Traditional herbal medicine in preventing recurrence after resection of small hepatocellular carcinoma: a multicenter randomized controlled trial

Xiao-feng Zhai¹, Zhe Chen¹, Bai Li¹, Feng Shen², Jia Fan³, Wei-ping Zhou², Yun-ke Yang⁴, Jing Xu⁵, Xiao Qin⁵, Le-qun Li⁶, Chang-quan Ling¹

1. Changhai Hospital of Traditional Chinese Medicine, Second Military Medical University, Shanghai 200433, China
2. Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai 200438, China
3. Liver Cancer Institute, Fudan University, Shanghai 200032, China
4. Department of Traditional Chinese Medicine, Zhongshan Hospital, Fudan University, Shanghai 200032, China
5. Department of Hepatic Surgery, the First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China
6. Department of Hepatobiliary Surgery, Tumor Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China

BACKGROUND: Disease recurrence is a main challenge in treatment of hepatocellular carcinoma (HCC). There is no generally accepted method for preventing recurrence of HCC after resection.

OBJECTIVE: To compare the efficacy of a traditional herbal medicine (THM) regimen and transarterial chemoembolization (TACE) in preventing recurrence in post-resection patients with small HCC.

DESIGN, SETTING, PARTICIPANTS AND INTERVENTIONS: This is a multicenter, open-label, randomized, controlled study, which was undertaken in five centers of China. A total of 379 patients who met the eligibility criteria and underwent randomization were enrolled in this trial. One hundred and eighty-eight patients were assigned to the THM group and received Cinobufacini injection and Jiedu Granule, and the other 191 patients were assigned to the TACE group and received one single course of TACE.

MAIN OUTCOME MEASURES: Primary outcome measures were the annual recurrence rate and the time to recurrence. Incidence of adverse events was regarded as the secondary outcome measure.

RESULTS: Among the 364 patients who were included in the intention-to-treat analysis, 67 patients of the THM group and 87 of the TACE group had recurrence, with a hazard ratio of 0.695 (P = 0.048). Median recurrence-free survival of the patients in the THM and TACE groups was 46.89 and 34.49 months, respectively. Recurrence rates at 1, 2 and 3 years were 17.7%, 33.0% and 43.5% for the THM group, and 28.8%, 42.5% and 54.0% for the TACE group, respectively (P = 0.026). Multivariate analysis indicated that the THM regimen had a big advantage for prolonging the recurrence-free survival. Adverse events were mild and abnormality of laboratory indices of the two groups were similar.

CONCLUSION: In comparison with TACE therapy, the THM regimen was associated with diminished risk of recurrence of small-sized HCC after resection, with comparable adverse events.

TRIAL REGISTRATION IDENTIFIER: This trial was registered in the Chinese Clinical Trial Registry with the identifier ChiCTR–TRC-07000033.

KEYWORDS: hepatocellular carcinoma; recurrence; traditional Chinese medicine; transarterial chemoembolization; randomized controlled trial

DOI: 10.3736/jintegrmed2013021
Received February 8, 2013; accepted February 27, 2013.
Open-access article copyright ©2013 Xiao-feng Zhai et al.
Correspondence: Chang-quan Ling, MD, Professor; Tel: +86-21-81871551; E-mail: lingchangquangmail.com

1 Introduction

Hepatocellular carcinoma (HCC), a common type of primary liver cancer (PLC), is a malignant disease with the fifth highest incidence and the third highest mortality worldwide[1,2]. An estimated 748 300 new PLC cases and 695 900 cancer deaths occurred worldwide in 2008[3,4]. Currently, liver resection remains the most effective treatment for HCC. Advancements in early diagnosis of PLC and operative techniques are steadily improving PLC patient outcomes after liver resection, such that the 5-year survival rate after resection can exceed 50%[3,5]. However, long-term survival rate of patients with PLC is still far from satisfactory due to a high incidence of post-resection recurrence (more than 70% in 5 years), which may be the main cause of poor prognosis[3,5]. Resection of small HCC — one single tumor less than 5 cm in diameter or two tumors in the same lobe less than 5 cm in total diameter — shows better prognosis; nevertheless, it also faces a high rate of recurrence, reaching 50% within 5 years[6-7].

