RESEARCH ARTICLE

Phase II Study on Safety and Efficacy of Yadanzi® (Javanica oil emulsion injection) Combined with Chemotherapy for Patients with Gastric Cancer

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Abstract

Objective: To investigate the efficacy and safety of Yadanzi® (Javanica oil emulsion injection) combined with chemotherapy for treatment of patients with advanced gastric cancer. Methods: From January 2011 to December 2012, we recruited 75 patients with advanced gastric cancer, who received javanica oil emulsion injection together with chemotherapy. After two cycles of treatment, efficacy and safety of the combined therapies were evaluated. Results: Overall response rate of 75 patients after treatment was 85.3% (CR+PR+SD). Treatment related side effects were recorded. No treatment related death occurred. Conclusions: Javanica oil emulsion injection combined with chemotherapy could be considered as a safe and effective regimen in treating patients with advanced gastric cancer. Further randomized clinical trials should be conducted to confirm whether the addition of Yadanzi® to chemotheraphy could be associated with reduced toxicity, enhanced tolerability and improved quality of life for patients with advanced gastric cancer.

Keywords: Javanica oil emulsion injection - chemotherapy - advanced gastric cancer

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Introduction

Gastric cancer is one of the most common malignant tumors in china. It continues to be a fatal disease with majority of cases presenting with advanced disease (Blum et al., 2013). Chemotherapy is a main treatment option for patients with advanced gastric cancer. However, chemotherapy is reported to be associated with a series of adverse reaction, eg, bone marrow suppression, gastrointestinal toxicity, immunosuppression, etc (Yamamoto and Iwase, 2012). Traditional Chinese Medicine (TCM) is widely used in treating patients with gastric cancer in China (Liu et al., 2011). On this background, it is possible to develop a chemotherapy regimen containing TCM to enhance response rate, reduce toxicity and improve quality of life for patients in this setting (Man et al., 2012).

Yadanzi® (Javanica oil emulsionsemulsion) is a product with Brucea Jen petroleum ether extracts as raw materials, and purified soybean lecithin as emulsifier. The 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 includes inhibition of topoisomerase II, blockage of cell cycle in S phase and a direct damage on the structure of plasma membrane. Our hypothesis is that the addition of Yadanzi® to chemotherapy could increase the response rate of chemotherapy and quality of life of patients with advanced gastric cancer.

Materials and Methods

Patients

Patients were required to be pathologically/cytologically diagnosed with gastric cancer in Jiangsu Cancer Hospital & Research Institute from January 2011 to December 2012; 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) ≥ 70; to be 25 to 75 years of age. Other eligibility criteria included: adequate hematological (white blood cell count > 3.0×10^9 and platelet count > 150×10^9), liver (bilirubin and transaminases < 1.5 times the upper normal limit) and renal function (creatinine leval < 1.5 times the upper normal limit); patients were excluded from this study if they failed to complete two cycles of chemotherapy, or with any serious medical or psychiatric condition, or other malignancies. Pregnant or lactating women are also excluded from this study.

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Table 1. Patient Characteristics (n = 75)

Characteristic	No. of patients	%
Sex		
Male	47	62.66
Female	28	37.33
Age (years)		
Median	61	
25-35	4	5.33
36-45	8	10.67
46-55	16	21.33
56-65	34	45.33
66-75	13	17.33
Histology type		
tubular adenocarcinoma	39	52
poor differentiated adenocarcinoma	22	29.33
mucinous adenocarcinoma	4	5.33
signet ring cell carcinoma	9	12
squamous cell carcinoma	1	1.33
Bone marrow suppression (I°-IV°)		
I°	14	18.67
II°	8	10.67
III°	6	8
IV°	6	8
Chemotherapy medicines		
DOC	15	
OXA	31	
CPT-11	11	
FT-207	13	
Others	5	
TS-1	9	
Xeloda1	14	

Methods

Chemotheraphy agents including oxaliplatin, irinotecan, paclitaxel, docetaxel, fluorouracil, tegafur, etc. And combination is as following: DOC regimen, which consisted of docetaxel, oxaliplatin and capecitabine; Xelodal-contained chemotherapy regimens, which consisted of xelodal and oxaliplatin; tegafur-based regimen, which consisted of tegafur, taxol and leucovorin; and other regimens. Detailed information of these chemotherapy was reported elsewhere (Li et al., 2011; Xu et al., 2011). Chemotherapy for all patients was applied with javanica oil emulsion injection (Yadanzi®, made by ZheJiang Jiuxu Pharmaceutical Co., Ltd.). Yadanzi® 30 ml, dissolved in 250 ml normal saline, was intravenous infused during chemotherapy, once daily and continued for 2 cycles. Routine blood test, blood biochemistry and tumor markers were reviewed prior, during and after chemotherapy. CT scan was reviewed after two cycles of treatment to evaluate efficacy.

