Application of Traditional Chinese Medicine injection in treatment of primary liver cancer: a review

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Abstract

OBJECTIVE: To investigate the application of Traditional Chinese Medicine Injections (TCMIs) for treatment of primary liver cancer (PLC).

METHODS: A literature review was conducted using PubMed/Medline, Cochrane Library Controlled Clinical Trials Database, China National Knowledge Infrastructure (CNKI), China Scientific Journal Database (CSJD) and China Biology Medicine (CBM). Online websites including journal websites and databases of ongoing trials, as well as some Traditional Chinese Medicine journals that are not indexed in the electronic databases were also searched.

RESULTS: The literature review showed that TCMIs as adjunctive medication for the treatment of PLC could regulate patient immunity, reduce bone marrow suppression, relieve clinical symptoms, and improve quality of life, as well as control disease progression and prolong survival time.

CONCLUSION: Within the limitations of this review, we conclude that application of TCMIs as adjunctive medication may provide benefits for patients with PLC. Further large, high-quality trials are warranted.

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Key words: Traditional Chinese Medicine injection; Carcinoma; Hepatocellular

INTRODUCTION

Primary liver cancer (PLC) is the sixth most common cancer worldwide, and the third most common in China.1 In 2005, the incidence of PLC in China was about 345,000, which accounted for >50% of those worldwide.1 Surgical resection is still the dominant therapy for PLC, but many patients have lost the opportunity for surgery by the time their diagnosis has been confirmed.2 At the same time, the postoperative recurrence rate of PLC is high. As the result, multidisciplinary therapy is essential for PLC patients. In China and some Southeast Asian countries, Chinese herbal medicine has been used to treat malignant tumors, including PLC, for a long time. With the development of Chinese herbal pharmaceutical technology, more Traditional Chinese Medicine injections (TCMIs) have been used for treatment of PLC in China. TCMIs are particularly preferred for elderly patients or those with advanced disease.
It has been revealed that TCMIs have variable effects, such as activity against tumor angiogenesis, induction of cancer cell apoptosis, regulation of immunity, and analgesia.\textsuperscript{3,4} Therefore, TCMIs are becoming popular for antineoplastic therapy. In this paper, we give an overview of the application of TCMIs in PLC.

**METHODS**

**Data sources**
A review of the medical literature to March 13, 2011 was conducted using PubMed/Medline, Cochrane Library Controlled Clinical Trials Database, China National Knowledge Infrastructure (CNKI), China Scientific Journal Database (CSJD) and China Biology Medicine (CBM). Language was limited to English when searching PubMed/Medline and the Cochrane Library. The search terms used were ((primary liver cancer) AND injection). Searching was conducted to identify all relevant studies regardless of publication status. We also searched online websites including journal websites and databases of ongoing trials. In addition, some TCM journals that were not indexed in the electronic databases were retrieved, and articles listed in the references of our retrieved papers or listed in conference proceedings were also included.

**Inclusion criteria**
Articles were included if: 1) all reported cases of PLC were diagnosed by pathological or imaging data; 2) they were about clinical trials of TCMIs for treatment of PLC; 3) TCMIs were used exclusively or in combination with other therapeutic methods; 4) they were all read, and data were extracted based on predefined selection criteria by reviewers — agreement between reviewers for inclusion of studies was recorded.

**RESULTS**
Thirty-four papers on TCMI treatment of PLC were generated from the initial search. Among those TCMIs, 12 commonly used ones which high frequency of use in the literatures were Brucea Javanica oil emulsion injection, Aidi injection, Cinobufacini injection, arsenic trioxide injection, Kang-Lai-Te injection, Xiao'aipin injection, Composite Danshen injection, Composite Sophrae Flavescantis injection, Kang Ai injection, Sheng Mai injection, Shen Qi Fu Zheng injection, and Shen Fu injection. Brief descriptions of the TCMIs mentioned above are listed in Table 1. The clinical application of the TCMIs is outlined below.