Various methods have been employed clinically to prevent post-resection recurrence, including transarterial chemoembolization (TACE)[8], adoptive immunotherapy[9], and interferon therapy[10]. However, results of meta analyses indicate that none of these therapies show sufficient evidence in reducing the recurrence rate[4,11,12].

The usage of complementary and alternative medicine (CAM) among patients with cancer in Western countries has been increasing in recent years. Across Europe, 40% of cancer patients utilize some form of CAM, mostly herbs[13], and up to 60% of cancer patients in the United Stated use herbal supplements during or after chemotherapy[14]. Traditional herbal medicine (THM), as a main CAM therapy, has already become a commonly used treatment for cancer in China[15] due to its unique advantages in controlling symptoms[16], improving quality of life[17], and preventing disease recurrence.

From the practice around China and East Asia, we can find that participation of the THM in comprehensive regimen is one of the important ways to improve the curative effect of HCC. THM should be and can be used throughout the whole course of prevention and treatment of HCC[15].

We have been working on HCC treatment with THM for decades. Our rich clinical experience has yielded a comprehensive treatment regimen that includes Cinobufacini Injection (aqueous extract from Bufo bufo gargarizans Cantor) and Jiedu Granule (a compound herbal medicine). Previous studies have demonstrated that the herbs in this regimen exhibit significant anticancer effects in both in-vitro[18-21] and clinical studies[22-24].

This regimen has been utilized for preventing tumor recurrence in post-operative HCC patients for more than 10 years, but it still lacks support from comparative studies involving other approaches. In order to collect more evidence for such support, we conducted a randomized controlled trial based on this THM regimen to verify its efficacy and safety. Owing to the absence of standard adjuvant therapy, many Chinese hepatobiliary surgeons use TACE to prevent recurrence, which is performed on at least two-thirds of HCC patients after resection. In light of this situation in China, we chose TACE as a control, and designed a multicenter randomized controlled trial that was conducted in five hospitals located in the East and Southwest China, in order to compare the effects of the THM regimen with TACE in preventing recurrence of HCC after resection.

2 Materials and methods

2.1 Study patients

This multicenter, randomized, controlled study was undertaken at five centers of China, including three in Shanghai located in the East China (Shanghai Changhai Hospital, Eastern Hepatobiliary Surgery Hospital and Zhongshan Hospital) and two in Nanning, Guangxi Zhuang Autonomous Region located in the Southwest China (the First Affiliated Hospital of Guangxi Medical University and Tumor Hospital of Guangxi Medical University). Patients were enrolled from April 2006 to May 2010.

2.1.1 Inclusion criteria

Patients with HCC of either gender, aged between 18 and 75 years who received radical hepatectomy within three months and diagnosed by histopathological test were screened. At the time of surgery, all patients were routinely checked by intra-operative ultrasonography to verify that all tumors had been extirpated. Hepatic resection was considered radical only when the histologic resection margin was clear and the postoperative computed tomography (CT) scan showed no residual tumors. Other eligibility criteria for inclusion included: (1) single tumor with diameter less than 5 cm on histopathological examination; (2) Eastern Cooperative Oncology Group (ECOG)[25] performance status less than 3.

Journal of Integrative Medicine 91 March 2013, Vol.11, No.2
2.1.2 Exclusion criteria
Patients with either of the following conditions were excluded: (1) hepatic insufficiency (Child-Pugh class C); (2) existing recurrence or metastasis; (3) treatment with other antineoplastic medication after resection; (4) renal insufficiency (serum creatinine ≥ 133 μmol/L); (5) participating in other clinical trials.

2.2 Ethics
The study protocol was approved by the ethics committee of each participating center. Patients were informed of the study procedure details and agreed to participate by signing written informed consent. This study was conducted and reported in conformity with the CONSORT Statement[26] and in accord with the Declaration of Helsinki (2008 revised edition).

