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Efficacy and Safety of Shen Fu Injection Alleviating Chemotherapy-Induced Peripheral Neurotoxicity: A Randomized Controlled Trial

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Abstract

Objective: To analyze the effect of Shenfu injection on Chemotherapy-Induced Peripheral Neuropathy (CIPN) at different stages of tumor chemotherapy.

Method: An analysis of 153 patients who were divided into chemotherapy group and combined group was performed chemotherapy within two to six cycles with oxaliplatin or paclitaxel, and combined with or without Shenfu injection. Efficacy evaluation was divided into two phases, including the short-term incidence of CIPN and the long-term incidence of CIPN. Subgroup analysis was performed on the combined group to compare the incidence of CIPN in different usage time of Shenfu injection. Preliminary comparison of the incidence of common side effects.

Results: The short-term incidence rates of CIPN in the combined group and chemotherapy group were 27.85% and 66.22%, respectively (P<0.01), and the long-term incidence rates were 17.72% and 45.95%, respectively (P<0.01). In the combined group of 5-6 cycles chemotherapy, divided into two groups according to the time used of Shenfu injection, greater than 3 weeks and less than 3 weeks, and the short-term incidence rates of CIPN were 28.57% and 69.23%, respectively, and the long-term incidence rates of CIPN was 14.29% and 46.15%, respectively. Adverse reactions evaluation showed that the occurrence of bone marrow suppression were 35.44% and 60.81% (P<0.05) in the combined group and chemotherapy group, and there was no significant difference in digestive tract reaction, liver and kidney toxicity.

Conclusion: Shenfu injection significantly reduced the incidence of CIPN and had a good security.

Keywords: ShenFu injection; Oxaliplatin; Paclitaxel; Peripheral neurotoxicity.

Background

With the increasing number of tumor patients, Chemotherapy is still the main treatment for patients with advanced or recurrent cancer. At the same time, chemotherapy can cause a series of adverse reactions such as myelosuppression, nausea, vomiting, renal or hepatic impairment, cardiotoxicity and so on [1-3]. As these adverse reactions are gradually controlled, CIPN (Chemotherapy-Induced Peripheral Neuropathy, CIPN) has become another major challenge that needs to be faced during chemotherapy.

The symptoms of CIPN include pain, tingling, cold-sensitivity and numbness that typically presents in a stocking glove distribution [4,5], which are needed to be treated with drugs for mild

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cases, and chemotherapy may even be interrupted for severe cases, which affects the effect of treatment. The main drugs that are likely to cause peripheral neurotoxicity include taxanes, platinum, vincristine and so on. According to reports, the clinical incidence of peripheral neurotoxicity caused by paclitaxel (Paclitaxel-induced Peripheral Neuropathy, PIPN) is 59%-80%, and the clinical incidence of peripheral neurotoxicity caused by oxaliplatin (Oxaliplatin-induced Peripheral Neuropathy, OIPN) is 85%-95% [6-8].

CIPN is a challenging and complex pain syndrome that we have no effective preventive and limited treatment options for currently [9]. Although nutritional nerves (such as mecobalamin), antiepileptic (such as gabapentin) and antidepressant (such as Duloxetine [10]. drugs have been shown in clinical trials to reduce the incidence of CIPN, the uncertain efficacy, serious adverse reactions and high price still keep us from choosing these drugs.

The clinical manifestations of CIPN are consistent with the arthralgia of Traditional Chinese Medicine (TCM). In this regard, the main treatment principles should be warming yang and replenishing qi, dispelling cold and eliminating maladies. Shenfu injection is a representative prescription in Chinese medicine that have the effect of warming Yang and replenishing Qi.

Shenfu injection is derived from Shenfu Decoction which confirmed by clinical and basic experiments to have the effect of preventing and treating CIPN. Our previous small sample clinical trial confirmed the efficacy of Shenfu injection in reducing CIPN. The incidence of CIPN in patients treated with oxaliplatin or paclitaxel chemotherapy was 66.66% and the incidence of CIPN in the combined Shenfu injection group was only 32.43% [11]. Moreover, basic experiments also confirmed that Shenfu Injection can reduce the peripheral neurotoxicity of paclitaxel by promoting the expression of NGF in serum [12,13]. Therefore, we designed this study by expanding the sample size to explore whether chemotherapy combined with Shenfu injection is of significance in the prevention and treatment of CIPN and whether the use time of Shenfu injection can affect the curative effect.

