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Clinical Effects of *Shenqi Fuzheng* Injection in the Neoadjuvant Chemotherapy for Local Advanced Breast Cancer and the Effects on T-lymphocyte Subsets

Dai Zhijun 代志军, Wang Xijing 王西京, Kang Huafeng 康华峰, Ji Zongzheng 纪宗正, Liu Lei 刘蕾, Liu Xiaoxu 刘小旭, Song Lingqin 宋玲琴, Min Weili 闵卫利 & Ma Xiaobin 马小斌
The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710004, China

Objective: To evaluate clinical effects of *Shenqi Fuzheng* Injection (参芪扶正注射液) in the neoadjuvant chemotherapy for local advanced breast cancer and the effects on T-lymphocyte subsets. **Methods:** During the period from 2000 to 2005, 126 patients with local advanced breast cancer were treated with the neoadjuvant chemotherapy. They were randomly divided into the following two groups: a control group of 61 cases treated by chemotherapy alone and a study group of 65 cases treated by chemotherapy plus *Shenqi Fuzheng* Injection. All the cases of both groups were given the CEF (CTX 500 mg/m^2, d1, 8; EPI 40 mg/m^2, d1, 8; and 5-Fu 500 mg/m^2, d1,8) regimen. The clinical effects, the effects on T-lymphocyte subgroup and NK cells, and the toxic side effects were observed. **Results:** All the patients completed two cycles of the chemotherapy, and the efficacy and the toxic side effects were evaluated. For the primary tumor in the breast, the total effective rate was 69.2% (45/65) in the study group and 49.2% (30/61) in the control group with a statistically significant difference in the intergroup comparison (χ^2=5.251, P=0.022, < 0.05). There was no progression of the disease in both the groups, and there were no grade IV toxic side effects in the two groups. The major toxic responses were myelosuppression and gastrointestinal reaction, which were milder in the study group than the control group, and with a shorter recovery course in the former than the latter. Besides, an obvious rise of the T-lymphocyte subgroup and NK cells was found in the study group after the neoadjuvant chemotherapy, with a very significant difference from the controls (P<0.01). **Conclusions:** *Shenqi Fuzheng* Injection can improve and regulate immune function of the patients with local advanced breast cancer given the neoadjuvant chemotherapy, and therefore it can enhance the curative effect and reduce the side effect as well.

Key words: Breast cancer; Neoadjuvant chemotherapy; *Shenqi Fuzheng* Injection; Cellular immunity

Shenqi Fuzheng Injection is composed of two Chinese crude drugs, Dang Shen (党参 Radix Codonopsis) and Huang Qi (黄芪 Radix Astragali). Both of them can enhance the immune function of human body. The neoadjuvant chemotherapy, also called preoperative chemotherapy, has the merits such as decreasing the tumor stage, and enhancing the operability and the survival rate.[1] Nowadays, the neoadjuvant chem- otherapy has been adopted for the treatment of breast cancer, especially for the local advanced breast cancer. [2] From January 2000 to December 2005, 126 patients with stage IIb-III breast cancer were treated with the neoadjuvant chemotherapy. This study is designed to evaluate the

clinical effects of *Shenqi Fuzheng* Injection in the neoadjuvant chemotherapy for breast cancer and the effects on immune function.

GENERAL DATA

During the period from 2000 to 2005, 126 cases of local advanced breast cancer at stage IIb-III were randomly divided into the following two groups: a control group of 61 cases treated by chemotherapy alone and a study group of 65 cases treated by chemotherapy plus *Shenqi Fuzheng* Injection.

In this series, all the breast cancer patients were comfired by cytology or biopsy, and they had not been treated by radiotherapy, chemotherapy or endocrine therapy. The karnofsky score for all of them was over 80, and with no obvious abnormal findings in the cardiac, hepatic and renal functions. The general data were comparable between the two groups (see Table 1).

Table 1. General data of the two groups

Group	*n*	Age (years)	Primary tumor stage			Lymph node stage		TNM stage		
			T2	T3	T4	N1	N2	IIb	IIIa	IIIb
Study	65	45.5±26.8(27-69)	30	24	11	37	28	31	21	13
Control	61	46.1±27.5(26-70)	29	21	11	34	27	29	20	12

METHODS

Neoadjuvant chemotherapy: The patients of both groups were given the CEF regimen (CTX 500 mg/ m^2, d1, 8; EPI 50 mg/ m^2, d1, 8; 5-Fu 500 mg/ m^2, d1, 8), with 28 days as one cycle. And all of them underwent the modified radical mastectomy after two cycles of the neoadjuvant chemotherapy. But from the first day of chemotherapy, the study group was additionally given intravenous dripping of *Shengqi Fuzheng* Injuection, 250 ml once a day during the two cycles of chemotherapy.

The Indexs bserved

1. Measure and compare the max-diameter and vertical diameter with one of the three methods (physical examination, B-ultrasonography of the mammary gland or radiography with molybdenum target tube) before and after the neoadjuvant chemotherapy, with re-examination given after each cycle of the chemotherapy, and then evaluate the clinical curative effect. The postoperative evaluation is based on the pathological findings.