2.3 Study design and randomization
In each center, patients were randomly assigned to receive either THM regimen (THM group) or TACE therapy (TACE group) in a 1:1 ratio. Randomization was performed in each center by using a permuted-block design, and stratified according to clinical center in blocks of eight. The randomization code was generated by an external statistician before the trial was initiated, and was kept by a research assistant before it was assigned to patient who entered the study. Treatment procedures could not be blinded to either doctors or patients because of the differences of administration methods between the THM regimen and TACE (THM drugs were administered orally and intravenously, while TACE was performed transarterially). The statistician who evaluated the study outcomes was blinded to treatment regimen. Data of the study were collected by clinical researchers using the unified case report form.

We estimated that the recurrence would occur in 30% of patients within one year after resection in the control group[6,27], so a sample size of 283 was deemed sufficient for the detection of a 50% reduction in this outcome calculated by computer software PASS 2000, with a type I error (two-sided) of 5% and a power of at least 90%. On the assumption of a rate of 20% loss to follow-up, we established a target sample size of 340.

2.4 Interventions
Patients were recruited from each center’s outpatient department. There was a primary investigator in each center who was in charge of screening and making the decision of enrollment. Patients assigned to the THM group received treatment in the hospital immediately after randomization. This comprehensive regimen contained two drugs, Cinobufacini Injection (Jinchan Biochemistry Company Ltd., Huaibei, China) and Jiedu Granule (Tianjiang Pharmaceutical Co., Ltd., Jiangyin, China). Patients received Cinobufacini Injection at a dose of 50 mL per day by intravenous infusion for 10 d as one course, repeating the course every three months for up to 12 months. Jiedu Granule 4.5 g (mixed aqueous extraction of four herbs: the root of Actinidia valvata Dunn (Mao-ren-shen), the root of Salvia chinensis Benth (Shi-jian-chuan), the tuber of Pseudobulbus cremastrae seu Pleiones (Shan-chi-gu) and the gizzard membrane of Gallus gallus domesticus Brisson (Ji-nei-jin) with the ratio of 3:3:1:1 in dosage) was taken orally twice a day for 6 months.

Patients in the control group received one single course of TACE therapy. After conventional celiac angiography, a catheter was inserted superselectively into the hepatic artery and the adjuvant hepatic arterial infusion chemotherapy was administered by means of the catheter, including a solution that contained 10 mg of pirarubicin (THP; Main Luck Pharmaceuticals Inc., Shenzhen, China), and 10 mg of mitomycin C (Kyowa Hakko Kogyo Co Ltd, Kyodo, Japan) mixed with iiodized oil (Aulnay-Sous-Bios, France).

2.5 Outcome measures
2.5.1 Follow-up program
Clinical assessment was performed at the time of screening and randomization at baseline, and study follow-ups were scheduled every three months after randomization. The follow-up program included an ultrasonographic examination of the liver and the epigastrium, a serum α-fetoprotein (AFP) assay and safety assessment. The record of all actual arrival time was used as estimation for the adherence to the study. Dynamic CT and chest radiography were performed every 6 months. Suspected recurrence or distant metastasic lesions were confirmed by another imaging method such as dynamic contrast enhanced magnetic resonance imaging (MRI). We defined recurrence as the appearance of new lesions with typical radiological appearances of HCC verified by both CT and MRI[26], or confirmed by histologic/cytologic examination.

2.5.2 Primary outcome measures
The primary outcome measures were time to the first recurrence and annualized recurrence rate measured from the date of randomization.

2.5.3 Secondary outcome measure
The secondary outcome measure was safety assessment which was conducted in all patients receiving at least one course of treatment, with the use of version 3.0 of the Common Terminology Criteria for Adverse Events (CTCAE V3.0)[28].

2.6 Study monitoring
This study was monitored by an independent monitoring committee appointed by the Ministry of Science and Technology of China. Study data were collected by the investigators and entered into an online database administrated by the Department of Clinical Pharmacology, Affiliated Hospital of Nanjing University of Chinese Medicine, China.
2.7 Statistical analyses

The analysis was performed according to the intention-to-treat (ITT) principle. According to the guidance from the International Conference on Harmonization E9 Expert Working Group[29], there were a limited number of circumstances that might lead to excluding randomized patient from the full analysis set including eligibility violations, failure to take at least one dose of the drugs and lack of any data after randomization. A secondary analysis was based on the treatment actually received.