Material and methods

Diagnostic

Patients who were diagnosed as malignant tumor (lung cancer, colon cancer, cervical cancer, ovarian cancer and gastric cancer) which pathological stage was stage II-IV by histopathology or pathology cytology. The diagnostic criteria] and the staging criteria refers to National Comprehensive Cancer Network, NCCN [14-18].

Inclusion criteria

1) Pathologically diagnosed as patients with malignant tumors such as lung cancer, grastric cancer, colorectal cancer, ovarian cancer, and cervical cancer; 2) the pathological diagnosis of stage II-IV; 3) The disease state is postoperative adjuvant treatment, such as postoperative recurrence or late progression, it belongs to first-line chemotherapy; 4) Eastern Cooperative Oncology Group Performance Status Scale (ECOG-PS) 0-2 points; 5) Age: between 18 and 70 years old; 6) The chemotherapy regimen contains oxaliplatin or paclitaxel for 2-6 cycles; 7) All enrolled patients signed an informed consent form.

Exclusion criteria

1) Patients with neurological symptoms due to tumor brain metastasis or spinal cord metastasis; 2) There are other diseases that cause peripheral nerve damage, such as electrolyte disorders, diabetes; 3) Patients with skin lesions in the hand and foot parts (such as hand-foot syndrome caused by chemotherapy); 4) Patients who have caused peripheral neuropathy such as radiotherapy, or are undergoing other treatments that can cause neurotoxicity; 5) Patients who have been using antidepressants, antiepileptic drugs, and analgesics within one week of the efficacy evaluation.

Study design

This is a cohort study that included a total of 162 patients who had undergone chemotherapy with paclitaxel or oxaliplatin regimens. Eligible patients were recruited from First Hospital Affiliated Hospital of Chongqing Medical University and Affiliated Hospital of Chengdu University of Traditional Chinese Medicine. Patients were divided into chemotherapy group (74 cases), combined group (79 cases). Patients in the chemotherapy group were administered the whole course of treatment for 2-6 cycles, the combined group were administered Shenfu injection during the same period of chemotherapy. By calculating the long-term and short-term incidence of CIPN and analyzing the side effects as evaluation criteria.

Drug administration

Patients in the all groups were administered guidelines standard regimen chemotherapy according to the National Comprehensive Cancer Network (NCCN). Combined group and sequential group were administered Shenfu injection (Shenfu injection production company: Ya'an Sanjiu Pharmaceutical Co., Ltd. Production batch number: 071115 Specification: 50 ml/bottle) which requires Shenfu injection 50-100 ml and 0.5% glucose injection 250 ml to prepare for intravenous injection once a day.

Evaluation index

Peripheral neurotoxicity was graded according to the WHO Anticancer Drug Peripheral Neurotoxicity Grading Criteria Evaluation [19], which divided into 5 levels to evaluate the severity of neuropathy symptoms. (Grade 0: no symptoms; Grade I: paraesthesia and/or decreased tendon reflexes; Grade II; severe paraesthesia and/or mild weakness; Grade III: intolerable paraesthesia and/or marked motor loss; Grade IV: paralysis). The incidence of CIPN is the main evaluation index of this study, which is divided into short-term curative effect and long-term curative effect.

Short-term efficacy: 1 to 2 months after the last chemotherapy in the chemotherapy group and the combined group, the incidence of CIPN in the two groups.

Long-term efficacy: 11 to 12 months after the last chemotherapy, the incidence of CIPN in each group. The secondary evaluation index is side effects. In this study, common toxic and side effects of Shenfu injection were evaluated for the combined group and chemotherapy group, including gastrointestinal adverse reactions (nausea and vomiting); severity of bone marrow suppression (white blood cells, platelets, hemoglobin); Liver and kidney function damage (Alanine aminotransferase, creatinine).

Refer to the WHO's adverse reaction classification as follows:

Table 1: WHO patient chemotherapy adverse reaction score table.

