Effect of Xiaoaiping injection on advanced hepatocellular carcinoma in patients

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Abstract

OBJECTIVE: To investigate the effect of Xiaoaiping Injection (XAP) on advanced hepatocellular carcinoma (HCC) in patients.

METHODS: Sixty-eight patients with advanced HCC were assigned to a control group of 36 and a treatment group of 32. The control group was treated with best supportive treatment (BST) and the treatment group was given XAP plus BST. XAP was administered daily by iv and the treatment course was lasted for 30 days for both groups. The immediate therapeutic efficacy, Karnofsky performance status (KPS) scores, and the changes in immunity indicators (CD3⁺, CD4⁺ and CD8⁺ T cells) were measured and compared before and after treatment. The progression-free survival (PFS) rate and overall survival (OS) rate in the 2 groups were analyzed.

RESULTS: The immediate therapeutic efficacy and KPS of the treatment group were better than those in the control group (P<0.05). Patients in the treatment group had higher percentages of CD3 and CD4 T-lymphocytes in peripheral blood than those in the control group (P<0.05). The median survival time was 27.0 weeks in the treatment group and 24.5 weeks in the control group. The 6-months cumulative survival rates in the treatment and control groups were 33.3% and 25.0%, respectively, with no significant difference (P>0.05). The PFS was 18 weeks in the treatment group and 15 weeks in control group (P<0.05).

CONCLUSION: XAP enhances the quality of life (QOL) of patients with advanced HCC, improves their immunity and extends their PFS.

Key words: Carcinoma, hepatocellular; Karnofsky performance status; Disease-free survival; Xiaoaiping injection

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common tumours. It is difficult to diagnose HCC at its early stage due to its fast progress. When definitely diagnosed, HCC usually has already developed to its advanced stage. Moreover, the fatality rate of HCC is very high, making it the third cause of cancer death. Conventional treatment for HCC include surgical removal, liver transplant, ablation, chemoembolization and molecular targeted therapy. However, none of these methods is ideal due to various reasons. For example, it is estimated the treatment with surgical removal or radiofrequency ablation can only be offered to 10% of HCC patients with smaller size of tumors. Additional reasons include innate or low specific immunity,
MATERIALS AND METHODS

Patients
All patients signed a consent form according to the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Fujian University of Traditional Chinese Medicine. Patients diagnosed with advanced HCC at our hospital from September 2009 to March 2011 (China Classification System III A/III B) were included in this study. Patients who underwent surgery and received or were receiving intervention therapy were excluded. Diagnosis of HCC was based on the level of serum alpha-fetoprotein (AFP ≥ 400 ng/mL), imaging of ultrasound (iU22, Philips Healthcare, Bothell, WA, USA) and computed tomography (Asteion multiple, Toshiba, Kawasaki, Japan), or liver biopsy with AFP < 400 ng/mL. Patients with a KPS score ≥ 60 and an estimated life expectancy of > 3 months were recruited in the study.

Sixty-eight subjects of advanced HCC were randomly assigned to the treatment group and control group for a single-blind clinical study. Among the 32 cases in the treatment group were 23 males and 9 females aged 32 to 75 years, 49 years on average, 10 cases of portal vein thrombosis and 30 cases of hepatitis B virus (HBV) infection, 13 cases of massive type of tumour, 7 cases of nodular type of tumour and 12 cases of diffuse type of tumour, and 24 cases at grade A, 6 cases at grade B and 2 cases at grade C according to Child-Pugh’s classification.

Among the 36 cases in the control group were 26 males and 10 females aged 36 to 78 years, 51 years on average, 15 cases of portal vein thrombosis and 33 cases of HBV infection, 15 cases of massive type of tumour, 4 cases of nodular type of tumour and 17 cases of diffuse type of tumour, and 22 cases at grade A, 10 cases at grade B and 4 cases at grade C according to Child-Pugh’s classification.

There was no significant difference between the two groups in age, gender and clinical stage.

Treatment
In the treatment group, while the patients were receiving BST including nutritional support, improving liver function and relieving pain, intravenous drip was administered with 40 mL of XAP (Sanhome Pharmaceutical Co. Ltd., Nanjing, China) added to 250 mL of 5% glucose or normal saline, QD, for 30 consecutive days as one therapeutic course. Another 30-day treatment course was conducted after a 2-week interval. In the control group, only BST was administered for 30 days.

Evaluation
Evaluation of immediate efficacy: before and after one month of treatment, immediate efficacy was evaluated according to response evaluation criteria in solid tumors (RECIST) with ultrasonography or computed tomography. The efficacy is classified into 4 grades: complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD). The total effective rate was calculated with the formula: [(Number of cases with CR + PR + SD)/Total number of cases] x 100%.

Assessment of general immune function
In order to evaluate the effect of XAP injection on general immune function, CD3+, CD4+ and CD8+ T-lymphocyte counts before and after treatment were measured with flow cytometry (Becton Dickinson Calid, Franklin Lakes, NJ, USA).

