treatment CT scans.

**Statistical Analysis**

Continuous variables were summarized as medians and ranges, and categorical variables as percentages. Patients’ basal characteristics were analyzed by descriptive statistical methods. Time to progression (TTP) and overall survival (OS), both calculated from the date of cryoablation until objective disease progression or death, respectively, were estimated using the Kaplan-Meier method and compared with the log-rank test. Cox proportional hazards model was used for assessment of the independent predictors for TTP and OS with adjustment for confounding variables. All variables with \(p<0.05\) on univariate analysis were introduced into the subsequent multivariate analysis. All analyses were performed using the statistical software package SPSS (version 15.0; SPSS Inc., Chicago, IL).

**RESULTS**

**Patient Characteristics**

From June 2007 to June 2009, seventy-eight patients with unresectable HCC were recruited in this study. Table 1 shows the demographic data of these patients. The median age was 52 years (range, 22-81 years), and 85.9% were men. According to BCLC staging classification, 9 patients were at stage A, 24 patients were at stage B and 45 patients were at stage C. Thirty-two patients had not received any therapies for HCC at the entry time. In 46 patients who had received previous treatment, the most frequent procedures were TACE/TAE (n=33) with chemotherapeutic regimens including cisplatin and 5-fluorouracil; 8 patients had undergone prior systemic chemotherapeutic regimens including cisplatin, 5-fluorouracil, mitomycin-C (FAM) and adriamycin; 12 patients had experienced two or more therapeutic treatments. No patients had received previous surgery.

**Tumor Characteristics**

Percutaneous cryotherapy was used to treat 90 tumors in 78 patients during 96 procedures. Patients had an average of 2.68±0.64 tumors treated. The average size of the tumors treated was 4.6±1.1 cm. The largest tumor treated per patient was 7.5±1.8 cm. No patient had more than a total of 4 tumors treated.

**Treatment Efficacy**

The median time of follow-up was 11.3 months (range, 1.6-24 months). Sixty-six cases were evaluable for objective responses. Nine patients discontinued sorafenib before the first evaluation because of serious adverse events, and three refused further treatment because of the other diseases. Twenty-eight patients had the dose reduced by half during the treatment cycles because of treatment-related toxicities. Patients who had achieved complete response (CR), partial response (PR), or stable disease (SD) were defined as achieving clinical benefits. Of the 66 evaluable patients, 5 achieved CR, and 34 achieved SD, making the disease control rate (DCR) of 50% by intention to treat (ITT) analysis and 59% by per-protocol analysis. Progressive disease (PD) was observed in 27 patients with sorafenib duration of 4.9 months (range, 2.2-11.5 months), but none achieved CR.
Table 1. Patient characteristics at baseline

| Items                               | n (%) |
|-------------------------------------|-------|
| Age (y)                             |       |
| Median                              | 52    |
| Range                               | 22–81 |
| Sex                                 |       |
| Male                                | 67 (85.9%) |
| Female                              | 11 (14.1%) |
| Etiology of liver disease           |       |
| HBV                                 | 63 (80.8%) |
| HCV                                 | 5 (6.4%) |
| Other                               | 2 (2.6%) |
| ECOG score                          |       |
| 0                                   | 31 (39.8%) |
| 1                                   | 43 (55.1%) |
| 2                                   | 4 (5.1%) |
| Child–Pugh class                    |       |
| A                                   | 53 (67.9%) |
| B                                   | 25 (32.1%) |
| Liver cirrhosis                     |       |
| Present                             | 61 (78.2%) |
| Absent                              | 17 (21.8%) |
| Antiviral therapy                   |       |
| Ongoing                             | 29 (38.7%) |
| Pre-emptive                         | 12 (16.0%) |
| Absent                              | 34 (45.3%) |
| Serum α-FP (ng/ml)                  |       |
| <400                                | 41 (52.6%) |
| ≥400                                | 37 (47.4%) |
| BCLC stage                          |       |
| A                                   | 9 (11.5%) |
| B                                   | 24 (30.8%) |
| C                                   | 45 (57.7%) |
| Intrahepatic tumor morphology       |       |
| Uninodular tumor                    | 5 (6.4%) |
| Multinodular tumor                  | 32 (41.0%) |
| Massive tumor                       | 41 (52.6%) |
| Invasion of major vessels           |       |
| Portal vein invasion                | 32 |
| Hepatic vein invasion               | 5 |
| Inferior vena cava invasion         | 1 |
| Distant metastases                  |       |
| Present                             | 42 (53.8%) |
| Absent                              | 36 (46.2%) |
| Metastasis site(s)                  |       |
| Lung                                | 28 (35.9%) |
| Bone                                | 3 (3.8%) |
| Peritonium                          | 3 (3.8%) |
| Adrenal                             | 6 (7.7%) |
| Brain                               | 2 (2.6%) |
| Previous treatment(s)               |       |
| None                                | 32 (41.0%) |
| Surgery                             | 0 |
| RFA                                 | 3 (4.8%) |
| TACE                                | 33 (42.3%) |
| Radiotherapy                        | 2 (2.6%) |
| Systemic chemotherapy               | 8 (10.3%) |

