RESEARCH ARTICLE

Clinical Study on Safety of Cantharidin Sodium and Shenmai Injection Combined with Chemotherapy in Treating Patients with Breast Cancer Postoperatively

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Abstract

Objectives: To assess side effects on Cantharidin sodium and Shenmai injection combined with chemotherapy in treating patients with breast cancer postoperatively. Method: Patients with breast cancer receiving postoperative chemotherapy were retrospectively collected, and divided into four groups: group A with cantharidin sodium injection combined with chemotherapy; group B with Shenmai injection combined with chemotherapy; group C with both cantharidin sodium and Shenmai injection combined with chemotherapy; while group D (control group) received chemotherapy alone. All patients were administered docetaxel at a dose of 75 mg /m^2 on day 1, epirubicin hydrochloride at a dose of 60 mg /m^2 on day 1, and cyclophosphamide at a dose of 500 mg/m^2 on day 1 for 3 cycles (repeated at 21 day intervals). After ≥ three courses of treatment, quality of life and side effects were evaluated. Results: There were a total of 78 patients in this study, and the incidence of leukopenia and gastrointestinal reactions in groups A and B were lower than those in the control group and lowest in group C (p<0.05). Conclusions: Thus cantharidin sodium and Shenmai injection combined with chemotherapy reduce side effects and deserve to be further investigated in randomized clinical control trials.

Keywords: Cantharides sodium injection - Shenmai injection- chemotherapy - breast cancer treatment

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Introduction

Breast cancer is one of the leading causes of death for women worldwide, chemotherapy is one of the important treatment for breast cancer. Chemotherapy may relieve breast cancer-related symptoms, improve quality of life and prolong survival in some patients with breast cancer. At present a number of chemotherapitic options exist, including CM, PAC, NACT, etc.

However, dose-limiting toxicities are the most critical limitations of chemotherapy. Therefore, agents with the ability to increase efficacy without increasing toxicity are needed.

Cantharidin sodium injection, which is a semi-synthetic derivative of cantharidin, has been developed 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 breast cancer (Wang et al., 2009; Huang et al., 2010; Zhang et al., 2012).

Shenmai injection has a long history of application in China. It is developed and manufactured by Hangzhou Chiatai qingchunbao pharmaceutical co., LTD in China, and is composed of two herb ingredients, namely ginsenosides and ophiopogonis.It was initially used for the treatment of a dual deficiency of qi and yin with symptoms of thirst and general weakness while suffering from heat stroke, fatigue, etc. According to TCM theory, Shenmai injection can reduce fatigue, thirst, general weakness, etc. It is widely used now to treat patients with cardiac disease, fatigue and cancer. Many patients have symptoms of general weakness, thirst, and fatigue after chemotherapy. These symptoms are similar to the syndrome of qi and yin deficiency diagnosed by TCM theory. So, our hypothesis is that the combination of Chemotherapy and cantharidinate sodium and Shenmai injection could be superior to chemotherapy alone or chemotherapy combined with only one of them in terms of efficacy and toxicity when treating patients with breast cancer.

Materials and Methods

Patient eligibility

All the Patients were diagnosed pathologically as breast cancer, with radical mastectomy, with karnofsky performance status ≥60, aged between 18-75 years, predicted survival time ≥3 months, with adequate bone marrow (white blood cell count >4.0×109 and

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platelet count >100×109), 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 three cycles of chemotherapy, with any serious medical or psychiatric condition, other malignancies, Pregnant or lactating women are excluded from the study.

Treatment method

Eligible patients were divided into cantharidin sodium injection group (Group A), Shenmai injection group (Group B), cantharidin sodium and Shenmai injection group (Group C) and control group (Group D). Each patient received chemotherapy of EC-T (CTX 500 mg/m^2 by intravenous infusion (iv) on day 1, EPI 60 mg/m^2 by intravenous infusion (iv) on day 1, DOX 75 mg/m^2 by intravenous infusion (iv) on day 1), Group A : cantharidin sodium injection 0.5 g iv on day 1. Group B: Shenmai injection 50 ml iv on day 1. Group C: both cantharidin sodium injection 0.5 g and Shenmai injection 50ml iv on day 1. GroupD:just chemotherapy.

