Arsenic Trioxide Combined with Chinese Traditional Jianpiliqi Formula in the Treatment of Advanced Hepatocellular Carcinoma: An Analysis of 32 Cases*

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Abstract: Objective To evaluate the therapeutic results and the toxicity of the combination of arsenic trioxide and the Chinese Traditional Jianpiliqi (JPLQ) formula in the treatment of advanced hepatocellular carcinoma (HCC). **Methods** Patients with advanced HCC, and not suitable for resection but with normal major organ functions, were enrolled to receive a therapeutic regimen consisting of intravenous arsenic trioxide (6 mg/m^2) administration from days 1-14, and an oral administration of JPLQ formula twice daily from days 1-28. Each cycle was composed of 28 days and treatment could expand up to 4 cycles if no evidences of intolerable toxicity or disease progression. Tumor responses were evaluated every 2 cycles, and patients were followed up for one year. **Result** Thirty-two patients (84.4% male, median age 51) received a total of 101 cycles (median, 4) of treatments. One (3.1%) patient had partial response, one (3.1%) had minor response, 15 (46.9%) showed stable disease and 15 (46.9%) had disease progression. Overall responses were: total disease control rate was 53.1%, median survival time was 5.8 months (2-23.9 ms), and median time to progression was 4.2 months (1-16.9 months). The major toxicities included depression of bone marrow and gastrointestinal reactions. The incidences of grade 1 and 2 leukocytopenia, thrombocytopenia and anemia were 46.9% (15/32), 31.3% (10/32) and 43.8% (14/32), respectively. The incidences of grade 1-3 abdominal distention and nausea/vomiting were 65.6% and 37.5%, respectively. Glutamic-pyruvic transaminase increases were found in 4 patients (2 grade 2, 1 grade 3, and 1 grade 4) and serum creatinine increases in 2 patients (1 grade 3 and 1 grade 4), respectively. **Conclusion** Compared with the single arsenic trioxide treatment reported in past literature, treatment by arsenic trioxide combined with JPLQ showed modestly higher anti-tumor activity and tolerable toxicity in patients with advanced HCC; its manageable toxicity and increased tumor response rate may offer a better treatment regimen, and deserve further investigation.

Key words: hepatocellular carcinoma; arsenic trioxide; Chinese herb medicine; clinical trial

INTRODUCTION

Primary liver cancer is one of the most common malignant tumors in the world, 90% of which is Hepatocellular Carcinoma (HCC). China is one of the countries with the highest incidences, having almost 50% of

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the cases of the world. Liver cancer is also the second leading cause of cancer-related deaths in both the cities and the countryside[1-2]. In China, patients with stage IV HCC mostly receive systemic chemotherapy. Since this type of therapy does not always improve the survival rate, medicines aimed to protect and support liver functions, as well as Chinese medicines, are also used.

Among the Chinese medicines used for cancer treatment, arsenic trioxide (As_2O_3), from the traditional Chinese medicine arsenicum sublimatum, attracted a lot of attention due to its mechanism of promoting apoptosis[4-5]. Both vitro experiments and clinical trials demonstrated that As_2O_3 induced apoptosis[5-12], and achieved great clinical benefits[13]. However, due to its side effects such as abdominal distention, nausea, and emaciation, alternative methods that reduce these side effects are highly desired.

In traditional Chinese medicine, it is believed that liver cancer originates from dysfunctions of the stomach and spleen. It is also believed that the stomach and spleen are the foundations and the control points of all postnatal organ functions, and that their damages will result in loss of homeostasis of the whole body and accumulation of many "evil" toxic substances, leading to cancers. Professor YU Er-xin, a renowned liver cancer specialist, has studied liver cancers for years at a comprehensive level[14]; he discovered that, among 169 successfully treated cases of liver cancer, 80.4% were treated with the traditional Chinese medicine JPLQ formula. Given the many known digestive tract symptoms in patients receiving arsenic trioxide, and the philosophy of Chinese medicine[14], we hypothesize that a combination with JPLQ formula may help to decrease the toxicities of arsenic trioxide in the HCC treatment. This article summarizes the data on the survival, clinical responses and toxic reactions obtained from 32 HCC patients treated by the combination of arsenic trioxide and JPLQ formula.