RFA: Radiofrequency ablation; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

Survival Analysis

During the entire follow-up period, median TTP and OS for all enrolled patients were 6.6 months (95% CI: 1.6–9.8) and 12.2 months (95% CI: 4.5–24) respectively. Median TTP and OS for patients with low α-FP (<400 ng/ml) were 7.1 months (95% CI: 2.1–9.8) and 13.1 months (95% CI: 5.5–24). For high α-FP (≥400 ng/ml) patients, median TTP and OS were 5.2 months (95% CI: 1.6–8.1) and 10.1 months (95% CI: 4.5–19) respectively. There was statistical difference between TTP (P=0.001) and OS (P=0.009). Of the 39 patients who had demonstrated clinical benefits of PR and SD in this study, the median TTP and OS were 7.1 months (95% CI: 2.1–9.2) and 13.6 months (95% CI: 4.8–22.1), respectively. In contrast, with respect to the 27 patients who had PD, their median TTP and OS were 5.2 months (95% CI: 1.9–8.4) and 10.8 months (95% CI: 4.2–19.8), respectively. Of note, there were significant differences in TTP (P=0.003) and OS (P=0.001) between patients who demonstrated clinical benefits and patients who did not.

Factors Predictive of Clinical Benefits

Table 2 lists the results of univariate analysis and multivariate analysis of potential clinical factors predictive of clinical benefits with cryoablation and sorafenib treatment. Serum α-FP <400 ng/ml (P=0.023), no portal vein invasion (P=0.018), absence of extrahepatic metastasis (P=0.043), in particular the absence of lung metastasis (P=0.011), significantly predicted clinical benefits in this study. However, all other patients and tumor characteristics, including age, sex, ECOG performance status, Child–Pugh class, ongoing antiviral therapy, BCLC stage, and prior systemic treatment had no effect on clinical benefits. Multivariate analyses showed that serum α-FP <400 ng/ml (P=0.031) was a significant independent factor.

Adverse Events

Table 3 shows the details of treatment-related nonhematologic and hematologic toxicities in the patients. With regard to nonhematologic toxicities, diarrhea was the most commonly encountered toxicity, followed by fatigue and skin rash/desquamation. The commonest grade 3 or 4 nonhematologic toxicities were diarrhea and hand-foot skin reaction (HFSR). Hemorrhagic complications occurred in 6 patients, including upper gastrointestinal bleeding in 4 patients because of disseminated intravascular coagulopathy (DIC) in 2 patients. With respect to hematological toxicities, thrombocytopenia was the commonest toxicity and was also the most frequently encountered grade 3 or 4 toxicity. Cryoablation-related complications were also observed. Atelectasis in the right lung base developed in 4 patients with right liver lobe cryoablation because of injury to the right lung and right hemidiaphragm due to the close proximity of the liver to the right lung. Two Patients developed mild form of acute respiratory distress syndrome (ARDS) at 3 and 9 days after the cryoablation. Three patients developed bile duct strictures after the cryoablation and the problem was partly corrected with placement of several stents into the bile ducts. Two patients developed bilomas and required repeated drainage procedures. One patient developed a fistula between the liver and colon after the cryoablation.

