RESEARCH ARTICLE

Safety of *Brucea javanica* and Cantharidin Combined with Chemotherapy for Treatment of NSCLC Patients

Zhu-Qing Ji[1], Xin-En Huang[1]*, Xue-Yan Wu[1], Jin Liu[1], Lin Wang[1], Jin-Hai Tang[2]*

Abstract

Objective: To assess the safety of B*rucea javanica* and Cantharidin combined with chemotherapy in treating patients with non-small-cell lung carcinoma. Method: A consecutive cohort of patients with NSCLC were divided into four groups: experimental group A treated with *Brucea javanica* injection combined with chemotherapy; experimental group B with Cantharidin injection combined with chemotherapy; experimental group C treated with *Brucea javanica* and Cantharidin injection combined with chemotherapy; and the control group receiving only chemotherapy. After more than two courses of treatment, safety, quality of life and side effects were evaluated. Results: The incidences of myelosuppression in groups A, B and C were lower than that in Control group ($p<0.05$), but without significant differences among A, B and C. Adverse effects on the gastrointestinal tract also were lower than in controls ($p<0.05$) without variation amnog the combined treatment groups. Conclusions: *Brucea javanica* or Cantharidin combined with chemotherapy could in both cases improve quality of life in our cohort of NSCLC patients without any increase in toxicity. However, further clinical experiments should be conducted to evaluate the efficacy of *Brucea javanica* and Cantharidin combined with chemotherapy for patients with NSCLC.

Keywords: *Brucea javanica* - Cantharidin - chemotherapy - combination approach - NSCLC

Asian Pac J Cancer Prev, **15 (20)**, 8603-8605

Introduction

According to WHO statistics, the incidence and mortality rate of lung cancer increase year by year. And in China, more than 75% of patients with non-small cell lung cancer (NSCLC) present with locally advanced (stage III) or metastatic (stage IV) disease at diagnosis (Rosell et al., 2011). Chemotherapy is a main treatment option for patients with advanced or metastatic lung cancer. However, chemotherapy is reported to be associated with a series of adverse reaction, e.g., bone marrow suppression, gastrointestinal toxicity, immunosuppression, etc (Yamamoto and Iwase, 2012). It was reported that Chinese herbal medicine (CHM) could increase effectiveness of platinum based chemotherapy in this setting (McCulloch, M., et al., 2006).

Brucea javanica oil emulsion is extracted from the Chinese herbal medicine Brucea Javanica, a new generation of anticancer drugs. It is reported that the mechanisms of its pharmaceutical action contains following aspects: decrease the number of G2/M phase cells, suppress the proliferation of cancer cells and induce the apoptosis of cancer cells; involve in immune regulation; increase the sensitivity of cancer cells to chemotherapeutic agents; containing some anti-thrombotic effects and without any adverse effects. Cantharidin is one of the components of natural mylabris. Numerous studies have shown that Cantharidin induced cytotoxic effects on cancer cells. Results indicated that Cantharidin significantly induced cell morphological changes and decreased the percentage of viable H460 cells. Cantharidin induced apoptosis based on the occurrence of sub-G1 phase and DNA fragmentation. Cantharidin promoted ER stress associated protein expression such as GRP78, IRE1α, IRE1β, ATF6α and caspase-4. On this background, we conduct this study to detect the safety of *Brucea javanica* and Cantharidin combined with chemotherapy in treating patients with non-small-cell lung carcinoma.

Materials and Methods

All patients were required to be pathologically/cytologically diagnosed with metastatic (stage IV) NSCLC in Jiangsu Cancer Hospital & Research Institute from June 2011 to July 2014, have or have not receive treatment of chemotherapy; predicted survival time≥3 months; to sign an informed consent before treatment; to have a score of karnofsky performance status≥70; to be 30 to 80 years of age. Other eligibility criteria included: adequate hematological (white blood cell count

*[1]Department of Chemotherapy, [2]Department of General Surgery, the Affiliated Jiangsu Cancer Hospital of Nanjing Medical University & Jiangsu Institute of Cancer Research, Nanjing, China *For correspondence: huangxinen06@aliyun.com; zgzlwkzz@139.com*

> 3.0×10^x9/L and platelet count > 100×10^x9/L), liver (bilirubin and transaminases < 1.5 times the upper normal limit) and renal function (creatinine leval < 1.5 times the upper), no heart and kidney disease. Patients excluded from this study if they failed to complete two cycles of chemotherapy, with any serious medical or psychiatric condition, or other malignancies.

Treatment

Patients were divided into A, B, C and Control groups randomly. In the A, B, C and Conrtol groups, chemotherapy used as mainly Pemetrexed (PEM) chemotherapy regimens. PEM was given at a dose of 500 mg/m^2 with a platinum that is recommended by NCCN. In experimental group A: teated with Brucea javanica injection combined with chemotherapy, patients received Brucea javanica Injection 30 ml, dissolved in normal saline 250ml daily intravenous. In experimental group B: treated with Cantharidin injection combined with chemotherapy, patients received Cantharidin Injection 0.5mg, dissolved in normal saline 250ml daily intravenous. In experimental group C: treated with Brucea javanica and Cantharidin injection combined with chemotherapy. In Control group: received only chemotherapy. Treatment was lasted 3 days and repeated every 3 weeks. While in control group, chemotherapy alone was administered. All the four groups received routine blood test, blood biochemistry and tumor markers were reviewed during and after chemotherapy.