CASES AND METHODS

1. Patient Registration

Inclusion criteria: (1) HCC diagnosed by pathohistology, cytology, or radiology with AFP according to the national standards for HCC diagnosis[15]; (2) Clinical stage IV confirmed according to TNM staging system by UICC in 1997[16]; (3) Measurable lesions; (4) No prior chemotherapy, radiotherapy and interventional therapy within 2 months, or disease progression with recent treatment; (5) Ages 18-79 year old; (6) PS (ECOG) score 0-2 with adequate bone marrow, heart, kidney, and lung functions; (7) Liver function grade A or B according to liver function Child-Pugh classification[17]; (8) Expected survival time more than 2 months.

Informed consents were obtained from all eligible patients.

Exclusion criteria: (1) Pregnant women; (2) Allergy to aresenic trioxide; (3) Complication with active tuberculosis; (4) Severe active infection; (5) Mental disorder; (6) Complication with other not well-controlled malignant tumors; (7) Complication with active, not well-controlled brain metastasis.

2. Therapeutic Regimen

Combination of arsenic trioxide and JPLQ formula: arsenic trioxide was added into 500 ml glucose 5% solution at 6 mg/m^2, and administrated as an intravenous infusion at d 1-14; at the same time, JPLQ Chinese medicine was taken orally one dose everyday at d 1-28 for 4 cycles.

JPLQ formula containing the following major Chinese herbs were prescribed based on the literature[14]: heterophylly falsestarwort root 30 g, atractylodes macrocephala 10 g, tuckahoo 15 g, akebiae 30 g, herba hedyotis diffusae 30 g, sun-plant 30 g, pearl barley 30 g, danfuzi 10 g, stir-baked Fructus Crataegi 15 g, massa medicata fermentata 15 g, stir-baked Fructus Hordei Germinatus 30 g, stir-baked setariae germinatus 30 g, aurantii 6 g, licorice root 6 g. All these ingredients were mixed and simmered, and one dose of the medicine soup was taken

into two separate and oral intakes daily during d 1-28, continuity of 4 cycles. The amount of individual component in each dose may be modified based on the severity of the symptoms.

3. Evaluation of Outcomes

At the end of 4 cycles treatments or the time of disease progression before 4 cycles, tumor lesions were examined by abdominal CT or MRI scans, and therapeutic outcomes were evaluated according to the WHO standards and the response rate was calculated[18]. Body weight, physical examination and disease symptoms were also evaluated at the end of each treatment cycle.

4. Evaluation of Toxicity

Toxicity was recorded daily into observation tables after treatment according to the WHO's grading system for acute and sub-acute toxicity of anticancer drugs[19]. Weekly blood tests were performed to evaluate the hematological toxicity, and tissue/organ functions, including liver, kidney, and heart functions, as well as other clinical symptoms, such as vomiting, diarrhea, hypodynamia, abdominal distension, pain, hemorrhage, and fever were evaluated.

5. Statistics Analysis

The important points of this study were the objective response rate and the survival time, the secondary points were toxic reactions and quality of life. SPSS15.0 was used to analyze all clinical data, ANOVA was used to analyze measurements, and Kaplan-Meier curve and Log-Rank were used to analyze survivals.

RESULTS

1. Patient Data

From September, 2005 to June, 2007, 32 patients with stage IV liver cancer and ECOG scores of 0-2 were enrolled into this clinical trial. Patients demographics and clinical presentations were listed in Table 1. These patients received a total of 101 cycles with 1-6 cycles and a median value of 4 cycles for each patient. Of those, 23 patients died, the rest of 9 patients have been followed up, and the last data entrance was in June of 2008.