Outcomes of Patients with TACE

Thirty-three patients who had received TACE procedure...
Table 2. Best response assessment according to RECIST assessment

| Best response                        | No. | ITT (%) | Assessable (%) | Duration of sorafenib therapy (months) |
|--------------------------------------|-----|---------|----------------|---------------------------------------|
|                                      | All | ≥80% C  | All ≥80% C      | All ≥80% C                            |
| Complete response (CR)               | 0   | 0       | 0              | 0                                     |
| Partial response (PR)                | 4   | 6.4     | 7.8            | 7.6                                   |
| Stable disease (SD)                  | 28  | 43.6    | 54.9           | 51.5                                  |
| Progressive disease (PD)             | 10  | 34.6    | 19.6           | 40.9                                  |
| Not assessable                       | 9   | 15.4    | 17.6           |                                       |

Table 3. Clinical variables predicting clinical benefits

| Variable                        | Clinical benefits (n=39), No. of patients (%) | No clinical benefits (n=27), No. of patients (%) | p     | ρ  |
|---------------------------------|-----------------------------------------------|-----------------------------------------------|-------|---|
| Age (y)                         |                                               |                                               | 0.421 | 0.321 |
| Median                          | 52                                            | 52                                            |       |   |
| Range                           | 30-79                                         | 22-81                                         |       |   |
| Sex                             |                                               |                                               | 0.613 | 0.554 |
| Male                            | 37 (95)                                       | 23 (85)                                       |       |   |
| Female                          | 2 (5)                                         | 4 (15)                                        |       |   |
| ECOG scores                     |                                               |                                               | 0.521 | 0.642 |
| 0 or 1                          | 31 (79)                                       | 18 (67)                                       |       |   |
| 2                               | 8 (21)                                        | 9 (33)                                        |       |   |
| Hepatitis B status              |                                               |                                               | 0.141 | 0.215 |
| Carrier                         | 36 (92)                                       | 24 (89)                                       |       |   |
| Noncarrier                      | 3 (8)                                         | 3 (11)                                        |       |   |
| Child–Pugh class                |                                               |                                               | 0.252 | 0.365 |
| A                               | 23 (59)                                       | 18 (67)                                       |       |   |
| B                               | 16 (41)                                       | 9 (33)                                        |       |   |
| Liver cirrhosis                 |                                               |                                               | 0.589 | 0.612 |
| Present                         | 25 (64)                                       | 19 (70)                                       |       |   |
| Absent                          | 14 (36)                                       | 8 (30)                                        |       |   |
| Ongoing antiviral therapy       |                                               |                                               | 0.398 | 0.426 |
| Present                         | 17 (44)                                       | 8 (28)                                        |       |   |
| Absent                          | 22 (56)                                       | 19 (72)                                       |       |   |
| Over 80% cryoablation rate      |                                               |                                               | 0.013 | 0.021 |
| Present                         | 32 (82)                                       | 10 (37)                                       |       |   |
| Absent                          | 7 (18)                                        | 17 (63)                                       |       |   |
| Serum α-FP <400 ng/ml           |                                               |                                               | 0.023 | 0.031 |
| Present                         | 29 (74)                                       | 10 (37)                                       |       |   |
| Absent                          | 10 (26)                                       | 17 (63)                                       |       |   |
| Portal vein invasion            |                                               |                                               | 0.018 | 0.316 |
| Present                         | 11 (28)                                       | 20 (74)                                       |       |   |
| Absent                          | 28 (72)                                       | 7 (26)                                        |       |   |
| Hepatic vein invasion           |                                               |                                               | 0.059 | 0.112 |
| Present                         | 17 (44)                                       | 16 (59)                                       |       |   |
| Absent                          | 22 (56)                                       | 11 (41)                                       |       |   |
| Extrahepatic spread             |                                               |                                               | 0.043 | 0.251 |
| Present                         | 8 (21)                                        | 17 (63)                                       |       |   |
| Absent                          | 31 (79)                                       | 10 (37)                                       |       |   |
| Lung metastasis                 |                                               |                                               | 0.011 | 0.178 |
| Present                         | 3 (8)                                         | 13 (48)                                       |       |   |
| Absent                          | 36 (92)                                       | 14 (52)                                       |       |   |
| Prior systemic treatment        |                                               |                                               | 0.889 | 0.632 |
| Present                         | 25 (64)                                       | 16 (59)                                       |       |   |
| Absent                          | 14 (36)                                       | 11 (41)                                       |       |   |