**Combination with intervention therapy**
For combined treatment of PLC with intravenous Brucea Javanica oil emulsion injection and transcatheter arterial chemoembolization (TACE), the partial remission (PR) and stable disease (SD) rates and Karnofsky Performance Scale (KPS) score in the treatment group were higher than those in the control group.\textsuperscript{7} Combined treatment of mid to late stage PLC by Brucea Javanica oil emulsion injection and TACE improved quality of life (QOL) and relieved nausea, vomiting, fever, thrombocytopenia, leukocytosis, and renal and hepatic dysfunction;\textsuperscript{8} it also relieved nausea, vomiting and leukocytosis, improving QOL markedly, especially for patients aged >50 years.\textsuperscript{9} You, et al.\textsuperscript{10} found that 10 patients who underwent percutaneous injection of Brucea Javanica oil emulsion injection plus ethanol and B ultrasound therapy all lived for >6 months. Studies on Aidi injection revealed that the PR and SD rates and KPS scores in the treatment group were higher than those in the control group; furthermore, there was also a higher negative conversion rate and descending amplitude of a-fetoprotein (AFP), as well as a high 6-month survival rate.\textsuperscript{11,12}

Daily Cinobufacini injection for 4 weeks improved bone marrow protection, alleviated clinical symptoms, and increased peripheral white blood cells (PWBCs), CD3\textsuperscript{+} and CD4\textsuperscript{+} cells, CD4\textsuperscript{+}/CD8\textsuperscript{+} cell ratio and natural killer (NK) cells.\textsuperscript{13,14} At the same time, there was a significant increase in 6-month survival rate, median survival time, and 1- and 2-year survival rates.\textsuperscript{15,16} As to the antifebrile effect, Intravenous Cinobufacini injection had a superior antifebrile effect than oral indo- methacin after TACE.\textsuperscript{17}