Table 1 Demographics and clinical presentation of 32 samples with stage IV HCC enrolled in this study

Parameters	Number of patients	Percentage %
Sex		
Male	27	84.4
Female	5	15.6
Age		
＜65 years	25	78.1
≥65 years	7	21.9
ECOG score		
0-1	23	71.9
2	9	28.1
HB virus infection		
	28	87.5
Hepatic cirrhosis		
	12	37.5
Liver function by Child-Plug		
Grade A	24	75
Grade B	8	25

(to be continued)

Family tumor history		
Yes	13	40.6
No	19	59.4
Clinical symptoms		
Hepatalgia	19	59.4
Anorexia	13	40.6
Hypodynamia	16	50
Abdominal disention	11	34.4
Swollen limbs	12	37.5
Diarrhea	8	25
Fever	4	12.5
Hemorrhage	1	3.1
Lesion by abdominal CT		
Massive	29	90.6
Diffused	3	9.4
Portal vein or inferior vena tumor emboli	13	40.6
Hepatic portal or peritoneal lymphadenectasis	6	18.8
Esophageal and gastric varices	10	31.3
Metastatic lesion		
Lung	10	31.3
Brain	0	0
Bone	2	6.3
Adrenal gland	5	15.6

2. Evaluation of Therapeutic Outcomes

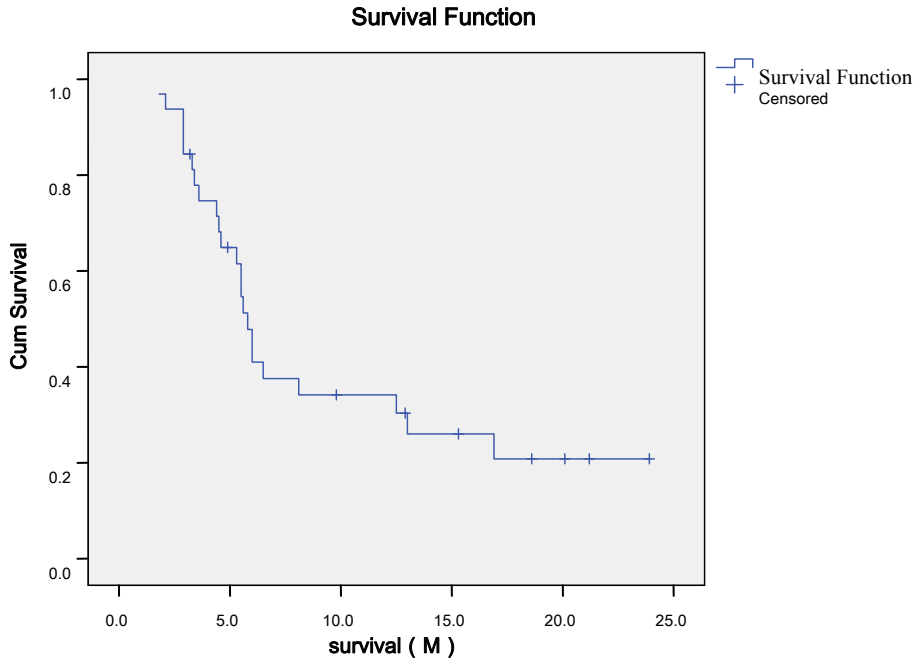

Fig. 1 Survival curve of 32 patients with advanced HCC after the treatment by arsenic trioxide combined with JPLQ formula