			Severity		
Adverse Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Nausea and Vomiting	Nausea and Vomiting absent	Nausea	temporary vomiting	vomiting requiring treatment	uncontrollable vomiting
Anemia (g/L)	110	95-109	80-94	65-79	<65
Leukopenia (x 10^9/L)	4.0	3.0-3.9	2.0-2.9	1.0-1.9	<1.0
Platelet (x10^9/L)	100	75-99	50-54	25-49	<25
ALT/AST increasing	<1.25xN	1.26-2.5xN	2.6-5.0*N	5.1-10.0*N	>10xN
Creatinine increasing	<1.25xN	1.26-2.5xN	2.6-5.0*N	5.1-10.0*N	>10xN

N: highest value of normal range.

Table 2: Characteristics of patients (n(%)).

Characteristics	combined group (n=79)	chemotherapy group (n=74)	χ2	P
Sex			1.454[a]	0.228
Male	35(44.30%)	40(54.05%)		
Famale	44(55.70%)	34(45.95%)		
Age			0.958[a]	0.328
<60 years	26(32.91%)	30(40.54%)		
≥60 years	53(67.09%)	44(59.46%)		
PS Score			6.442[a]	0.04
0	15(18.99%)	27(36.48%)		
1	40(50.63%)	26(35.14%)		
2	243(0.38%)	21(28.38%)		
Tumor type			8.824[a]	0.066
Lung cancer	37(46.84%)	19(25.68%)		
Oophoroma	4(5.06%)	10(13.51%)		
Colorectal cancer	26(32.91%)	31(41.89%)		
Gastric cancer	10(12.66%)	12(16.22%)		
Cervical carcinoma	2(2.53%)	2(2.70%)		
Pathological stage			5.787[a]	0.055
Stage II	13(16.45%)	24(32.44%)		
Stage III	32(40.51%)	32(43.24%)		
Stage IV	34(43.04%)	18(24.32%)		
Chemotherapy Regimen			1.322[a]	0.25
Oxaliplatin containing	31(39.24%)	42(56.76%)		
Paclitaxel containing	48(60.76%)	32(43.24%)		
Chemotherapy Cycle			0.007[a]	0.933
2-3 cycles	23(29.11%)	22(29.73%)		
4-6 cycles	56(70.89%)	52(70.27%)		
[a]Represents the χ^2 value for the chi-square test.				

Statistical analysis

The SPSS 26.0 software was used for analysis, the measurement data was compared by the chi-square test, and the grade data was compared by the rank sum test. P<0.05 means that there is a statistical difference.

Results

Characteristics of study participants

From February 2015 and February 2018, 161 patients who have undergone chemotherapy with paclitaxel or oxaliplatin regimens were included in the study. Among them, 3 patients were

excluded because they did not meet the criteria, 5 patients were excluded because they were unwilling to participate in the trial and 2 patients were excluded due to personal reasons. Finally, they were randomly divided into divided into chemotherapy group (78 cases) and combined group (79 cases) according to the ratio of 1:1. During the follow-up period, 2 cases were lost in the combined group, 2 case was lost and 4 case was withdrawn due to severe chemotherapy reaction in the chemotherapy group. There was no significant difference in age, gender, clinical, stage, PS score, tumor type, average chemotherapy cycle, and average Shenfu injection days between the three groups (P>0.05). The baseline conditions of the enrolled patients are shown in Table 2.

CIPN incidence

Comparison of short-term and long-term incidence rates of CIPN by combined group and chemotherapy group

The short-term incidence rates of CIPN: The incidence rates of CIPN in the combined group and chemotherapy group were 27.85% and 66.21% (Z=-4.863, P=0.000). The patients of grade III-IV CIPN in the combined group and chemotherapy group were 2 cases (2.53%) and 10 cases (13.51%).

Table 3: Comparison of short-term incidence rates of CIPN by combined group and chemotherapy group.

Group	Severity of CIPN	Incidence
Combined group (n=79)	Grade 1- Grade 2	20(25.32%)
	Grade 3- Grade 4	2(2.53%)
	Total	22(27.85%)*
Chemotherapy group (n=74)	Grade 1- Grade 2	39(52.70%)
	Grade 3- Grade 4	10(13.51%)
	Total	49(66.22%)
Z=-4.863, *P=0.000		

The long-term incidence rates of CIPN: The incidence rates of CIPN in the combined group and chemotherapy group were 17.72% and 45.95% (Z=-4.863, P=0.000). The incidence of grade III-IV CIPN in the combined group and chemotherapy group were 0% (0) and 6.76% (5 cases).