Table 1. Patient Characteristics (n = 70)

Characteristic	No. of patients	%
Gender		
Male	30	42.90%
Female	40	57.10%
Age (years)		
Median	59.61	
31-40	3	4.30%
41-50	9	12.90%
51-60	24	34.30%
61-70	17	24.20%
>70	17	24.20%
Pathology type		
Poor differentiated carcinoma	2	2.80%
Adenosquamous Carcinoma	1	1.40%
Squamous cell carcinoma	8	11.20%
Adenocarcinoma	59	84.20%
main Chemotherapy medicines		
PEM	55	78.60%
CPT-11	5	7.10%
TXT	4	5.70%
Others	6	8.60%

To observe adverse reaction method:

Before treatment with recording history collection, record the weight, height, body surface area; chest X-ray, electrocardiogram before and after treatment, B Ultrasound, C T examination, according to the condition of patients choose whether to bronchoscopy, before treatment and after examination, peripheral hemogram, liver and kidney function, tumor marker. Check weekly treatment in peripheral blood in 7 days time, a detailed record ofadverse reaction.

Group A: Brucea javanica injection combined with chemotherapy

Group B: Cantharidin injection combined with chemotherapy

Group C: Brucea javanica and Cantharidin injection combined with chemotherapy

Group D: Control group (treated with chemotherapy only)

Results

From January 2011 to July 2014, 70 patients with metastatic (stage IV) non-small-cell lung carcinoma satisfied all study criteria. Group A contains 18 patients, group B contains 18 patients, group C contains 16 patients and group D contains 18 patients. They fulfilled eligibility had completed at least 2 cycles of treatment. All patients underwent toxicities assessment. Treatment related side effects were reversible, and no termination of chemotherapy or death caused occurred. General characteristics of patients are listed in Table 1. There were 30 male and 40 female patients, the average age was 59.61 years. Of all 70 patients, 59 diagnosed with adenocarcinoma, 8 with squamous cell carcinoma, 1 with adenosquamous carcinoma and 2 with poor differentiated carcinoma.

After 2 cycles of treatment, the adverse effects were recorded in Table 2, the main adverse effects were myelosuppression and gastrointestinal. Aglobulia rate of group A to D was 66.7%, 66.7%, 68.8% and 83.3%. Leukopenia rate of group A to D was 44.4%, 66.7%, 43.8% and 72.2%. Thrombocytopenia rate of group A to D was 11.1%, 22.2%, 6.3% and 22.2%. Gastrointestinal rate of group A to D was 72.2%, 72.2%, 50% and 88.9%. Patient with grade IV myelosuppression in Control group was obviously higher than 3 experimental groups (p<0.05), and no grade III-IV myelosuppression in group C. Liver dysfunction of the 4 groups was not significantly different from each other (p>0.05). All of 4 groups were not observed with impaired renal function.

Table 2. Toxicity in Four Groups

	group A (n=18)				group B (n=18)				group C (n=16)				group D (n=18)			
Toxicity Grade	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
Aglobulia	6	6	0	0	7	4	0	0	11	0	0	0	8	5	1	1
Leukopenia	4	2	2	0	9	2	0	0	4	3	0	0	6	5	1	2
Thrombocytopenia	2	0	0	0	1	2	0	0	0	1	0	0	1	1	0	2
Nausea,vomiting	11	1	0	0	13	0	0	0	8	0	0	0	12	4	0	0
Elevated ALT	1	2	0	0	2	1	0	0	1	1	0	0	2	2	0	0
Elevated Cr	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

ALT, Cereal third transaminase; Cr, Creatinine clearance

Discussion

There is an increasing number of patients suffering from NSCLC every year. Most of the patients with NSCLC are diagnosed in advanced stage and can not be treated by surgery.The principle of advanced cancer treatment is to prolong survival time of patients and improve the quality of life. Combination chemotherapy can significantly prolong the survival of patients with advanced NSCLC and improve the quality of life. However, chemotherapy will cause toxicity such as myelosuppression and gastrointestinal, seriously affect the life quality of patients, many patients had to discontinued therapy due to chemotherapy reactions. Therefore, how to reduce side effects of chemotherapy, in the mean time it must be safety and improve quality of life have aroused more and more attention.

This study suggested that incidence of myelosuppression in III-IV lever in experimental group A, B andC was lower than that in Control group ($p<0.05$), but no significant differences between group A, B and C ($p>0.05$). and the group C were not associated with more toxicities in treatment. The adverse effects of gastrointestinal among the experimental group A, B, C have no significant difference but lower than Control group ($p<0.05$). And no kidney toxicity (Elevated Cr) was found in all 4 groups.