Another study showed that intratumoral arsenic trioxide injection after TACE increased complete remission (CR) and PR rates, and 1-, 2- and 3-year survival rates.\textsuperscript{18} Applying continuous intravenous pump injection of arsenic trioxide in combination with TACE improved QOL and 1-year survival rate.\textsuperscript{19} Kang-Lai-Te injection after TACE increased CR, PR and no change rates,\textsuperscript{20} as well as significantly alleviating the symptoms of hepatalgia, abdominal distension, anorexia and fatigue.\textsuperscript{21} In the Kang-Lai-Te injection group, the descending amplitude of AFP and 6-month survival rate were higher than those in the control group.\textsuperscript{22} For intravenous Shen Fu injection after TACE, KPS score was higher,\textsuperscript{23} and intravenous Shen Qi Fu Zheng injection significantly increased the number of CD3\textsuperscript{+} and CD4\textsuperscript{+} cells, and the CD4\textsuperscript{+}/CD8\textsuperscript{+} cells ratio.\textsuperscript{24} Du Zhiqiang, et al. found that intravenous Cinobufacini injection and Sheng Mai injection after treatment with the Cryocare Surgical System significantly increased CD3\textsuperscript{+}, CD4\textsuperscript{+} and NK cell levels and CD4\textsuperscript{+}/CD8\textsuperscript{+} cell, and there was no evidence of liver injury, such as elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBLI), and reduced albumin (ALB). The recurrence rate of patients with tumor ≥3 cm was significantly lower than that in the control group.\textsuperscript{25}
<table>
<thead>
<tr>
<th>TCMI (Chinese Name)</th>
<th>Drug Source</th>
<th>Main Pharmacological Composition</th>
<th>Drug Function Mechanism</th>
<th>Indications</th>
<th>Side-effects of Drugs</th>
<th>Pharmaceutical Company</th>
<th>Company Location</th>
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<tr>
<td>Aidi Injection</td>
<td>Cantharis, Panax, Astragalus, Acanthopanax</td>
<td>Norcantharidin, Ginsenoside Rg3, Rb2, Acanthopanax polysaccharide, et al.</td>
<td>Inhibiting tumor angiogenesis; inducing apoptosis in tumor cell; improving activity of T lymphocytes and NK cells; reducing radioactive pneumonias; protecting the liver function: promote bone marrow stem cells hematopoiesis</td>
<td>Primary liver cancer; Lung cancer; Rectal cancer; Malignant lymphoma; Gynecologic malignant tumors</td>
<td>Minority of patients have Uricaria or pyrexia. Very small minority of patients have palpitation, chest distress or nausea.</td>
<td>Yibai pharmaceutical Co., Ltd</td>
<td>Gaiyang City, Guangzhou province China</td>
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<tr>
<td>Aescin Tinoside Injection</td>
<td>Aescin</td>
<td>As$_2$O$_3$,</td>
<td>Inducing apoptosis in H epatocarcinoma cell; inhibiting Vascular Endothelial Growth Factor; inhibiting telomerase activity; improving cellular immunity</td>
<td>Acute promyelocytic leukemia; Primary liver cancer; Lung cancer; Gastric cancer; Prostate cancer</td>
<td>Dizziness; encephalagia; emesis; languor; aphonia; exanthema; xerodema; limbs numbness. Some patients have mild liver and kidney function damage.</td>
<td>Yida pharmaceutical Co., Ltd</td>
<td>Harbin City, Heilongjiang province China</td>
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<tr>
<td>Brucea Javanica Oil Emulsion Injection</td>
<td>Dry and ripe fruit of Quassia Brucea javanica.</td>
<td>Oleic acid</td>
<td>Inhibiting DNA synthesis and cell growth; selective damage cell membrane and mitochondria of cancer cells; enhance cellular immunity and humoral immunity; promote bone marrow stem cells hematopoiesis</td>
<td>Esophageal cancer; Gastric cancer; Colorectal cancer; Primary liver cancer; Pancreatic cancer; Lung cancer; Cervical cancer; Bladder cancer; Prostate cancer; Metastatic cancer</td>
<td>Mild stimulation for blood vessels; cause Phlebitis or venous thrombosis for long. Minority of patients have abdominal pain, diarrhea, exanthema, atrophia, allergic shock or arrhythmia. Phtlebitis; mild heart toxicity</td>
<td>Baiyun Mountain pharmaceutical Co., Ltd</td>
<td>Guangzhou City, Guangdong province China</td>
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<tr>
<td>Cinobufacini Injection</td>
<td>Dry skin of toad</td>
<td>Indolylalkylamine alkaloid, serotonin, bufotene and toad poison aglucone, et al.</td>
<td>Antitumor; improving humoral immunity and cellular immunity; increasing leucocytes; analgesia; sedation</td>
<td>Malignant tumor; Acute phthisis; Epidemic hemorrhagic fever</td>
<td></td>
<td>JinChan biochemical Co., Ltd</td>
<td>Huanghe City, Anhui province China</td>
</tr>
<tr>
<td>TCM (Chinese Name)</td>
<td>Drug Source</td>
<td>Main Pharmacological Composition</td>
<td>Drug Function Mechanism</td>
<td>Indications</td>
<td>Side-effects of Drugs</td>
<td>Pharmaceutical Company</td>
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<tr>
<td>Composite Danshen Injection</td>
<td>Labiatae Salvia; Miliotrichiza; dry trunk of Leguminosae Rosewood Heart Wood</td>
<td>Tanshinone, cryptotanshinone, flavonoid, isoflavanone and two terpenoids, et al.</td>
<td>Protecting myocardial ischemia and hypoxia; removing free radicals; protecting liver damage; improving The hemorheology indexes</td>
<td>Angina pectoris; Acute myocardial infarction; cerebral thrombosis Chronic hepatitis</td>
<td>Small minority of patients have drug rash or urticaria.</td>
<td>Chiatai qinghunbao pharmaceutical Co., Ltd.</td>
<td>Hangzhou, Zhejiang province, China</td>
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<tr>
<td>Composite Sophorae Flavescentis Injection</td>
<td>Leguminosae Sophora flavescens; dry sclerium of Polyboraceae Indian Buead</td>
<td>Matrine, sophorflavoside, paclitaxel and pachyminic acid and pachy-man, et al.</td>
<td>Antitumor; improving humoral immunity and cellular immunity; analgesia</td>
<td>Malignant tumor; Cancerous pain</td>
<td>Injection local mild stimulation</td>
<td>Zhendong pharmaceutical Co., Ltd.</td>
<td>Changshi, Shandong province, China</td>
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<tr>
<td>Kang Ai Injection (Kang’ai Zhusheye)</td>
<td>Astragalus Panax; Sophora Flavescentis</td>
<td>Astragaloside IV, Kushenin and ginsenoside Rg1, Re, Rf, Rb1, et al.</td>
<td>Inhibiting cancer cell growth; improving immunity; increasing leucocytes; analgesia; anti-antiemic</td>
<td>Primary liver cancer; Lung cancer; Rectal cancer; Malignant lymphoma; Gynecologic malignat tumors; Leucopenia; Chronic Hepatitis B</td>
<td>No clear</td>
<td>Changbai mountain pharmaceutical Co., Ltd.</td>
<td>Jilin city Jilin province, China</td>
</tr>
<tr>
<td>Kang-Lai-Te Injection (Kanglaite Zhusheye)</td>
<td>Dry and ripe seed of Gramineous Coix</td>
<td>Coix lachryma-jobi oil and soybean phospholipid, et al.</td>
<td>Inducing apoptosis in tumor cell; inhibiting tumor angiogenesis; kill cancer cells; improving immunity; anti-cachexia; analgesia</td>
<td>Primary liver cancer; Nonsmall cell lung cancer; Colon cancer; Metastatic lung cancer</td>
<td>Small minority of patients have shivering, pyrexia, nausea, liver transaminase reversible increases or mild Phlebitis.</td>
<td>Kanglaite pharmaceutical Co., Ltd.</td>
<td>Hangzhou city Zhejiang province, China</td>
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<tr>
<td>Shen Fu Injection (Shenfu Zhusheye)</td>
<td>Red ginseng; Acontum Fischieri</td>
<td>Ginsenoside and aconitine, et al.</td>
<td>Enhancing myocardial contractility; improving cellular immunity; analgesia</td>
<td>Arrhythmia; Heart failure; Shock; Aplastic anemia; Leucopenia and Thrombocytopenia caused by radiotherapy and chemotherapy</td>
<td>Small minority of patients have anaphylactic reaction.</td>
<td>999 pharmaceutical Co., Ltd.</td>
<td>Yaan city Sichuan province, China</td>
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</table>
Clinical observations showed that, in patients treated concurrently with Cinobufacini or Kang-Lai-Te injection and radiotherapy, KPS scores were increased, appetite improved, and pain was relieved. Also, the CR and PR rates were higher when using Kang-Lai-Te injection.26,27