2. Evaluate the general condition and disease stage by routine physical examination, blood examination (including blood picture, hepatic and renal function), ECG, X-ray, abdominal B-ultrasonography and bone scanning before the neoadjuvant chemotherapy and operation, with re-examination done one day before and one week after each cycle of the chemotherapy.

3. Immunology index[3]: The T-lymphocyte subsets (CD_3^+, CD_4^+, $CD_8^+$and CD_4^+/CD_8^+) were measured by Flow Cytometry; and the activity of NK cells ($CD_{16}^+/56^+$) by ^{3}H-TdR; and all the indexes were measured once before and after the treatment.

Criteria for therapeutic effects

The criteria suggested by UICC were adopted. 1) Pathological complete remission (pCR): No invasion of carcinoma cells was found in the primary tumor region. 2) Clinical complete remission (cCR): The tumor completely disappeared in clinical examination. Clinical partial remission (cPR): The product of max-diameter and max-vertical diameter of the tumor decreased by at least 50%. Stabilization of the disease (SD): The product of max-diameter and max-vertical diameter of the tumor decreased by less than 50%, or increased by less than 25%. Progression of the disease (PD): The product of max-diameter and max-vertical

diameter of the tumor increased by more than 25%. The remission rate = complete remission + partial remission. The toxic side effects can be divided into grade 0、I、II、III and IV according to the Acute and Subacute Toxicity Grading Standards for the Chemotherapy Drugs stipulated by WHO, which were evaluated after each cycle of the neoadjuvant chemotherapy.

Statistical processing

The SPSS 10.0 statistical software was used for processing of the experimental data. χ^2 test and t test were adopted for the intergroup comparison of the mean values, with $P<0.05$ considered to be significantly different.

RESULTS

1. Short-term therapeutic effects of the neoadjuvant chemotherapy (see Table 2):

No progression of the disease was found in both of the two groups. Two cases of the study group and one case of the control group showed pathological complete remission (pCR). The total remission rate (RR) was 69.2% (45/65) in the study group and 49.2% (30/61) in control group, with a significant difference between the two groups ($\chi^2=5.251$, $P=0.022$, < 0.05). In study group, complete remission was found in 5 cases (7.7%), partial remission (PR) in 40 cases (61.5%) and stabilization of the disease in 20 cases (30.8%). While in the control group, 2 cases (3.3%) had complete remission, 28 cases (45.9%) had partial remission, and 31 cases (50.8%) with stabilization of the disease.

Table 2. The therapeutic effects in the two groups

Group	*n*	pCR	cCR	cPR	SD	Total remission rate (%)
Study	65	2 (3.1)	5 (7.7)	40 (61.5)	20 (30.8)	69.2*****
Control	61	1 (1.6)	2 (3.3)	28 (45.9)	31 (50.8)	49.2

*There is a significant difference between the study group and control group ($P<0.05$)

2. Changes in T-lymphocyte subsets before and after the neoadjuvant chemotherapy (see Table 3):

After two cycles of the treatment, the number of both the T lymphycytes and NK cells decreased in the control group. But in the study group, all the number of CD_3^+, CD_4^+, CD_4^+/CD_8^+ and the NK cells increased in varying degrees, showing significant difference with the control group ($P<0.05$).

Table 3.T-lymphocyte subsets before and after neoadjuvant chemotherapy in the two groups ($\bar{x} \pm s$)

Group		*n*	CD_3^+	CD_4^+	CD_8^+	NK	CD_4^+/CD_8^+
Study group	pretreatment	65	52.24±5.54	37.16±3.78	24.95±5.37	40.13±4.33	1.43±0.65
	posttreatment	65	54.11±4.31*$^{\Delta}$	40.26±5.15*$^{\Delta}$	25.54±4.13$^{\Delta}$	42.56±4.16*$^{\Delta}$	1.61±0.52*$^{\Delta}$
Control group	pretreatment	61	52.58±4.33	36.53±3.37	24.82±4.63	39.76±3.83	1.45±0.73
	posttreatment	61	47.15±5.22	33.84±4.53	23.91±5.12	36.15±4.27	1.41±0.56

*****There is a significant difference ($P<0.05$) in the study group after treatment.

$^{\Delta}$There is a significant difference ($P<0.05$) between the study group and control group after treatment.

3. Toxic effects:

The major problems caused by chemotherapy are bone marrow depression and the gastrointestinal reactions. However, no toxic reactions of grade IV were found in both the two groups. In study group of 65 cases, neutropenia appeared in 36 cases (55.4%),

with grade II-III neutropenia found in 17 cases; while the occurrence rate in the control group was 77.1% (47/61), with grade II-III neutropenia found in 28 cases. The difference was significant between the two groups (P<0.01). G-CSF support was required in 16.9% (11/65) of the patients in the study group, and in 31.1% (19/61) of the control group. Anemia was found in 44.6% of the patients (29/65) in the study group, with grade II-III anemia found in 10 cases; while in the control group of 61 cases, anemia appeared in 38 cases (62.3%), with grade II-III anemia found in 17 cases. The difference was significant between the two groups (P<0.05). The occurrence rate of thrombocytopenia was similar in the two groups (P>0.05).