This study suggest that Brucea javanica combined with chemotherapy or Cantharidin combined with chemotherapy could both improve quality of life in the patients. Brucea Javanica and Cantharidin combined with chemotherapy for patients with NSCLC were not associated with more toxicities.So, this study suggest that it is safe to treat patients with Brucea Javanica and Cantharidin combined with chemotherapy. However, the efficacy of Brucea Javanica and Cantharidin combined with chemotherapy for patients with NSCLC was not evaluated in this sdudy, further clinical experiments should be conducted to evaluate the response rate of Brucea Javanica and Cantharidin combined with chemotherapy for patients with NSCLC.

Acknowledgements

Dr. Xin-En Huang is supported by Traditional Chinese Medicine Scientific Research Project (LZ11091) and Jiangsu Province fourth stage “333 high- level Personnel Training Project” third levels of talent cultivating object.

References

Dai LL (2012). Mylabris sodium vitamin B 6 combined chemotherapy in treatment of NSCLC (the clinical curative effect of Meta analysis). *J Pract Oncol*, **27**, 6.

Fei ZH, Yao CY, Yang XL, Huang XE, Ma SL (2013). Serum BMP-2 up-regulation as an indicator of poor survival in advanced non-small cell lung cancer patients. *Asian Pac J Cancer Prev*, **14**, 5293-9.

Gu M, Li SY, Huang XE, et al (2012). A phase II study on continuous infusional paclitaxel and 5-Fu as first-line chemotherapy for patients with advanced esophageal cancer. *Asian Pac J Cancer Prev*, **13**, 5587-91.

Huang XE, Tian GY, Cao J, et al (2013). Pemetrexed as a component of first-, second- and third- line chemotherapy in treating patients with metastatic lung adenocarcinoma. *Asian Pac J Cancer Prev*, **14**, 6663-7.

Liu J, Huang XE, Tian GY, et al (2013). Phase II study on safety and efficacy of Yadanzi® (Javanica oil emulsion injection) combined with chemotherapy for patients with gastric cancer. *Asian Pac J Cancer Prev*, **14**, 2009-12.

Lu YY, Huang XE, Cao J,, et al (2013). Phase II study on Javanica oil emulsion injection (Yadanzi®) combined with chemotherapy in treating patients with advanced lung adenocarcinoma. *Asian Pac J Cancer Prev*, **14**, 4791-4.

Nie YL, Liu KX, Mao XY, et al (2012). Effect of injection of brucea javanica oil emulsion plus chemoradiotherapy for lung cancer: a review of clinical evidence. *J Evid Based Med*, **5**, 216-25.

Torbeck R, Pan M, DeMoll E, Levitt J (2014). Cantharidin: a comprehensive review of the clinical literature. Dermatol Online J, 20, pii: http://www.escholarship.org/uc/item/45r512w0.

Wang Q, Wang M, He X (2013). [Meta-analysis on treatment of non-small cell lung cancer with brucea javanica oil emulsion in combination with platinum-contained first-line chemotherapy]. *Zhongguo Zhong Yao Za Zhi*, **37**, 2022-9. (Article in Chinese)

Wei GL, Huang XE, Huo JG, Wang XN, Tang JH (2013). Phase II study on pemetrexed-based chemotherapy in treating patients with metastatic gastric cancer not responding to prior palliative chemotherapy. *Asian Pac J Cancer Prev*, **14**, 2703-6.

Xu X, Wang L, Xu HQ, et al (2013). Clinical comparison between paclitaxel liposome (Lipusu®) and paclitaxel for treatment of patients with metastatic gastric cancer. *Asian Pac J Cancer Prev*, **14**, 2591-4.

Yan HA, Shen K, Huang XE (2013). Clinical study on mannan peptide combined with TP regimen in treating patients with non-small cell lung cancer. *Asian Pac J Cancer Prev*, **14**, 4801-4.

Zhan YP, Huang XE, Cao J, et al (2012). Clinical safety and efficacy of Kanglaite® (Coix Seed Oil) injection combined with chemotherapy in treating patients with gastric cancer. *Asian Pac J Cancer Prev*, **13**, 5319-21.

Zhan YP, Huang XE, Cao J, et al (2013). Clinical study on safety and efficacy of Qinin® (cantharidin sodium) injection combined with chemotherapy in treating patients with gastric cancer. *Asian Pac J Cancer Prev*, **13**, 4773-6.

Zhang WD, Zhao H (2006). Role and molecular mechanism of cantharidin in cell cycle arrest of A549 human lung carcinoma cells through mitogen-activated protein kinase pathway. *J Chin Med Univ*, 0258-4646 (2006) 04-0382-0.

Zhang XJ, Wang XL (2013). Inhibitory effect of Brucea javanica oil emulsion on proliferation of NCI-H460 cells and underlying mechanism. *Chin J Cancer Biother*, **18**, 5.