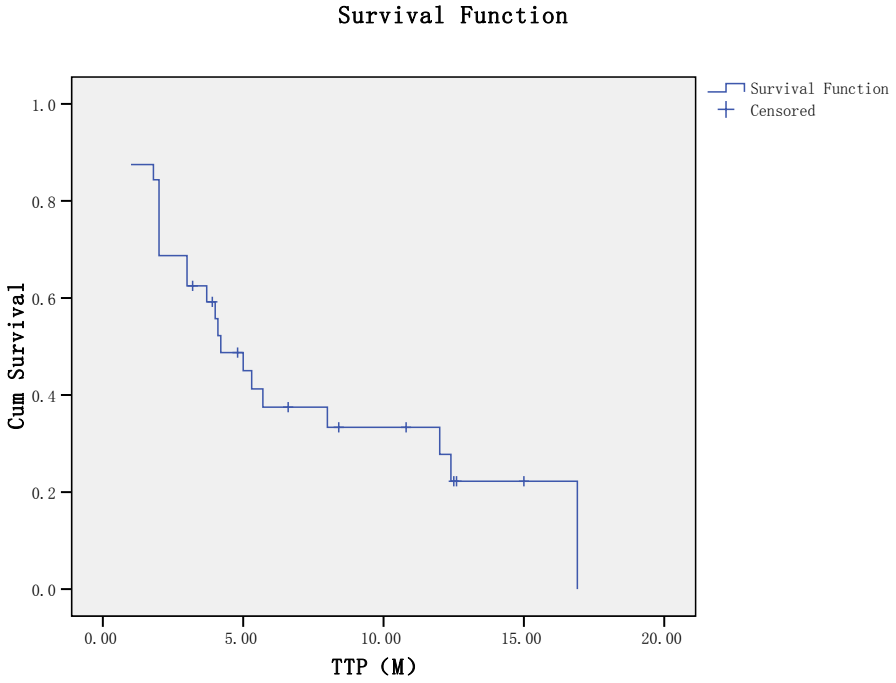

Fig. 2 TTP curve of 32 patients with advanced HCC after the treatment by arsenic trioxide combined with JPLQ formula

Clinical evaluation on patients with advanced HCC after treatment of arsenic trioxide and JPLQ formula showed a response rate of 7.4%, a partial response (PR) of 3.7%, and minimal response (MR) of 3.7%, the stable disease (SD) rate of 81.5%, median survival time (MST) of 5.8 months (95% CI: 5.19-6.40), averaged time to progression (TTP) 4.2 months (95% CI: 2.61-5.79), and 1 year survival rate 28.1%. The survival curve of 32 patients was shown in Fig. 1, and their TTP function curve was shown in Fig. 2.

3. Evaluation of Toxicity

Among these 32 patients of advanced HCC receiving a combined treatment of arsenic trioxide and JPLQ formula, bone marrow depression and gastrointestinal tract reaction were the main toxic effects. The three major hematopoietic systerms were all decreased: leukocytes, hemoglobins, platelets; incidences of grade I or II neutropenia, hypocythemia, and thrombocytopenia were 46.9% (15/32), 43.8% (14/32), and 31.3% (10/32), respectively, none were grade III or IV. Gastrointestinal reactions were mainly abdominal distension and vomiting. The incidences of grade 1-3 abdominal distention and nausea/vomiting were 65.6% and 37.5% respectively and the rest had sporadic diarrhea, pain, fever, hematochezia, and pruritus. Glutamic-pyruvic transaminase increased in 4 patients (2 grade 2, 1 grade 3, and 1 grade 4) and serum creatinine increased in 2 patients (1 grade 3 and 1 grade 4), respectively. All these symptoms of toxicity reactions resolved at the end of treatment.

DISCUSSION

Since the 1950's, the HCC therapy has gradually developed from a single treatment model to the combined treatment model in multiple disciplines. Currently, these treatments include surgery and interventional therapy, but they bring little benefits to patients who have multiple tumors, or complicated with portal vein tumor thrombus and distant metastasis, or those who do not meet the surgical pre-requirement after palliative treatment, as well as those with contraindication of surgery such as the postoperative recurrence and intolerance to the

operation. While other treatments such as radiation therapy, systemic chemotherapy, electrochemical treatment, and biological therapy, also do not achieve significant responses, so the survival of such patients is mostly less than two months[20]. Therefore, the treatment of HCC remains an unresolved global problem.

In China, most of such patients discontinue all treatments, or only seek palliative treatments to enhance liver functions; a small portion may also try to use Chinese medicines. Chinese medicine believes that the etiology and pathogenesis of hepatocellular carcinoma originated from the accumulation of "Tan"(sputum), "Yu"(blood stasis), and "Du"(poison), which cause weakening of Zheng-Qi (Immune system) and the increase of "Xie-Qi" (evil factors); therefore, dispelling these pathogenic factors and strengthening the patient's resistance are used to prolong life and reduce pain.