Statistical analysis

SPSS13.0 statistical software was used for statistical analysis. Statistically significant difference was set at $p<0.05$. We have enough experience in conducting medical researches, and have published some results elsewhere (Gong et al., 2012; Li et al., 2012; Yu et al., 2012; Deng et al., 2013; Huang et al., 2013; Huang et al., 2013; Liu et al., 2013; Wu et al., 2013; Lu et al., 2013; Shen et al., 2013; Yan et al., 2013).

Table 1. Clinical Characteristics

Variable	Group A (n=20)	Group B (n=19)	Group C (n=19)	Group D (n=20)
Median age (years)	48.2 (30-66)	51.6 (37-71)	48.6 (34-64)	46 (31-65)
Surgery				
breast-conserving operation	5	2	4	1
Modified radical mastectomy	15	17	15	19
Histological subtype IDC	20	19	19	20
Tumour stage				
I-II	16	17	18	18
III-IV	4	2	1	2

IDC, invasive duct carcinoma

Results

Seventy-eight patients meet the study criteria and entered four study groups and completed more than three cycles of chemotherapy. General characteristics of patients are shown in Table 1.

Efficacy Observation

There are 20 patients in group A, D each , 19 in group B, C each. Efficacy 78 patients fulfilled eligibility had completed at least 3 cycles of treatment. we reviewed the imaging studies performed at the initiation of therapy. Follow-up imaging was performed after three cycles of chemotherapy. All imaging was reviewed by one thoracic radiologist. And three cycles nobody was disease progression.

Toxicity

In 4 groups, main adverse reactions are hematologic, gastrointestinal, and fatigue ($p<0.05$). The difference of incidence in baldness, renal function abnormality, peripheral neuritis among four groups is not statistically significant ($p>0.05$), but the incidence of nausea and vomiting, bone marrow suppression in III-IV lever and fatigue in group A and group B is lower than those in group D, but higher than those in group C, with statistically significant difference ($p<0.05$) and there's no significant difference between group A and group B ($p>0.05$). Otherwise, the incidence of elevated ALT among group A, B, D is not statistically significant, but lower in group C (Table 2).

Discussion

An increasing number of patients suffering from breast cancer were diagnosed yearly, and patients with advanced disease should be treated with adjuvant chemotherapy after surgery. Many side effects, such as lower white blood cell count, general weakness and loss of appetite are reported during and after adjuvant chemotherapy. These side effects may lower the quality of life of these patients.

Cantharidin is a sesquiterpene derivatives extracted from the Mylabris body (Verma et al., 2012). Cantharidin

Table 2. Adverse Reactions

Adverse reactions	Group A n=20					Group B n=19					Group C n=19					Group D n=20				
	I °	II °	III °	IV °	Incidence rates/%	I °	II °	III °	IV °	Incidence rates/%	I °	II °	III °	IV °	Incidence rates/%	I °	II °	III °	IV °	Incidence rates/%
Leukocytopenia	3	3	2	0	40	7	0	1	0	50	4	2	0	0	32	1	4	3	2	50
Nausea and vomiting	5	2	0	0	35	5	2	0	0	37	1	0	0	0	5	7	5	0	0	60
Baldness	2	10	8	0	100	2	12	5	0	100	1	12	6	0	100	2	11	7	0	100
Liverdysfunction	2	3	0	1	30	3	2	0	0	26	1	0	0	0	5	1	2	0	1	20
Fatige	3	2	1	0	30	4	2	0	0	32	2	0	0	0	10	7	3	2	2	70
Renal function abnormality	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Peripheral neuritis	1	0	0	0	5	0	0	0	0		0	0	0	0	0	1	0	0	0	5

sodium is a semi-synthetic derivative of cantharidin. 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 (Zhang et al., 2012).

Shenmai injection is derived from a famous traditional Chinese herbal prescription Shendong yin, and was first recorded in Zhengyin Maizhi (Pattern, Cause, Pulse, and Treatment) by Jing-Ming Qin in 1702 AD. It was found to be effective for treating chemotherapy related adverse reactions in patients with breast cancer (Wang et al., 2011)

This study suggested that the incidence of nausea and vomiting, Leukopenia in III-IV lever and fatigue in group A and B was lower than those in group D, but higher than in group C. Thus, Each of cantharidin and Shenmai injection combined with Chemotherapy could reduce side effects caused by chemotherapy and could improve quality of life and this result is consistent with previous studies (Wang et al., 2011, Zhang et al., 2012), and this effect was suggested to be more remarkable when both of them are administered together. However, our results deserve to be further investigated by randomized controlled clinical trails.

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