RESEARCH ARTICLE

Clinical Study on Safety and Efficacy of Qinin® (Cantharidin Sodium) Injection Combined with Chemotherapy in Treating Patients with Gastric Cancer

Yi-Ping Zhan[1,2], Xin-En Huang[1]*, Jie Cao[1], Yan-Yan Lu[1], Xue-Yan Wu[1], Jin Liu[1], Xia Xu[1], Lin Xu[3]*, Jin Xiang[4], Li-Hong Ye[2]*

Abstract

Objectives: To assess the efficacy, side effects, and the impact on quality of life with Qinin® (Cantharidin sodium) injection combined with chemotherapy for gastric cancer patients. Method: A consecutive cohort of 70 patients were divided into two groups: experimental group with cantharidin sodium injection combined with chemotherapy, while the control group received chemotherapy alone. After more than two courses of treatment, efficacy, quality of life and side effects were evaluated. Results: The response rate of experimental group was not significantly different from that of the control group (P>0.05), but differences were significant in clinical benefit response and KPS score. In addition, gastrointestinal reactions and the incidence of leukopenia were lower than in the control group (P<0.05). Conclusions: Qinin® (Cantharidin sodium) injection combined with chemotherapy enhances clinical benefit response, improving quality of life of gastric cancer patients and reducing side effects of chemotherapy. Thus Qinin® (Cantharidin sodium) injection deserves to be further investigated in randomized control clinical trails.

Keywords: Cantharides sodium injection - chemotherapy - gastric cancer treatment

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Introduction

Based on the GLOBOCAN 2008 estimates, stomach cancer is the third most common cause of death from cancer in males and the forth in females,with 989,600 new cancer cases and 738,000 deaths in this year (Jemal et al., 2011). The highest incidence rates are in Eastern Asia including China. Therefore, now, Stomach cancer has become the common and frequently-occurring disease which seriously hazard to human health (Ferlay et al., 2010). Chemotherapy is one of important treatment of gastric cancer and is the only treatment option available in advanced gastric cancer. Chemotherapy may relieve gastric cancer-related symptoms, improve quality of life and prolong survival in some patients with gastric cancer. how to increase efficacy and decrease toxicities of chemotherapy remains a focus in this area.

Qinin® (Cantharidin sodium) injection, which is Semi-synthetic derivative of cantharidin, has been developed and manufactured by Guizhou magic Pharmaceutical Co., Ltd in China, Cantharidinate sodium Injection is one of Chinese herbal preparation with anti-cancer activity, which mainly used for the treatment of solid tumor including gastric cancer (Cui et al., 2008; Guo et al., 2009; Liang et al., 2011). So, our hypothesis is that the combination of Chemotherapy and Canthar-idinate sodium Injection could be superior to Chemotherapy alone in treatment efficacy and toxicity regarding gastric cancer.

Materials and Methods

Patient eligibility

All the Patients were diagnosed pathologically as stomach cancer, with karnofsky performance status≥60, age between 18 to 75 years, the survival time≥3 months, adequate bone marrow (white blood cell count > 3.0×10^9 and platelet count >80×10^9), liver function (bilirubin and transaminases < 2 times the upper limit normal), no evidence of heart and kidney disease, signed an informed consent before chemotherapy.

Patients excluded from the study if they failed to complete more than two cycles of chemotherapy, candidate with any serious medical or psychiatric condition, other malignancies, or pregnant and lactating women.

Treatment

In experimental group, Qinin® (Cantharidin sodium) injection was combined with chemotherapy, which

*[1]Department of Chemotherapy, Nanjing Medical University Affiliated Cancer Hospital of Jiangsu Province, Cancer Institution of Jiangsu Province, [3]Department of Thoracic Surgery, [4]Department of Research, Jiangsu Cancer Hospital & Research Institute, [2]Nanjing University of Traditional Chinese Medicine, Nanjing, China *For correspondence: huangxinen06@yahoo.com.cn, xulin83@vip.sina.com, cocolihongye@126.com*

Table 1. Comparison of Treatment Efficacy in Two Groups

Treatment	N	CR	PR	SD	PD	CR+PR	CR+PR+SD
Experimental group	35	0	12	16	7	12	28
Control group	35	0	9	11	15	9	20

*N, number cases; CR, Complete Remission; PR, Partial response; SD, stable disease; PD, progressive disease; *Experimental group was chemotherapy combined with cantharidin sodium injection.which is developed and manufactured by Guizhou magic Pharmaceutical Co., Ltd in China. Control group. Control group was given chemotherapy alone

used mainly fluoropyrimidine-based chemotherapy regimens, while in control group was administered with chemotherapy alone. The experimental group received cantharidin sodium Injection 0.5 mg, which dissolved in normal saline 250 ml or 500 ml daily, intravenous infusion during chemotherapy. Routine blood test, blood biochemistry and tumor markers were reviewed during and after chemotherapy.