Table 4: Comparison of long-term incidence rates of CIPN by combined group and chemotherapy group.

Group	Severity of CIPN	Incidence of CIPN
Combined group(n=79)	Grade 1- Grade 2	14(17.72%)
	Grade 3- Grade 4	0(0)
	Total	14(17.72%)*
Chemotherapy group(n=74)	Grade 1- Grade 2	29(39.19%)
	Grade 3- Grade 4	5(6.76%)
	Total	34(45.95%)
Z=-4.863, *P=0.000		

Subgroup efficacy analysis

Whether different usage time (more or less than 3 weeks) of Shenfu injection will interfere with the short-term and long-term efficacy in the combined group during long-term chemotherapy (5-6 cycles).

The short-term incidence rates of CIPN

The incidence rates of CIPN in the group which cumulative use time of Shenfu injection more than 3 weeks and the group which cumulative use time of Shenfu injection less than 3 weeks were 28.57% and 69.23%(Z=-2.128,P=0.029). The incidence of grade III-IV CIPN in the group which cumulative use time of Shenfu injection more than 3 weeks and the group which cumulative use time of Shenfu injection less than 3 weeks were 0% (0) and 7.69% (1 cases).

Table 5: Comparison of short-term incidence rates of CIPN by the group which cumulative use time of Shenfu injection more than 3 weeks and the group which cumulative use time of Shenfu injection less than 3 weeks.

Group	Severity of CIPN	Incidence of CIPN
Group of the dosing time of Shenfu injection >3 weeks (n=14)	Grade 1	3(21.43%)
	Grade 2	1(7.14%)
	Grade 3	0(0)
	Total	4(28.57%)*
Group of the dosing time of Shenfu injection ≤3 weeks (n=13)	Grade 1	5(38.46%)
	Grade 2	3(23.08%)
	Grade 3	1(7.69%)
	Total	9(69.23%)
Z=-2.128,*P=0.029		

The long-term incidence rates of CIPN

The incidence rates of CIPN in the group which cumulative use time of Shenfu injection more than 3 weeks and the group which cumulative use time of Shenfu injection less than 3 weeks were 14.29% and 53.85% (Z=-2.122,P=0.034). No grade III to IV neurotoxicity in both group. Only 2 cases (14.29%) of grade I neurotoxicity in the group which cumulative use time of Shenfu injection more than 3 weeks and 3 cases (23.08%) of grade II neurotoxicity and 4 cases (30.77%) of grade I neurotoxicity in the group which cumulative use time of Shenfu injection less than 3 weeks.

Table 6: Comparison of long-term incidence rates of CIPN by the group which cumulative use time of Shenfu injection more than 3 weeks and the group which cumulative use time of Shenfu injection less than 3 weeks.

Group	Severity of CIPN	Incidence of CIPN
Group of the dosing time of Shenfu injection >3 weeks (n=14)	Grade 1	2(14.29%)
	Grade 2	0(0)
	Total	2(14.29%)*
Group of the dosing time of Shenfu injection ≤3 weeks (n=13)	Grade 1	4(30.77%)
	Grade 2	2(15.38%)
	Total	6(46.15%)
Z=-2.122,*P=0.034)		

Table 7: Comparison of the incidence of adverse reactions in the combined group and chemotherapy group.

Group	Severity	Nausea and Vomiting	ALT/AST increasing	Creatinine increasing	Leukopenia	Platelet	Anemia
	Grade 1	14(17.72%)	4(5.06%)	2(2.53%)	17(21.52%)	7(8.86%)	13(16.46%)
	Grade 2	16(20.25%)	2(2.53%)	0(0.00%)	9(11.39%)	3(3.80%)	6(7.59%)
Combined group (n=79)	Grade 3	2(2.53%)	0(0.00%)	0(0.00%)	2(2.53%)	0(0.00%)	0(0.00%)
	Grade 4	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
	Total	32(40.51%)	6(7.59%)	2(2.53%)	37(35.44%)	10(12.66%)	19(24.05%)
	Grade 1	13(17.57%)	5(6.76%)	3(4.05%)	14(18.92%)	16(21.62%)	17(22.97%)
	Grade 2	16(21.62%)	2(2.70%)	0(0.00%)	19(25.68%)	6(8.11%)	13(17.57%)
Chemotherapy group (n=74)	Grade 3	3(4.05%)	0(0.00%)	0(0.00%)	11(14.86%)	2(2.70%)	3(4.05%)
	Grade 4	0(0.00%)	0(0.00%)	0(0.00%)	1(1.35%)	0(0.00%)	0(0.00%)
	Total	32(43.24%)	7(9.46%)	3(4.05%)	45(60.81%)	24(32.43%)	33(44.59%)