Recurrence rate was estimated by using Kaplan-Meier method, and the difference in the two groups was compared by using log-rank test. Hazard ratio and 95% confidence interval (CI) were calculated by using Cox proportional-hazard model. Univariate screening and multivariate analyses were performed to evaluate the interaction between the baseline characteristics and the effect of THM regimen by using Cox proportional-hazards model followed by a stepwise variable-selection procedure[30]. All the statistical analyses were performed by using SPSS software, version 15.0. All the statistical tests were two-tailed. P values of less than 0.05 were considered to indicate significance.

3 Results

3.1 Characteristics of the patients

From April 2006 to May 2010, a total of 1 125 patients were screened. Out of these patients, 379 met the inclusion eligibility criteria and underwent randomization, with 188 patients assigned to the THM group and 191 patients assigned to the TACE group. Four patients (3 in the THM group and 1 in the TACE group) who withdrew the informed consent and did not receive any treatment were excluded from the safety analysis and ITT analysis. Another 1.3% (5/379) patients did not meet the inclusion eligibility criteria in the additional examination after randomization (two with incorrect histological diagnosis and three had already had recurrence), and 1.6% (6/379) patients who had severe protocol violation were excluded from the ITT analysis. A total of 29 patients were excluded from per-protocol analysis mainly because they were lost to follow-up or had protocol violations. The flow of patients through the study is shown in Figure 1. The baseline characteristics of the patients were well balanced between the two treatment groups (Table 1).

Figure 1 Enrollment, randomization, and follow-up of the patients
THM: traditional herbal medicine; TACE: transarterial chemoembolization.
### Table 1  Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>THM group (n = 180)</th>
<th>TACE group (n = 184)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>0.194</td>
</tr>
<tr>
<td>&lt; 60 years</td>
<td>154 (85.56)</td>
<td>148 (80.43)</td>
<td></td>
</tr>
<tr>
<td>≥ 60 years</td>
<td>26 (14.44)</td>
<td>36 (19.57)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.053</td>
</tr>
<tr>
<td>Male</td>
<td>147 (81.67)</td>
<td>164 (89.13)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>33 (18.33)</td>
<td>20 (10.87)</td>
<td></td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
<td>0.576</td>
</tr>
<tr>
<td>0</td>
<td>119 (66.11)</td>
<td>117 (63.59)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>60 (33.33)</td>
<td>64 (34.78)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 (0.56)</td>
<td>3 (1.63)</td>
<td></td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td></td>
<td></td>
<td>0.368</td>
</tr>
<tr>
<td>A</td>
<td>166 (92.22)</td>
<td>174 (94.57)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>14 (7.78)</td>
<td>10 (5.43)</td>
<td></td>
</tr>
<tr>
<td>Serum AST</td>
<td></td>
<td></td>
<td>0.965</td>
</tr>
<tr>
<td>&lt; 100 U/L</td>
<td>164 (91.11)</td>
<td>169 (91.85)</td>
<td></td>
</tr>
<tr>
<td>≥ 100 U/L</td>
<td>13 (7.22)</td>
<td>12 (6.52)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (1.67)</td>
<td>3 (1.63)</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
<td></td>
<td>0.054</td>
</tr>
<tr>
<td>Presence</td>
<td>93 (51.67)</td>
<td>102 (55.44)</td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>79 (43.89)</td>
<td>81 (44.02)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (4.44)</td>
<td>1 (0.54)</td>
<td></td>
</tr>
<tr>
<td>Diameter of tumor</td>
<td></td>
<td></td>
<td>0.060</td>
</tr>
<tr>
<td>≤ 2 cm</td>
<td>19 (10.56)</td>
<td>32 (17.39)</td>
<td></td>
</tr>
<tr>
<td>2-5 cm</td>
<td>161 (89.44)</td>
<td>152 (82.61)</td>
<td></td>
</tr>
<tr>
<td>Microvascular invasion</td>
<td></td>
<td></td>
<td>0.087</td>
</tr>
<tr>
<td>Presence</td>
<td>16 (8.89)</td>
<td>27 (14.67)</td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>164 (91.11)</td>
<td>157 (85.33)</td>
<td></td>
</tr>
<tr>
<td>Edmondson grade</td>
<td></td>
<td></td>
<td>0.527</td>
</tr>
<tr>
<td>I, II</td>
<td>92 (51.11)</td>
<td>87 (47.28)</td>
<td></td>
</tr>
<tr>
<td>III, IV</td>
<td>79 (43.89)</td>
<td>83 (45.11)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (5.00)</td>
<td>14 (7.61)</td>
<td></td>
</tr>
<tr>
<td>Serum AFP</td>
<td></td>
<td></td>
<td>0.906</td>
</tr>
<tr>
<td>&lt; 30 μg/L</td>
<td>136 (75.56)</td>
<td>140 (76.09)</td>
<td></td>
</tr>
<tr>
<td>≥ 30 μg/L</td>
<td>44 (24.44)</td>
<td>44 (23.91)</td>
<td></td>
</tr>
</tbody>
</table>