To the lung, abdominal cavity lymph node, bone, adrenal gland.

before the cryoablation were included in the analysis. Although the clinical benefits were higher (43.2% vs 36.5%) and the OS longer (11.2 months vs 9.8 months) compared to non-TACE patients, there were no significant differences (P=0.225 and P=0.154, respectively). In addition, there were no significant differences between TACE and non-TACE
patients with regard to grade 3 or 4 hematologic toxicities (33.3% vs 23.4%; P=0.118) and grade 3 or 4 nonhematologic toxicities (51.3% vs 46.2%; P=0.297) after sorafenib treatment.

**DISCUSSION**

In this prospective study, we analyzed the combination treatment of HCC demonstrated fairly good efficacy and acceptable tolerability.

Cryotherapy is most effective for tumors smaller than 5 cm. The reported 2-year survival rate after cryoablation of HCC was 30% to 60%.[11, 12] Combinations of therapies to potentiate the size of the ablation zone and more effectively treat intermediate and large tumors have been devised. Cryoablation in combination with percutaneous ethanol ablation has been shown by Xu, et al. to be a viable alternative treatment method for HCC patients with large, and unresectable tumors. In 105 unresectable tumors of 65 patients ranging from 4.8-15 cm, only 3 developed an ablation site recurrence over a follow-up period of 5–21 months.[13]

The difficulty in treating moderate to large tumors is often attributed to the powerful heat-sink effect of tumor blood flow, which draws heat away from the tumor site, substantially limiting the size and uniformity of tumor destruction.[14] Thus, concomitant administration of anti-vascular or antiangiogenic pharmaceutical agents capable of reducing tumor blood flow might be of considerable clinical value. One potential candidate is the new group of antiangiogenic agents that have been developed to block vascular endothelial growth factor (VEGF) receptor signaling and subsequent tumor angiogenesis.[15] In this study, all patients received sorafenib orally 400 mg twice daily on a continuous dosing schedule at the second day after percutaneous cryoablation. The 6.4% response rate and 43.6% disease-stabilization rate in this study are encouraging and comparable to the results reported in the phase III Sorafenib HCC Assessment Randomized Protocol (SHARP) trial and the latest Asian phase III trials.[16] All patients enrolled in these two pivotal trials had Child-Pugh A cirrhosis with favorable clinical parameters.

However, in daily clinical practice in most Asian countries, the patients with advanced HCC who are encountered are HBV carriers with suboptimal liver function, often Child-Pugh B or C cirrhosis. Most patients enrolled in our study had poor overall prognosis because of worsening underlying cirrhosis (Child-Pugh class B) or in infiltrating, far-advanced HCC. A recent phase 2 open-label study of single agent sorafenib in treating advanced HCC with similar study populations like us showed 8% response rate and 18% disease-stabilization rate.[17] The higher disease-stabilization rate and DCR rate observed in our study may be contributed to the necrosis induced by cryoablation and also sorafenib. Although RECIST[18] were utilized to measure tumor response, it may not be the best indicator for the treatment of this study, and enhances tumor stability rather than tumor shrinkage.[19] Cryoablation can induce coagulation necrosis. In addition, Sorafenib is also better related to the tumor necrosis documented in many patients, as has been demonstrated in studies with other biological agents, such as sunitinib and imatinib. New response criteria combining tumor density on contrast enhanced CT, as a measure of tumor necrosis, with conventional dimension measurement will probably allow better characterization of cryoablation and sorafenib response in HCC[19].