Comparison of the incidence of adverse reactions

No significant difference in the nausea, vomiting, liver function damage, and renal function damage between combined group and chemotherapy group (P>0.05). The incidence rate of leukopenia, thrombocytopenia and hemoglobin reduction in the combined group was less than in the chemotherapy group (P<0.05).

Discussion

Chemotherapy is still the mainstream method of medical oncology treatment. In addition to gastrointestinal reactions and bone marrow suppression, peripheral neurotoxicity is also a common side effect of chemotherapy whose incidence is next to blood toxicity caused by chemotherapy. The clinical incidence of Chemotherapy-Induced Peripheral Neuropathy (CIPN) is about 59-90%. Reducing the chemotherapy dose, changing the chemotherapy regimen and even being forced to interrupt chemotherapy when CIPN occurs [20]. Obviously, CIPN has become the main factor which affects the progress of chemotherapy. Interrupting chemotherapy or reducing the dose will seriously reduce the efficacy and cause tumor progression.

Among all the chemotherapeutic agents, oxaliplatin and paclitaxel which have been widely used in lung cancer, esophageal cancer, breast cancer, gynecological tumors, lymphomas and so on are most likely to cause CIPN. The main clinical manifestations of CIPN are numbness of the extremities, hypoesthesia, movement disorders, blurred vision. Proprioceptive disorders such as vibration and position perception, muscle or joints pain can appear in severe cases [4,5].

At present, no well-established drug are used in the prevention and treatment of CIPN. The antiepileptic drug gabapentin, the antidepressant duloxetine, gabapentin, nortriptyline, vitamins and topical ketamine/amitriptyline cream are often used to relieve some CIPN symptoms in clinical [21]. Although some drugs have been proven to be effective in preventing CIPN, they are not widely recognized because of conflicting conclusions from different trials with the same drugs and obvious side effects. For example, glutathione can be used to prevent CIPN in receiving cisplatin chemotherapy, but glutathione can also reduce the antitumor activity of cisplatin by increasing the elimination of cisplatin from the kidneys [22]. Duloxetine, gabapentin relieve pain caused by CIPN through central analgesic, but these drugs have no effect on other symptoms such as numbness and sensory disturbances. The NCCN guidelines recommend to use the antidepressant duloxetine for CIPN that has occurred and describe that duloxetine has the moderate degree of effectiveness, evidence and recommendation and the low degree of safety [7]. For CIPN that has not occurred, the current guidelines do not recommend any drugs for prevention and treatment.

Traditional Chinese medicine has its unique advantages in the treatment of tumors. It is a unique treatment method with obvious advantages in cancer treatment in China. Chinese medicine has a very early understanding of tumors. As early as 3,500 years ago, there was a record of «tumor» in the oracle bone inscriptions of the Shang Dynasty. With the development of medicine, TCM has changed from the past macro differentiation to the use of modern medical technology to use micro syndrome differentiation to unify prevention and treatment, formed a model of integrated Chinese and Western medicine treatment of tumors with Chinese characteristics. By reviewing many domestic and foreign experimental studies on the treatment of tumors with TCM, we found that TCM can effectively improve the sensitivity of radiotherapy and chemotherapy, minimize the toxic and side effects of radiotherapy and chemotherapy, reduce the recurrence and metastasis of tumor, completely cure the patients with tumors who have received radical treatment, improve the quality of life of patients with advanced tumors, and prolong the survival of patients to achieve «survival with tumors» [23]. As for the reports on the treatment of CIPN with Traditional Chinese Medicine, we have consulted related literatures that some kinds of decoctions can reduce the incidence of CIPN caused by oxaliplatin [7,24,25] for example, Huangqi Guizhi Wu Decoction. Modified Lizhong Decoction which composed of dried ginger and ginseng can reduce the severity and incidence of CIPN [26]. Tongmai Sini Decoction which composed of Aconite, Licorice can reduce the incidence of oxaliplatin CIPN [11]. Chinese medicine compatible with astragalus can reduce the neurotoxicity of paclitaxel chemotherapy [7]. Although many scholars have begun to pay attention to the prevention and treatment of CIPN with traditional Chinese medicine, the enthusiasm of research CIPN is still not high enough. Although the search is not limited to years, only 43 documents related to traditional Chinese medicine have been found so far. The focus is much lower than other chemotherapy toxicities such as gastrointestinal reactions and bone marrow suppression.