THM: traditional herbal medicine; TACE: transarterial chemoembolization; ECOG: Eastern Cooperative Oncology Group performance status; AST: aspartate aminotransferase; AFP: α-fetoprotein.
3.2 Recurrence

When the database was locked on June 30, 2011, among ITT population, recurrence was observed in 67 patients of the THM group (37.22%) and 87 patients of the TACE group (47.28%). Patients in the THM group had longer recurrence-free survival than those in the TACE group. Median recurrence-free survival was 46.89 months in the THM group (95% CI could not be obtained because far less than 50% patients had recurrence), and 34.49 months in the TACE group (95% CI: 25.434 to 43.546). The hazard ratio for recurrence in the THM group, as compared with the TACE group, was 0.695 (95% CI: 0.484 to 0.997; \( P = 0.048 \)), corresponding to a 30.5% reduction in the risk of recurrence. Estimated cumulative recurrence rates of years 1, 2 and 3 were 17.7%, 33.0% and 43.5%, respectively in the THM group and 28.8%, 42.5% and 54.0% in the TACE group, respectively (\( P = 0.026 \) by log-rank test). See Figure 2.

Exploratory univariate and multivariate analyses by using the Cox proportional-hazards model identified 11 baseline characteristics that may be prognostic indicators for recurrence (Table 2). Factors found to be significantly associated with microvascular invasion, Edmondson grade > II and THM therapy. Results of the multivariate analysis showed that serum aspartate aminotransferase (AST) > 100 U/L (hazard ratio, 2.092; 95% CI, 1.211 to 3.615; \( P = 0.008 \)), serum AFP > 30 μg/L (hazard ratio, 1.641; 95% CI, 1.099 to 2.451; \( P = 0.016 \)) and Edmondson grade > II (hazard ratio, 1.461; 95% CI, 1.023 to 2.086; \( P = 0.037 \)) were risk factors for recurrence, while THM therapy was a protective factor (hazard ratio, 0.695; 95% CI, 0.484 to 0.997; \( P = 0.048 \)).

Subgroup analyses indicated that the beneficial effect of THM treatment on recurrence-free survival was consistent in all subgroups defined on the basis of those most relevant prognostic factors. Furthermore this benefit may be more significant in patients without microvascular invasion, or AST lower than 100 U/L, or younger than 60 years old (Figure 3).