Efficacy Observation

Treatment efficacy was evaluated according to RECIST criteria (Sohaib, A. 2012) after more than two cycles of chemotherapy. In details Complete Remission (CR), partial response (PR), stable disease (SD), and progressive disease (PD) was seperately defined. General performance was evaluated in accordance with the Karnofsky Scale (Yates et al.1980). 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.

Toxicity Assessment

All Patients were assessed and graded for toxicities according to WHO criteria (De Angelis, V. 2004).

Statistical analysis

The study data were analyzed by t and enumeration data by χ^2 test. Statistic significance was determined if $p<0.05$. 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).

Results

Efficacy

70 patients fulfilled eligibility had completed at least 2 cycles of treatment. No CR was observed in both two groups. The response rate of experimental group (CR+PR)/(CR+PR+SD+PD) was 34%,while that in control group was 25%. The differences were not statistically significant ($p>0.05$). The disease control rates of two groups (CR+PR+SD)/(CR+PR+SD+PD) were 80% (experimental group), 57% (control group) respectively, with statistical significance ($p<0.05$) (Table 1).

Table 2. Karnofsky Performance Status Score in Two Groups*

Treatment	Increased	Stable	Decreased
Experimental group	18	12	5
Control group	10	17	8

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

Table 3. Toxicity in Two Groups*

Toxicity	Experimental group* Number				Control group Number			
Grade/	I	II	III	IV	I	II	III	IV
Leukopenia	7	7	3	0	6	11	7	2
Thrombocytopenia	4	2	1	0	6	5	3	0
Elevated ALT	7	1	0	0	8	3	0	0
Elevated Cr	0	0	0	0	0	0	0	0
Nausea,Vomiting	10	7	0	0	14	10	2	0

*ALT, alanine aminotransferase; Cr, creatinine

Quality of life before and after treatment

KPS score of experimental group increased in 18 cases (51%), 12 cases stable and 5 cases decreased, while that of control group increased in 10 cases (28%), 17 cases stable and 8 cases decreased. The difference between two groups was statistically significant ($p<0.05$) (Table2).

Toxicity

All patients underwent toxicities assessment. Treatment related side effects were reversible, and no termination of chemotherapy or death caused occurred. In table 3, the main adverse effects were myelosuppression and gastrointestinal reactions. In experimental group, leukopenia rate was 48%, 8% of them with grade III-IV; 17% patients showed grade I-II thrombocytopenia and 2% with grade III thrombocytopenia; grade I-II nausea and vomiting was 48%, and none of grade III-IV. In control group, leukopenia rate was 74%, 25% of them with grade III-IV; 31% patients with grade I-II thrombocytopenia and 8% with grade III thrombocytopenia; grade I-II nausea and vomiting was 68%, and 5% with grade III-IV. Liver dysfunction of the experimental group was significantly lower than the control group.Both of two groups were not observed with impaired renal function

Discussion

Chemotherapy for gastric cancer still is not normalized and standardized (Okines et al., 2010). Chemotherapy is reported with associated ability to improve the clinical symptoms, reduce the rate of recurrence and metastasis, and prolongs survival. But, chemotherapy is reported often brings about serious side effects. Therefore, how to reduce side effects of chemotherapy, in the mean time increase efficacy and improve quality of life have aroused more and more attention. It is a distinguishing feature of traditional Chinese medicine to contribute in this area (Xu et al., 2012).

Cantharidin is a sesquiterpene derivatives extracted from the Mylabris body (Verma et al., 2012). Cantharidin sodium is a semi-synthetic derivative of cantharidin. By

reducing the cancer cells to the uptake of amino acids, inhibit protein synthesis, stimulating macrophages, lymphocytes, polymorphonuclear cells produce interleukin, and finally to improve immunity and enhance anticancer efficacy (Bajsa et al., 2011; Hsieh et al., 2011).

Qinin® (Cantharidin sodium) injection has been developed and manufactured by Guizhou magic Pharmaceutical Co., Ltd in China. Studies have shown that the main active ingredient is cantharidin, which has characteristics of anti-cancer without causing myelosuppression, and it can promote hematopoietic stem cells to accomplish differentiation into myelomonocytic in order to increase the leukocyte (Liu et al., 2009). Our study shows that the differences of short-term efficacy in two groups were not statistically significant, but the clinical benefit rate, and KS score improvement of experimental group were significantly higher than that of control group. Thus, Sodium Cantharidinate Injection combined with Chemotherapy could reduce side effects causing by chemotherapy, and improve quality of life. However, our results deserves to be further investigated by randomized controlled clinical trails.

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