The Shenfu injection introduced in this study can be applied to the treatment of a variety of diseases. The Shenfu injection not only has a protective effect on the cardiovascular system and respiratory system [27], but also can reduce the toxicity of chemotherapy in the treatment of tumors [28]. At the same time, numerous studies have shown that Shenfu injection can reduce bone marrow suppression during chemotherapy. Ginseng is a plant of the Araliaceae family which main components are saponins and carbohydrates, and other components include organic acids, proteins, enzymes, flavonoids, vitamins and so on [29]. The attached piece is the root of Aconitum of the Ranunculaceae plant, the main components are a variety of diterpenoids, aconitine, flavonoids and isoliquiritigenin [30].

The study evaluated the occurrence of CIPN in each group of 1-2 months after the end of chemotherapy. At this time, shortly after the completion of chemotherapy, the result of study reflected the prevention and treatment effect of chemotherapy in the acute phase of nerve injury. The study also evaluated the occurrence of CIPN in each group of 11-12 months after the end of chemotherapy to obtain a comparison of long-term efficacy.

Analyzing the combined group and the chemotherapy group, we found that a total of 22 (27.85%) in the combined group and 49 in the chemotherapy group (66.22%) had neurotoxicity manifestations of varying degrees in the first phase of follow-up. By comparison, the CIPN incidence of the combined group was significantly less than the chemotherapy group ($P<0.01$). The grade III-IV CIPN occurred in 2 cases (2.53%) in the combined group and 10 cases (13.51%) in the chemotherapy group, which indicates Shenfu injection can significantly reduce the incidence of CIPN during chemotherapy. In the second phase follow-up, a total of 14 (17.72%) in the combined group and 34 people (45.95%) in the chemotherapy group developed CIPN. By comparison, the CIPN incidence of the combined group was significantly less than the chemotherapy group ($P<0.01$). Moreover, no patients occurred the grade III-IV CIPN in the combined group and 5 cases (6.76%) in the chemotherapy group ($P<0.01$). In summary, Combined use of Shenfu injection during chemotherapy can significantly reduce the incidence of CIPN.

After comparing the both groups, we found that the effect will be better when the use of Shenfu injection may be used at the same time as chemotherapy. In order to explore the relationship between the dosage of Shenfu injection and the curative effect, we conducted a subgroup analysis in the combined group who received medium and long term of chemotherapy (5-6 cycles). All the patients from combined group were divided into the group with the cumulative dosage of Shenfu injection greater than 3 weeks and the group less than or equal to 3 weeks.

During the first phase of follow-up, the incidence of CIPN was 28.57% (4/14) in the group with the cumulative dosage of Shenfu injection greater than 3 weeks and 67.23% (9/13) in the group with the cumulative dosage of Shenfu injection less than or equal to 3 weeks ($P<0.05$). During the second phase of follow-up, the incidence of CIPN was 14.29% (2/14) in the group with the cumulative dosage of Shenfu injection greater than 3 weeks and 46.15% (6/13) in the group with the cumulative dosage of Shenfu injection less than or equal to 3 weeks ($P<0.05$). Regardless of the short-term and long-term effects, the group with the cumulative dosage of Shenfu injection greater than 3 weeks better than the group less than or equal to 3 weeks.

Up to now, no serious adverse reactions have been found innumerous studies of Shenfu injection. The instructions only mention the possibility of allergies. The adverse reactions were analyzed in this study We found that three groups showed no difference in nausea, vomiting, liver and kidney function damage. The incidence of bone marrow suppression in the combined group was lower than the chemotherapy group.