Arsenic is a typical drug representing the philosophy of Chinese medicine "treating a toxifying disease with poisonous agents"; it has been applied in the treatment of various malignant diseases including tumors since the ancient time in China. There were some historical records for the use of arsenic: "Medical Primer. Materia Medica" recorded arsenic was used to deal with malignant sore, scrofula and carrion; "Holy Benevolent Prescriptions" recorded the external application of arsenic for hard to treat malignant sore; "Jixuanfang" recorded the external application of realgar and alumen for abdominal hypochondrium mass; *Shennong Materia Medica* stated that realgar is mainly used to control cold and heat, to treat rat flaccidity, malignant sore, hemorrhoids, an dead muscle, to reduce swelling caused by venom. The drug's analgesia and detoxication on cancer suggest its potential anti-tumor effects via dispelling the pathogenic factors and strengthening the patient's resistance.

At present, arsenous acid (AA) injection formula has passed rigorous clinical trials and been officially listed in 1999 as a second grade national new medicine. It can inhibit the activity of sulfhydryl enzymes in living cells to kill the cells. The preliminary in vitro experiments showed that AS_2O_3 inhibited the growth and proliferation of T402 human hepatocellular carcinoma cells BEI, and induced apoptosis, suggesting arsenic trioxide may become a new medicine for the treatment or adjuvant treatment of hepatocellular carcinoma[21]. QIN Shu-kui, et al[17-18] reported the objective response rates of advanced primary hepatocellular carcinoma and gallbladder cancer to the single AA treatment of 13.8% and 15.2%, respectively, and the total response rate of 25.0%. Moreover, AA injection also has significant analgesic effects on some patients with liver pain.

From our clinical experience, symptoms such as abdominal distention, nausea, and anorexia occurred in most HCC patients under the single AA treatment, making the treatment regimen hard to be complete. At the same time, the efficacy of arsenic trioxide alone in the treatment of primary HCC is below 20%[18,24-27]. Although the synergistic effect between AA and other drugs has been investigated[28-31], the treatment by AA injection combined with Chinese medicine has not been reported.

Based on the data obtained from this clinical trial by March 31, 2008, the evaluation of responses of measurable lesions in 32 patients are the following: 1 case of PR showed disappearance of the lung metastatic lesion, 1 case of MR showed reduced lung metastatic lesion; the total response rate was 6.2%. The rate of stable disease was 53.1%, similar to that reported from current chemotherapy and radiotherapy in the clinics. Evaluation on the survival showed that there were 9 patients survived; among the 32 patients being treated, an average survival time was a little longer than 9 months with the median of 167.5 days, and the disease free survival was 122 days. The 1 year survival rate reached 28.1%, which was higher than that reported in the literature[20]. Evaluation on toxicity of the treatment showed that the depression of bone marrow and gastrointestinal reactions were the main toxicities. 50% was leucocytopenia and 40% was thrombocytopenia and anemia, which are consistent with the known pharmacological characters of the arsenic trioxide toxicity in the blood system.

Digestive tract reactions were mainly abdominal distention and vomiting. Although the reason for abdominal distention is still unclear, it may be related to the neuron-toxic effect of AA injection. We found that Chinese medicine JPLQ can help XiaoZhangChuJi as well as the remission of abdominal distention in these patients.

Together, the treatment on HCC by arsenic trioxide injection combined with Jianpiliqi formula efficiently prolonged survival time of patients, stabilized tumor lesions, improved quality of life and the clinical symptoms of the patients. This treatment regimen showed tolerable side effects, mainly the depression of bone marrow and gastrointestinal reactions (below grade III). These findings were similar to what have been reported by others[23-28]. During and after the treatment of arsenic trioxide, JPLQ Chinese medicine can reduce the side effects and relieve the symptoms caused by arsenic trioxide, thus enhancing its clinical benefits of arsenic trioxide alone, and prolonging survival time and stabilize tumor lesions; therefore, arsenic trioxide combined with JPLQ formula may become a new treatment or adjuvant treatment of hepatocellular carcinoma, and deserve further studies.

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