RESEARCH ARTICLE

Phase II Study on Javanica Oil Emulsion Injection (Yadanzi®) Combined with Chemotherapy in Treating Patients with Advanced Lung Adenocarcinoma

Yan-Yan Lu[1], Xin-En Huang[1]*, Jie Cao[1], Xia Xu[1], Xue-Yan Wu[1], Jin Liu[1], Jin Xiang[2], Lin Xu[3]*

Abstract

Purpose: To investigate the efficacy and safety of Javanica oil emulsion injection (Yadanzi®) combined with pemetrexed and platinum (PP) for treating patients with advanced lung cancer. Patients and Methods: From June 2011 to June 2013, we recruited 58 patients with advanced lung cancer, and divided them into two groups. Twenty eight patients received Yadanzi® (from ZheJiang Jiuxu Pharmaceutical Co., Ltd.) together with PP chemotherapy (combined group), while the others were given only PP chemotherapy (control group). After two cycles of treatment, efficacy and safety of treatment were evaluated. Results: The overall response rate [(CR+PR+SD)/(CR+PR+SD+PD)] of the combined group was higher than that of control group (89.7% vs. 86.2%, $p>0.05$). Regarding rate of life improvement, it was 82.8% in combined group, and 51.7% in the control group ($p<0.05$). In terms of side effects, leukopenia in combined group was less frequent than that in control group ($p<0.05$). More patients in the control group were found to suffer liver toxicity. Conclusions: Javanica oil emulsion injection combined with chemotherapy could be considered as a safe and effective regimen in treating patients with advanced lung adenocarcinoma. It can improve the quality of life and reduce the possibility of leukopenia. Further clinical trials with a large sample size should be conducted to confirm whether addition of Yadanzi® to chemotherapy could increase the response rate, reduce toxicity, enhance tolerability and improve quality of life for patients with advanced lung cancer.

Keywords: Javanica oil emulsion injection - lung adenocarcinoma - toxicity - tolerability

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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 R 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) may increase effectiveness of platinum based chemotherapy in this setting (McCulloch, M., et al.,2006).

Javanica oil emulsionsemulsion (Yadanzi®) is a product with Brucea Jen petroleum ether extracts as raw materials, and purified soybean lecithin as emulsifier. Although main active ingredient is not well clarified (Liu et al., 2012), javanica oil emulsion is reported to be active in treating patients with lung cancer, brain metastases from lung and gastrointestinal cancer (Wang et al., 2012). Possible mechanism of anti-cancer effect includes inhibition of topoisomerase II, blockage of cell cycle in S phase and a direct damage on plasma membrane.

On this background, we conduct this study to detect safety and efficacy of Javanica oil emulsion injection (Yadanzi®) when combined with chemotherapy.

Materials and Methods

Patients

Patients recruited in this study were required to be pathologically/ cytologically diagnosed with lung adenocarcinoma in Jiangsu Cancer Hospital & Research Institute; to sign an informed consent before treatment; to expose to long term chemotherapy or supportive care; to have a score of karnofsky performance status (KPS) ≥ 50 with expectancy life span more than 3 moths; to be classified in stage IVaccording to TNM-classification with no surgical indications and no contraindications for chemotherapy.

*[1]Department of Chemotherapy, [2]Department of Research, the Affiliated Jiangsu Cancer Hospital of Nanjing Medical University & Jiangsu Institute of Cancer Research,Nanjing, China *For correspondence: huangxinen06 @aliyun.com, xulin_83@yahoo.cn*

Table 1. Patient Characteristics

Variable	Combined group (N=29)	Control group (N=29)
Sex		
Male	17	21
Female	12	8
Age		
40-50	5	4
50-60	11	12
60-70	11	8
>70	2	5
KPS		
50-60	2	4
60-70	12	10
70-80	12	14
>80	3	1

Methods

Chemotherapy of pemetrexed and platinum (PP) was applied to all patients. The dose of pemetrexed and platinum was in accordance with NCCN guideline: PEM 500 mg/m^2 ,platinum (cisplatin 60~80 mg/m^2, ivgtt, d1~3; or carboplatin 300 mg/m^2, ivgtt, d1; nedaplatin 100 mg/m^2, ivgtt, d2).

For control group, only PP regimen was given. For combined group, PP regimen was combined with javanica oil emulsion injection (Yadanzi®, made by ZheJiang Jiuxu Pharmaceutical Co., Ltd.). Yadanzi® 30 ml, was dissolved in 250 ml normal saline, intravenously infused during chemotherapy, once daily and continued for 2 cycles. Antiemetics were given conventionally, and routine blood test, eg., blood biochemistry and tumor markers were examined prior, during and after chemotherapy. CT scan was reviewed after two cycles of treatment to evaluate efficacy.

Efficacy evaluation

Before chemotherapy, all patients received physical examination, routine blood test, and imaging test (including CT, MRI, or PET-CT).

Treatment efficacy was evaluated after at least two cycles of chemotherapy according to RECIST criteria (Response Evaluation Criteria In Solid Tumor) (Sohaib, 2012), in which complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) was separately defined. Toxicities were assessed and graded according to WHO criteria (De Angelis, 2004). Quality of life was designated increasing if KPS score increased by 10 after treatment, decreasing if the score decreased by 10 and otherwise stable.