Efficacy evaluation

Before the chemotherapy, all patients received physical examination, routine blood test and blood biochemical examination. Treatment efficacy was evaluated according to RECIST criteria (Response Evaluation Criteria In Solid Tumor) (Sohaib, 2012) after more than two cycles of chemotherapy. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) was separately defined. Quality of life was designated increasing if the KPS score increased by 10 after treatment, decreasing if the score decreased by 10 and otherwise stable. We have enough experience in conducting medical researches, and have published some results elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan 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; Li et al., 2012; Yu et al., 2012).

Table 2. Treatment Efficacy and Karnofsky Performance Status Score

Treatment	Number	%
CR	0	0
PR	21	28
SD	43	57.33
PD	11	14.67
CR+PR	21	28
CR+PR+SD	64	85.33
KPS score (after 2 cycles)		
Increased	9	12
Stable	48	64
Decreased	18	24

*N, number of patient; CR, Complete Remission; PR, Partial response; SD, stable disease; PD, progressive disease; *Experimental group was chemotherapy combined with javanica oil emulsion injection; *KPS, score; increased, ≥10 after treatment; stable, <10; decreased, ≥10

Table 3. Toxicity

Toxicity Grade	I	II	III	IV
Leukopenia	24	8	5	6
Thrombocytopenia	18	8	6	3
Elevated ALT	21	13	3	0
Nausea,Vomiting	25	11	2	1

*ALT, alanine aminotransferase

Toxicity Assessment and Safety:

All Patients were assessed and graded for toxicities according to WHO criteria (De Angelis, 2004). During the Yadanzi® (Javanica oil emulsion) Injection and chemotherapy, all adverse reactions were documented.

Results

From January 2011 to December 2012, we recruited 75 patients with gastric cancer satisfied all study criteria. General characteristic of patients is listed in Table 1. Among them, 47 were male and 28 female, average age was 61 years. All patients had completed medical records, including results of CT scan, endoscopy or pathology biopsy. Of all 75 patients, 39 diagnosed with tubular adenocarcinoma, 22 with poor differentiated adenocarcinoma, 4 mucinous adenocarcinoma, 9 signet ring cell carcinoma and 1 squamous cell carcinoma. After 2 cycles of Yadanzi® and chemotherapy, bone marrow suppression was recorded for 44 patients: I° in 24, II° in 8, III° in 6 and IV° in 6 patients. Forty patients reported of poor appetite and nausea, 5 watery diarrhea, 4 coprostasis, and 8 vomiting were recorded. One patient reported red skin rash with fever, and 17 cases with hepatic function enzymes higher than normal. One patient was diagnosed with allergy. Main side effects were listed in Table 3.

Efficacy

75 patients received javanica oil emulsion injection combined with chemotherapy for at least 2 cycles of treatment. No CR was observed after 2 cycles. The response rate of experimental group (CR+PR)/(CR+PR+SD+PD) was 28%.The disease control rates (CR+PR+SD)/(CR+PR+SD+PD) was 85.3%.

Discussion

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 gastric cancer, and improve the quality of life. However, in the treatment of advanced gastric cancer, chemotherapy will produce toxicity such as gastrointestinal reactions and bone marrow depression, seriously affect the quality of life of patients, many patients had to discontinued therapy due to inability to tolerate chemotherapy reactions. Javanica oil emulsion is product which use Brucea Jen petroleum ether extracts as raw materials, and purified soybean lecithin as emulsifier (Liu et al., 2012). The main active ingredient are oleic acid and linoleic acid, and the antitumor activity of both have already been confirmed. Javanica oil emulsion is mainly used in lung cancer, brain metastases from lung and gastrointestinal cancer treatment in clinical, and have achieved satisfactory results. Its possible mechanism of action includes specifically inhibit the vitality of topoisomerase II, arrest cell cycle in S phase and the directly damage the structure of plasma membrane. It can also kill tumor cells through regulating the body immune. Javanica oil emulsion can protect the bone marrow hematopoietic stem cells, and promote its proliferation. It can also enhance immunity, improve physical fitness and reduce chemotherapy side effects. The patient's quality of life has been improved. It subjectively enhance their confidence of overcoming the disease, and objectively create the conditions for better treatment. Our results show as follows: after 2 cycle, short-term effect is not obvious, probably due to the combination therapy cycle is short (2 cycles), older patients response slower to treatment (median age ≥ 60 years) and traditional Chinese medicine effects slowly. The significantly effective rate of improvement in quality of life was 12%. In conclusion, in this study, the effective rate of (Yadanzi®) combined with chemotherapy in treating patients with advanced gastric cancer was 85.3%. The KPS score improvement was 12%. Thus, Javanica oil emulsion injection combined with chemotherapy could reduce side effects caused by chemotherapy, and improve quality of life of patients. However, our results deserve to be further investigated by randomized controlled clinical trails.

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