**Combination with radiotherapy**

Aidi injection with percutaneous radiofrequency ablation (PRFA) significantly increased the CR and PR rates and the 12-, 18- and 24-month survival rates. Increases in CD3⁺ and CD4⁺ cells, CD4⁺/CD8⁺ cell ratio and NK cells, and alleviation of clinical symptoms such as hepatalgia, fever, abdominal distension, anorexia and jaundice were more evident in the treatment group, whereas descending amplitudes of AFP, ALT and AST were the same as in the control group.28-30 Similar effects were seen with Kang Ai injection.31 However, the recurrence rate of the patients with tumors ≥3 cm was significantly lower when PRFA was applied in combination with those two injections.31,32 Clinical observations have shown that Shen Qi Fu Zheng injection in combination with gamma knife radiosurgery increased KPS scores and body weight, but did not significantly affect PWBC count, hemoglobin, or platelet and CD4⁺ cell counts.33 Another study revealed that Xiao’ai’ping injection reduced the duration of fever after PRFA.34

**Combination with chemotherapy**

When chemotherapeutic drugs such as fluorouracil (5-FU) or meloxicam were used in combination with Aidi injection, the reduction in PWBC count and symptoms such as nausea, vomiting and low fever were significantly lowered in the treatment group compared with the control group.35,36 Moreover, in mid to late stage PLC, 5-FU in combination with Aidi injection increased the efficacy and 6- and 12-month survival rates, relieved the clinical symptoms, and reduced the nausea and leukocytosis for the patients in the treatment group compared with 5-FU alone, according to clinical observation.37 The same therapeutic efficacy were achieved when intravenous drip of Shengqi Fuzheng injection was combined with cisplatin, adriamycin, 5-FU plus interferon, as well as when intravenous drip of Cinobufacini injection was combined with 5-FU and hydroxyacamptothecin (HCPT).38,39 When Kang-Lai-Te injection was used with capetubicin, the total effectiveness, clinical benefit response rate, time-to-progression, and mean survival time were higher in the treatment group.30 Intravenous drip of Composite Sophorae Flavescentis injection combined with epirubicin, 5-FU plus cisplatin improved the curative effect, 1-year survival rate, cellular immune function, and QOL, and decreased the reduction in PWBC count, pain, and toxicity of chemotherapy in patients with advanced PLC.3,41 Another study showed that intra-abdominal injection with
HCPT, 5-FU plus dexamethasone in combination with Composite Sophorae Flavescentis injection increased the efficacy of treating cancerous ascites and reduced the side effects of intraperitoneal chemotherapy compared with intra-abdominal injection with HCPT. 5-FU plus dexamethasone. Similar effects could be seen when applying intra-abdominal injection of dopamine plus furosemide in combination with Composite Danshen injection.