In the study group, the gastrointestinal reactions appeared in 31 of the 65 cases (47.7%), with grade II-III toxic reations found in 14 cases (21.5%). In the control group, the gastrointestinal reactions appeared in 43 of the 61 cases (70.5%), with grade II-III toxic reactions found in 23 cases (37.7%). The difference was significant between the two groups (P<0.01).

DISCUSSION

Although the drugs used in conventional chemotherapy can effectively suppress or destruct the tumor cells, the toxic side effects and the drug resistance induced are the major clinical problems. Since 1980s, the neoadjuvant chemotherapy has been adopted for systemic treatment of the breast cancer, which can reduce the tumor size, depress the tumor cell activity, and prevent the tumor cells from diffusional transferring.[4] And a proper use of Chinese medicine may not only inhibit the tumor cell growth, but also enhance the body's immune function, promote the recovery of the body.[5-7]

The main ingredients of *Shenqi Fuzheng* Injection are Dang Shen（党参 Radix Codonopsis) and Huang Qi (黄芪 Radix Astragali). The modern researches have demonstrated that astragalus mongholicus polysaccharide extracted from Huang Qi may show anti-tumor effect by regulating the immune system with no cytotoxicity; it does not directly kill the tumor cells, but regulate the systemic immune system by promoting the formation of antibodies and the secretion of cytokine so as to improve the cellular immune function and certain non-specific immune function.[8] And it has been proved that Codonopsis pilosula polysaccharide extracted from Dang Shen can obviously inhance the humoral immunity, and improve the cellular immune function in a low dose administration; in the mice model of hemolytic anemia, it can increase the peripheral hemoglobin level, and in the ^{60}Co-ray irradiated mice, it can promote the spleen endogenous node formation.[9]

Chemotherapy with *Shenqi Fuzheng* Injection given at the same time can enhance the anti-tumor activity with an increased chemosensitivity.[7] It has been confirmed that *Shenqi Fuzheng* Injection can reduce the damage to the liver and kidney caused by chemotherapy, protect the hematopoietic system, and enhance the patients' tolerance to chemotherapy. [10]

In the present study, the count of T-lymphocyte subsets and the NK cells decreased in the control group；whereas CD_3^+, CD_4^+, $CD_4^+/CD_8^+$and the NK cells in the study group increased after treatment (P<0.05). The CD_3^+, CD_4^+, CD_8^+, CD_4^+/CD_8^+ and the NK cells were significantly higher as compared with the control group though no an obvious rise of CD_8^+ was found (P<0.01). In addition, the gastrointestinal reactions were milder in study group and with a shorter recovery time. To sum up, *Shenqi Fuzheng* Injection can improve the immune function and enhance the therapeutic effects in the course of neoadjuvant chemotherapy with less toxic side effects. Therefore, it can be used 0as an adjuvant therapy for advanced cancer.

REFERENCES

1. 赵群, 李勇, 王力利, 等. 参芪扶正注射液对胃癌患者手术及化疗时免疫功能的影响. 中国中西医结合杂志 2001; 21 (6): 424-426.
2. Sapunar F, Smith IE. Neoadjuvant chemotherapy for breast cancer. Ann Med 2000; 32: 43-50.
3. 浦红, 何成章, 王丰, 等.宫颈癌放疗前后免疫功能改变及其临床意义. 中国免疫学杂志 2002; 18 (10): 727-729.
4. Fisher B, Bryant J, Welmark N, *et al*. Effect of pre-operative chemotherapy on the outcome of woman with breast cancer:findings from NSABP-18. J Clin Oncol 1997; 15: 2488-2492.
5. 孙震晓, 孙晋华, 程霜, 等. 中药地椒提取物的抗肿瘤作用及对小鼠免疫功能的影响.中西医结合学报 2003; 1 (3): 209-211.
6. 李华山, 李华宏, 唐宗江, 等. 肠癌康复汤对大肠癌患者术后免疫功能的影响. 中国中西医结合杂志 2000; 20 (8): 580-582.
7. 蒋莹, 庄文斌, 周宁. 参芪扶正注射液配合化疗治疗晚期肺癌的疗效观察.中国药房 2005; 16(10): 772-773.
8. 张小梅. 黄芪多糖的免疫调节作用及抗肿瘤作用研究进展. 大连大学学报 2003; 24 (6): 101-104.
9. 张晓君, 祝晨, 胡黎, 等. 党参多糖对小鼠免疫和造血功能的影响. 中药新药与临床药理 2003; 14 (3): 174-176.
10. 刘城林, 陈为平, 崔书中, 等. 参芪扶正注射液辅助化疗治疗老年非小细胞肺癌临床观察. 中国中西医结合杂志 2004; 24 (10): 901-903.