3.3 Adverse events

Data of 185 patients in the THM group and 190 in the TACE group were analyzed for treatment-related adverse events. The overall incidence in the TACE group was 51.05%, higher than 35.14% in the THM group (\( P = 0.002 \)). Most adverse events in both groups were of grade 1 (76.96%) or 2 (20.00%) and no grade 4 toxicities were observed. Laboratory abnormalities were the major reaction of adverse events, including liver function abnormalities (i.e., elevated level of serum alanine aminotransferase, AST or total bilirubin) and hematologic (i.e., leucopenia or thromcytopenia) events, and the rates of these abnormalities

![Figure 2](image-url)  
Figure 2 Kaplan-Meier estimates of probability of recurrence after resection, according to different study groups. The hazard ratio for recurrence in the THM group as compared with the TACE group was 0.695 (95% CI: 0.484 to 0.997). THM: traditional herbal medicine; TACE: transarterial chemoembolization; CI: confidence interval.
were similar in the two study groups (Table 3).

Injection site reactions observed in 10 patients of the THM group mainly occurred within 3 d after intravenous infusion of Cinobufacini Injection. Among these patients, 9 had pain, itching or erythema at the skin around the venipuncture point, 1 had more serious symptoms of phlebitis. All these patients were given nursing treatment with external application of 2% magnesium sulfate solution or paste mixed with Jinhuang Powder (an anti-inflammatory traditional Chinese medicine), and all their symptoms were relieved within one week. Five patients had mild diarrhea and 1 had mild facial rash after taking THM.

Compared with patients in the THM group, patients who received TACE were more likely to experience symptoms like fatigue, fever, upper abdominal pain and nausea. None in both the treatment groups discontinued the treatment or withdrew from the study because of adverse events.
Discussion

Small HCC, when detected in the early stage, has a better outcome than those found in the middle or late stages, but patients with small HCC also face a high rate of recurrence, reaching 50% within 5 years [6,27]. As an adjuvant therapy, TACE may have some effect in preventing recurrence. Recent Chinese studies with patients mainly in the early stage showed better results with the use of adjuvant TACE [31] than those without use. But the real effect of post-operative TACE still needs rigorous evaluation. Based on our clinical experience, small HCC often leaves little or no residue of tumor cells in the liver after resection. Chemoembolization may offer very little help in improving prognosis; on the contrary, it may even damage liver function, with overall negative effect. Comprehensive therapy that addresses the patient’s overall physiology rather than only focusing on the liver is becoming more acceptable as an effective means of preventing HCC recurrence after resection [11]. When practiced appropriately, THM is a comprehensive, holistic healthcare modality that aids the body in fighting disease, and improves one’s overall health. THM is a promising tool in future treatments against HCC recurrence.

Jiedu Granule used in this study was a compound extract of four herbs. The active components of these herbs can inhibit tumor proliferation [19-21]. Bufalin, the main effective component of the Cinobufacini Injection, has cytotoxicity against hepatoma cells [32,33], and Cinobufacini Injection is also a conventional drug in treating hepatitis B due to its anti-inflammatory and antiviral actions [34]. So we combined Cinobufacini Injection with Jiedu Granule as one regimen with multiple actions targeting tumor, inflammation, and viral proliferation.

Tumor size is a major factor in determining the prognosis of HCC. In our study, we focused only on patients with small HCC whose resection margin was clearly verified.
by records of operation and histopathological examination. The mean value of tumor diameter was \((3.26\pm 0.08)\) cm in the THM group and \((3.39\pm 0.08)\) cm in the TACE group, with no significant difference.

We also analyzed other important predictors such as microvascular invasion, tumor capsule, cirrhosis, Edmondson grade, serum AST level, serum AFP level, ECOG performance status, age, and Child-Pugh score\(^{[35]}\). These factors were all statistically similar at baseline in the two groups. Presence of microvascular invasion and higher Edmondson grade (> II) were risk factors in univariate analysis; higher AST level, Edmondson grade and AFP level were risk factors in multivariable analysis. Microvascular invasion was excluded from the result of multivariable analysis at the last step of regression, but should remain as an important predictor. After adjusting for all the above variables, THM treatment was still a protective factor for the recurrence-free survival in both univariable and multivariable analyses. This benefit may be more significant in patients without microvascular invasion, or AST less than 100 U/L, or younger than 60 years old in the subsequent subgroup analysis.