QOL of patients
KPS scoring is used to quantify the QOL of cancer and other patients in terms of their general well-being and activities of daily life. The pre-treatment and post-treatment KPS scores of both groups were evaluated.

Survival rate
The primary and secondary end points for this study were PFS and OS. PFS was defined as the interval from the onset of treatment to disease progression or death. OS was defined as the time from the date of diagnosis to date of death or the date of the last follow-up visit. All patients were followed until death or November 1, 2011.
Adverse reactions
Adverse reactions due to XAP infusion, such as shivering, fever or allergy, were monitored and categorized into different degrees of severity. 0-IV, according to the World Health Organization (WHO) evaluation criteria 1998.

Statistical analysis
Differences of enumeration data were evaluated with Chi-square test and differences of measurement data with t-test at a 95% confidence level. Survival analysis was conducted with Kaplan-Meier and Long-rank tests. The survival rate was calculated in terms of weeks. All analyses were performed with SPSS 13.0 software (SPSS Inc, Chicago, IL, USA).

RESULTS
Immediate effect
The total effective rate was 71.8% in the treatment group and 47.2% in the control group with significant difference between the two groups (P<0.05) (Table 1).

Comparison of KPS scores
The pre-treatment KPS score was 63±6 in the control group and 62±6 in the treatment group (P≥0.05). After treatment, the KPS score was 53±9 in the control group and 67±6 in the treatment group (P<0.05) (Figure 1).

OS rate
The median survival rate was (24.5 ± 1.4) weeks [95% confidence interval (CI), 21.7-27.2 weeks] and

6-month cumulative survival rate is 25.0% in the control group. The median survival rate was (27.0 ± 2.4) weeks [95% CI, 22.3-31.7 weeks] and 6-month cumulative survival rate was 33.3% in the treatment group. The survival curves (Figure 2) of the two groups were not significantly different from one another by Log-rank test.

DISCUSSION
In summary, the results of this study indicated that XAP can not only prevent cultured cancer cells from tumour growth but also prevent tumour growth in xenograft models. In vitro, XAP can induce tumour cell apoptosis and inhibit survival. The promis-
group was significantly different from that in the control group by Log-rank test (P<0.05).
No toxic or side effects were found in the treatment.

DISCUSSION

Modern pharmacological studies have demonstrated that XAP can not only prevent cultured cancer cells from proliferation, such as Bel-7404, HepG2 and SGC-7901 cells, and induce their differentiation, but also improve the chemotherapy efficacy of 5-fluorouracil (5-FU). Moreover, XAP improved the sensitivity of non-small-cell lung cancer (NSCLC) cells carrying T790M or K-ras mutations to gefitinib. The promising anti-tumour effect of XAP in vitro encourage further study to explore its potential as an anti-cancer medication.

The chemical composition of Marsdenia tenacissima extract is complex. Studies have focused on the C21 steroidal glycosides, the main active substances. In addition, in chemical and pharmacological studies of XAP, the relationship between its pharmacodynamic properties and clinical action is not very clear, and systematic, multi-center clinical study on XAP are rare. In the majority of clinical studies, the main outcomes measured were short-term effects, QOL and immune function, but the survival rate of the patients was seldom addressed. This study showed that the SD rate (as an indicator of immediate efficacy) in the treatment group was significantly higher than that in the control group, indicating that XAP might inhibit tumour growth in clinical setting. There was a significant difference between the KPS scores in the two groups, indicating that XAP could significantly improve the QOL of advanced HCC patients. Most patients have an improvement in appetite, quality of sleep, intensity of pain and abdominal distension.

Chronic hepatitis B virus infection is a main cause of HCC. There are different functional immune deficiencies in patients with HCC, indicating reduction in CD3+ and CD4+ T lymphocytes, an increase in CD8+ T lymphocytes, and a decrease in the CD4+/CD8+ T lymphocyte ratio. These changes reduce the immune surveillance function, which in turn impairs the ability of the immune system to inhibit the development of tumours. In this study, the CD3+ and CD4+ T lymphocytes and the CD4+/CD8+ ratio in the treatment group increased significantly after treatment, compared to the corresponding values in the control group. There was also an increase in the CD8+ lymphocytes. These data demonstrated that XAP effectively alleviated the deficits in immune function caused by the proliferation of tumour cells in advanced HCC patients.

In our study, there was no difference in OS between both groups, but PFS was 15 weeks in the control group and 18 weeks in the treatment group (P<0.05). 3 weeks longer than that in the control group suggested XAP’s clinical significance for the patients with advanced HCC.

In summary, the results of this study indicated that XAP improved QOL, immune function, effectively inhibited further development of the cancer and delayed disease progression, which suggests that XAP may be an effective medication for patients with advanced HCC.

REFERENCES