**Combination with surgery**

Li et al. found that compared with operation alone, intravenous Shen Fu injection as preoperative adjuvant therapy increased the levels of CD3+ and CD4+ cells, protected liver function, shortened the length of stay in hospital or intensive care unit, and enabled earlier post-operative decannulation. And scores of KPS could be increased significantly 30 days after the surgery. Another study showed that compared with operation alone, intravenous Kang-ai injection as preoperative adjuvant therapy increased the levels of CD3+ and CD4+ cells and CD4+/CD8+ cell ratio in patients with primary hepatic carcinoma.

**Monotherapy**

Compared with liver-protecting treatment, Cinobufacini injection in combination with symptomatic treatment inhibited cancer proliferation, and protected liver function, improved QOL, and prolonged survival time. ALT and TBIL levels decreased significantly in patients in the treatment group.

Another study showed that hepatalgia was alleviated by Composite Sophorae Flavescentis injection. Tan found that compared with ascites drainage alone, intra-abdominal Composite Sophorae Flavescentis injection after ascites drainage could improve alleviation of cancerous ascites in PLC.

In a study that included 25 patients with advanced PLC treated with intravenous arsenic trioxide injection, the response rate was 13.8%. Compared with liver-protecting treatment alone, Arsenic trioxide injection increased the levels of CD3+, CD4+ and CD8+ cells, and CD4+/CD8+ cell ratio, and enhanced KPS score.

In patients with late-stage liver cancer, intravenous Aidi injection could increased daily food consumption and relieved pain after 2 months of treatment compared with symptomatic therapy, and KPS score was increased significantly in the treatment group.

Another study showed that compared with liver-protecting treatment, intravenous drip of arsenic trioxide injection plus Aidi injection also increased the CD3+, CD4+ and CD8+ cells and CD4+/CD8+ cell ratio, and reduced the level of AFP.

Wu et al. found that clinical symptoms were alleviated, KPS scores were increased, and toxicity was reduced in patients treated with Kang-Lai-Te injection compared with those in the control group treated with 5-FU plus oxaliplatin.

**DISCUSSION**

Herbs have long been used as antineoplastic medicine in China. In recent years, with improvement in preparation, many TCMIs have been developed and used to treat PLC, especially in patients with medium- or advanced-stage PLC. With advantages such as less toxicity, being more economical and multifunctional in regulating immunological function, as well as killing cancer cells, TCMIs have been widely used clinically in China. Besides PLC, TCMIs are indicated for various other malignant tumors, and their effects have been gradually testified by clinical trials. For example, Astragalus injection has been used to treat cervical cancer; Oleum Fructus Bruceae, Shengmai or Shenfu injection to treat non-small cell lung cancer; and Cinobufacini or Bettelemeine injection to treat progressive gastric cancer.

Many studies have shown that TCMIs had significant effects on reducing cancer-related fatigue and pain, alleviating respiratory tract infections and gastrointestinal symptoms, including diarrhea, nausea, and vomiting, protecting liver function, and even ameliorating the symptoms of cachexia.

However, in our review of the literature, we also found some problems with TCMIs that need to be resolved urgently. First, TCMIs are extracted from herbs, and although they have been widely used clinically, their major pharmacological active ingredients mostly remain unknown. Second, the side effects, contraindications and corresponding clinical data of TCMIs are rarely specified in the product instructions. Third, improvement in the preparation technology still cannot keep down the frequent occurrence of allergy and phlebitis. Fourth, clinical trials on TCMIs are abundant, and they do testify to the effects of TCMIs on PLC from different aspects. Unfortunately, none of them were large multicenter trials with strict criteria. Instead, most of the studies were not done under standard criteria, so it is difficult to draw persuasive conclusions about the effects of TCMIs for treating cancer when conducting a meta-analysis. Finally, but not the least, most of the clinical trials were conducted in China, and the pharmacological activities of TCMIs have not been tested in other areas and on other races. All the problems discussed above have greatly obstructed further application of TCMIs. Therefore, we call for large-scale high-quality trials, intensive basic research on and improvement of preparation of TCMIs, and more advocates to tap the potential of TCMIs.

In clinical practice, combination of TCMIs with surgery, TACE, percutaneous ethanol injection (PEI), radiotherapy or chemotherapy protect hepatic function, improve the immune system, increase sensitivity to chemo- and radiotherapy, reduce side effects and complications during chemo- and radiotherapy, improve QOL, increase CR, PR and SD rates and KPS scores, and prolong survival time. Even if TCMIs are taken solely as palliative treatment, they could alleviate patients’ symptoms.
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