Conclusion

In conclusion, combined use of Shenfu injection during chemotherapy can significantly reduce the incidence of CIPN. In long-term chemotherapy, the longer the combined use of Shenfu injection, the better the prevention and treatment effect of CIPN. Combined use of Shenfu injection during chemotherapy has no obvious side effects and can reduce the incidence of bone marrow suppression.

Declarations

Data availability: The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethical approval: This study involving human participants was reviewed and approved by the Medical Ethics Committee of the Hospital of Chengdu University of Traditional Chinese Medicine (No. 2015BL-003). And this study was performed in accordance with the Declaration of Helsinki. All patients provided his written informed consent to participate in this study.

Description: The material has not been published previously, and will not be submitted for publication elsewhere.

Conflicts of interest: All authors declare that they have no conflicts of interest.

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References

1 Bodensteiner DC, Doolittle GC. Adverse haematological complications of anticancer drugs. Clinical presentation, management and avoidance. Drug Saf. 1993; 8: 213-224. doi:10.2165/00002018-199308030-00003.

2 Navari RM. Management of chemotherapy-induced nausea and vomiting: Focus on newer agents and new uses for older agents. Drugs. 2013; 73: 249-262. doi:10.1007/s40265-013-0019-1.

3 Castel M, Despas F, Modesto A, Gales C, Honton B, et al. Cardiotoxicity of chemotherapies. Presse Med. 2013; 42: 26-39. doi:10.1016/j.lpm.2012.04.014.

4 Flatters, S. J. L., Dougherty, P. M. & Colvin, L. A. Clinical and preclinical perspectives on Chemotherapy-Induced Peripheral Neuropathy (CIPN): A narrative review. Br J Anaesth. 2017; 119: 737-749. doi:10.1093/bja/aex229.

5 Zhou H, Lin Z, Cai W, Lin Y, Hong S. Systematic Review on Efficacy and Safety of Domestic and Imported Paclitaxe in Anti-Tumor. Evaluation and Analysis of Drug-Use in Hospitals of China. 2018; 18: 211-214+220.

6 Han CH, Kilfoyle DH, Hill AG, Jameson MB, McKeage MJ. Preventing oxaliplatin-induced neurotoxicity: rationale and design of phase Ib randomized, double-blind, placebo-controlled, cross-over trials for early clinical evaluation of investigational therapeutics. Expert Opin Drug Metab Toxicol. 2016; 12: 1479-1490. doi:10.1080/17425255.2016.1223625.

7 Brewer JR, Morrison G, Dolan ME, Fleming GF. Chemotherapy-induced peripheral neuropathy: Current status and progress. Gynecol Oncol. 2016; 140: 176-183. doi:10.1016/j.ygyno.2015.11.011.

8 Ewertz M, Qvortrup C, Eckhoff L. Chemotherapy-induced peripheral neuropathy in patients treated with taxanes and platinum derivatives. Acta Oncol. 2015; 54: 587-591. doi:10.3109/0284186x.2014.995775.

9 Loprinzi CL, Lacchetti C, Bleeker J, Cavaletti G, Chauhan C, et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. J Clin Oncol. 2020; 38: 3325-3348. doi:10.1200/jco.20.01399.

10 Lu Y, Zhang P, Zhang Q, Yang C, Qian Y, et al. Duloxetine Attenuates Paclitaxel-Induced Peripheral Nerve Injury by Inhibiting p53-Related Pathways. J Pharmacol Exp Ther. 2020; 373: 453-462. doi:10.1124/jpet.120.265082.

11 Song T, Xiong S, Chen P, Li Y, Zou X, et al. A retrospective study of ginseng injection against peripheral neurotoxicity due to oxaliplatin and paclitaxel chemotherapy. Chinese Journal of Integrated Traditional and Western Medicine. 2019; 39: 28-32.

12 Xiong SQ, Zou XL, Zheng Q, Jin S, Xie M, et al. [Effects of ShenFu Injection on Peripheral Neurotoxicity of Paclitaxel]. Sichuan Da Xue Xue Bao Yi Xue Ban. 2018; 49: 44-47.