Table 4. Toxicity of Myelosuppression

Item	NO.	Toxicity extent according to NCI					
		O	I	II	III	IV	*P*
Leucopenia							
Combined group	29	13	12	3	1	0	0.038
Control group	29	21	6	2	0	0	
Hemoglobin							
Combined group	29	16	7	6	0	0	0.699
Control group	29	17	8	4	0	0	
Platelet							
Combined group	29	25	1	1	1	1	0.824
Control group	29	24	4	0	1	0	

Table 5. Toxicity of Liver Damage

Group	ALT, AST elevated	ALT, AST not elevated	*P*
Combined group	13	16	0.093
Control group	19	10	

*ALT, alanine aminotransferase; AST, glutamic oxalacetic transaminase enzyme

Research experience

We have enough experience in conducting medical researches, including clinical researches, and have published some results elsewhere (Jiang et al., 2010; Gao et al., 2011; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Gong et al., 2012; Gu et al., 2012; Li et al., 2012; Yu et al., 2012; Zhan et al., 2012; Zhan et al., 2012; Deng et al., 2013; Huang et al., 2013; Liu et al., 2013; Liu et al., 2013; Lu et al., 2013; Wu et al., 2013; Yin et al., 2013; Yin et al., 2013).

Results

From June 2011 to June 2013, we recruited 58 patients, including 29 patients (male 17, female 12, age 43~80) in combined group, and 29 (male 21, female 8, age 46~74) in control group. The general information between two groups e.g., sex, age, and Karnofsky performance status was comparable (Table 1).

The response rate [(CR+PR+SD)/(CR+PR+SD+PD)] of combined group was 89.7% while the control group 86.2% (p>0.05). The detail was listed in Table 2. Regarding rate of life improvement, that was 82.8% in combined group, and 51.7% in control group (p<0.05) (Table 3), indicating that combined group had advantages on the

Table 2. Treatment Efficacy of Two Groups

Group	NO.	CR	PR	SD	PD	(CR+PR+SD)%	P
Combined group	29	0	4	22	3	0.897	>0.05
Control group	29	0	5	20	4	0.862	

*NO., number of patient; CR, Complete Remission; PR, Partial response; SD, stable disease; PD, progressive disease; *combined group was chemotherapy combined with javanica oil emulsion injection; control group was chemotherapy

Table 3. Change of Karnofsky Performance Status Score

Group	NO.	Improvment	Stable	Ineffectiveness	(Improvment)%	P
Combined Group	29	24	2	3	0.828	<0.05
Control Group	29	15	8	6	0.517	

*KPS, score; increased, ≥10 after treatment; stable, <10; decreased, ≥10

improvement of quality of life. Both group experienced myelosuppression. In Table 4, it is demonstrated that leukopenia in combined group is less then control group with statistical significance ($p<0.05$). As for liver injury, no statistical significance was detected between two groups as showed in Table 5.

Discussion

The purpose of treating patients with advanced cancer is to prolong survival time and to improve quality of life. Combination chemotherapy is associated with significantly prolonged survival time and improved quality of life for patients with non-small-cell lung cancer (Bunn, 2002). However, chemotherapy is also associated with toxicities e.g., gastrointestinal reactions and bone marrow depression, affecting quality of life of patients, and resulting in discontinuation of therapy due to intolerability (Bunn, 2002). Chinese herbal medicine (CHM) is reported to reduce these side effects of chemotherapy (Taixiang et al., 2005; Liu et al., 2013). And further studies on CHM will focus on how to improve the quality of life and extend survival time for patients with advanced cancers.

Javanica oil emulsion is produced by using Brucea Jen petroleum ether extracts as raw materials, and purified soybean lecithin as emulsifier (Liu et al., 2012). The main active ingredient is oleic acid and linoleic acid, and the antitumor activity of both was confirmed by previous studies (Ding et al., 2006). Javanica oil emulsion is mainly used in lung cancer, brain metastases from lung or gastrointestinal cancer, with mild efficacy (Ma et al., 2004). Its possible mechanism of action includes specifically inhibiting the vitality of topoisomerase II, arresting cell cycle in S phase and directly damaging the structure of plasma membrane (Ding et al., 2006). It was also reported to control tumor through regulating immunological function. Javanica oil emulsion was suggested to protect bone marrow hematopoietic stem cells, and promote its proliferation (Ping et al ,1996).

In our study, it was demonstrated that the response rate of combined group was higher than control but was not statistically significant ($p>0.05$), probably due to inadequate sample size. From this perspective, further study with larger sample size and longer follow up period should be considered.

In conclusion, our study showed that Javanica oil emulsion injection combined with chemotherapy could be considered as a safe and effective regimen in treating patients with advanced lung cancer. It is able to improve quality of life of patient and reduce side effect of chemotherapy. And further study is needed to confirm whether the response rate of a combination of Javanica oil emulsion injection and chemotherapy is superior to chemotherapy alone.

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