The overall percentage of patients who developed treatment-related adverse events was 43.2% in this study, with a higher proportion in the TACE group (51.05%). Adverse events in both groups were mild, and 96.96% of which were grade 1 or 2 as defined by CTCAC V 3.0, and no patient discontinued the treatment or withdrew from the study because of adverse events. Among all the adverse events, 73.48% were laboratory abnormalities such as liver function tests and counts of white blood cells or platelets, mainly because 93.29% patients in this study had background of hepatitis B or liver cirrhosis. Some patients receiving Cinobufacini Injection had injection site reactions. Adverse events after TACE treatment mainly presented as embolism syndrome, and were usually relieved within three days.

There are some limitations of this study. First, due to the relatively long course from resection to recurrence of small HCC, endpoint events we observed may not have been sufficient for obtaining more accurate results. Second, the effective components of the THM regimen were not clearly identified. We have conducted some ongoing research projects focusing on these questions in our institute. Identifying the active ingredients in a traditional herbal regimen can be an extremely difficult process because of the sheer number of chemical constituents involved. Therefore, THM study analyses often regard the treatment as a whole entity, without deconstructing the THM formula into individual active ingredients. There are many difficulties that have to be overcome and many works should be done in the clinical research of the THM, including enhancing the research on rationalization and standardization of cancer treatment program of integrative medicine, strengthening the research on evaluation criteria of real-world effect of integrative medicine in treating cancer, and reinforcing the research on prevention and treatment of postoperative recurrence and metastasis of cancer by integrative medicine\(^{[36]}\).

In conclusion, this study shows that in patients who received surgical resection of HCC with tumor size less than 5 cm in diameter, the THM comprehensive regimen lowered the risk of recurrence, prolonged median recurrence-free survival time, and caused fewer adverse events, as compared with the TACE therapy commonly used at present in China.

5 Acknowledgements

We thank all the patients who participated in this study. We also thank Prof. Zhao-ri Getu and Prof. J. Thomas LaMont for their careful review of this article; Prof. Meng-chao Wu and Prof. Bo Wei for their advice during the design of the protocol; Prof. Weiliang Wang and his group for oversight of the study from the beginning; Prof. Nai-qing Zhao and Prof. Hong Meng for their assistance with statistical design and analyses; Prof. Chao-qin Yu, Prof. Ding-fang Cai, Prof. Wei-ping Yuan and Associate Prof. Xiao-qiang Yue for their helpful advice; Prof. Shuiting Liang, Qing-he Tang, Dr. Qing-bo Lang, Dr. Zhen Sun, and Dr. Yuan-hui Zhang for their help with data collection and management; Prof. Qing-hui Zhou, Dr. Xiao-qian Li, Dr. Hui-juan Dong, Dr. Kai-li Wang and Dr. Hong-juan Yu for their assistance in the study clinics.

6 Funding

Supported by a grant from the Ministry of Science and Technology of China (National Key Technology Research & Development Program, No. 2006BAI04A06).

7 Competing interests

The authors declare that they have no competing interests.

REFERENCES


Submission Guide

Journal of Integrative Medicine (JIM) is a PubMed-indexed, peer-reviewed, open-access journal, publishing papers on all aspects of integrative medicine, such as acupuncture and traditional Chinese medicine, Ayurvedic medicine, herbal medicine, homeopathy, nutrition, chiropractic, mind-body medicine, TaiChi, Qigong, meditation, and any other modalities of complementary and alternative medicine (CAM). Article types include reviews, systematic reviews and meta-analyses, randomized controlled and pragmatic trials, translational and patient-centered effectiveness outcome studies, case series and reports, clinical trial protocols, preclinical and basic science studies, papers on methodology and CAM history or education, editorials, global views, commentaries, short communications, book reviews, conference proceedings, and letters to the editor.

- No submission and page charges
- Quick decision and online first publication

For information on manuscript preparation and submission, please visit JIM website. Send your postal address by e-mail to jcim@163.com, we will send you a complimentary print issue upon receipt.

Editors-in-Chief: Wei-kang Zhao (China) & Lixing Lao (USA). ISSN 2095-4964. Published by Science Press, China.