13 Lv P, Zhu X, Wang J, Li G, Shen XY, et al. Experimental Study of Shenfu Injection on the Prevention and Treatment of Paclitaxel Chemotherapy DRG Neuron Injury. Evid Based Complement Alternat Med. 2020; 2020: 8239650. doi:10.1155/2020/8239650.

14 Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2.2021. J Natl Compr Canc Netw. 2021; 19: 254-266. doi:10.6004/jnccn.2021.0013.

15 Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, et al. Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021; 19: 329-359. doi:10.6004/jnccn.2021.0012.

16 Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, et al. Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019; 17: 64-84. doi:10.6004/jnccn.2019.0001.

17 Armstrong DK, Alvarez RD, Bakkum-Gamez JN, Barroilhet L, Behbakht K, et al. Ovarian Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021; 19: 191-226. doi:10.6004/jnccn.2021.0007.

18 Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Cooke D, et al. Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022; 20: 167-192. doi:10.6004/jnccn.2022.0008.

19 Yoon J, Jeon JH, Lee YW, Cho CK, Kwon KR, et al. Sweet bee venom pharmacopuncture for chemotherapy-induced peripheral neuropathy. J Acupunct Meridian Stud. 2012; 5: 156-165. doi:10.1016/j.jams.2012.05.003.

20 Kiya T, Kawamata T, Namiki A, Yamakage M. Role of satellite cell-derived L-serine in the dorsal root ganglion in paclitaxel-induced painful peripheral neuropathy. Neuroscience. 2011; 174: 190-199. doi:10.1016/j.neuroscience.2010.11.046.

21 Majithia N, Temkin SM, Ruddy KJ, Beutler AS, Hershman DL, et al. National Cancer Institute-supported chemotherapy-induced peripheral neuropathy trials: Outcomes and lessons. Support Care Cancer. 2016; 24: 1439-1447. doi:10.1007/s00520-015-3063-4

22 Cheng XL, Liu HQ, Wang Q, Huo JG, Wang XN,et al. Chemotherapy-induced peripheral neurotoxicity and complementary and alternative medicines: Progress and perspective. Front Pharmacol. 2015; 6: 234. doi:10.3389/fphar.2015.00234.

23 Lin H, Yang Y. TCM and Western medicine treatment of gastric cancer. 2022; 251-252. (People's Medical Pu Publishing House, 2002).

24 Zou S, Gao P, Zhang H. Clinical Observation of Huangqiguizhi Decoction Prevent and Cure Neurotoxicity of Oxaliplatin for 21 Cases. Chinese Medicine Modern Distance Education of China. 2015; 13: 55-56.

25 Wu G, Yao X, Wu X. Observation on the curative effect of Huangqi Guizhi Wuwu Decoction in the prevention and treatment of postoperative chemotherapy-induced peripheral neurotoxicity. Journal of Sichuan of Traditional Chinese Medicine. 2015; 33: 132-133.

26 Smith EM, Pang H, Ye C, Cirrincione C, Fleishman S, et al. Predictors of duloxetine response in patients with oxaliplatin-induced painful Chemotherapy-Induced Peripheral Neuropathy (CIPN): A secondary analysis of randomised controlled trial - CALGB/alliance 170601. Eur J Cancer Care (Engl). 2017; 26. doi:10.1111/ecc.12421.

27 Xiong Y, Chen Y, Xu G, Yan X, Nie P, et al. Research Progress of Shenfu Injection's Material Foundation and lts Mechanism on Shock. Modernization of Traditional Chinese Medicine and Materia Medica-World Science and Technology. 2018; 20: 294-297.

28 Qiu K, Liu L, Zhong B, Yang S, Zhi Z, Yin C. Observation on the effect of Shenfu injection combined with TEC neoadjuvant chemotherapy regimen in the treatment of premenopausal locally advanced breast cancer Shandong Medical Journal. 2018; 58: 71-73.

29 Gao J, Lu S. Research Progress in Chemical Constituents and Pharmacological Action of Renshen(Ginseng). 2021; 27: 127-130+137. doi:10.13862/j.cnki.cn43-1446/r2021.01.030.

30 Liu P. A Study on the Pharmacological Action and Clinical Application of Aconite Roots. Smart Healthcare. 2019; 5: 24-25.