Enhancement of the efficacy of sorafenib by its use in combination with cryoablation also has been observed with a median TTP of 7.6 months and a median OS of 12.2 months. The results were encouraging compared with the previous studies with sorafenib monotherapy[7] but less satisfactory than that of the randomized phase II study of sorafenib plus doxorubicin with a median TTP of 8.5 months and a median OS of 14.0 months[20]. This is expected, as the study population in our study had poor overall prognosis because of advanced tumors. In patients achieved PR, the duration of sorafenib therapy was 7.2 months whereas in 34 patients showing the best SD responses, the median duration of sorafenib therapy was 5.1 months (P=0.032). This interaction is likely mediated by the well-documented antiangiogenic properties of sorafenib. A reduction in blood flow could eliminate heterogeneous “heat sinks” that can occur in tumors of all sizes, thereby improving uniformity of cold deposition during cryoablation and potentially reducing the rate of incomplete treatment. TACE may also decrease the blood flow to the tumor. One advantage of performing TACE before cryoablation is a possible reduction in postoperative bleeding, as well as an increase in the rate of tumor ablation[21]. But in this study, there were no significant differences in terms of clinical benefits and OS between TACE and non-TACE before cryoablation procedure. It may be because of the possibility of rapid recanalization or collateralization after chemoembolization.

The toxicity pattern we observed was similar to that seen in previous clinical trials[22-23] with dermatologic and GI symptoms being common adverse events. Although further treatment was discontinued in 29 patients and modified in 28 patients because of clinical toxic effects, most toxicities were transient and easily resolved. Most initial dose reductions occurred during the first treatment cycle, suggesting the importance of assessing the appearance of toxic effects during early phases of sorafenib therapy.

Compared with the results of the reported studies of sorafenib monotherapy[7], there was a notably high incidence of liver function derangement in our present patient cohort. These results were most likely related to a high proportion of patients with suboptimal baseline liver function as a result of more advanced cirrhosis in this study and the destruction of tumor cells induced by cryoablation. The commonest liver function derangement observed was the change in transaminase levels. The majority of the liver derangements induced by cryoablation and sorafenib were transient and improved after stopping sorafenib. Furthermore, there are recent reports regarding the reactivation of hepatitis B infection in chronic hepatitis B carriers who received targeted therapy alone for the treatment of underlying malignancy[24, 25]. Thus, it is possible that the administration of sorafenib will likewise lead to the reactivation of the underlying hepatitis B infection and...
result in worsening liver function, because most patients with advanced HCC in Asia are chronic hepatitis B carriers. In this study, the HBV infection rate was as high as 80.8%. As two episodes of variceal bleeding developed during treatment, screening and prophylaxis of gastroesophageal varices are necessary at the time of treatment entry, although variceal bleeding is likely a progressive complication of portal hypertensive cirrhosis, and not directly associated with sorafenib use.

The major limitation of the current study is its nonrandomized design, and we could only compare the results with the other studies[7, 17]. We didn’t compare the patients who had metastasis (53.8%) with the others who had no far metastasis. Also, we did not compare the change of the metastasis sites.

In conclusion, the results of our study demonstrate good efficacy and reasonable tolerability of sorafenib as adjuvant therapy after cryoablation of unresectable HCC. This may because lower tumor burden can increase the efficacy of sorafenib and at the same time, antiangiogenic property of sorafenib may increase the efficacy of cryoablation therapy.

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