Original Article

Effect of Silybum Marianum on Reduction of Chemotherapy-Induced Peripheral Neurotoxicity with Cisplatin

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Abstract

Background: Chemotherapy-induced peripheral neurotoxicity (CIPN) is one of the major complications of chemotherapy regimens commonly used in the treatment of solid and hematologic cancers. Given the high incidence of CIPN in antitumor therapies in patients and limited studies on antioxidants, this study was aimed to investigate the effect of Silybum marianum (SM) on cisplatin-induced peripheral neuropathy.

Materials and Methods: This double-blind randomized clinical trial study was performed on 60 cancer patients treated with cisplatin chemotherapy at Seyyed-o-Shohada Hospital of Isfahan during 2019–2020. The patients were divided into two parallel groups as intervention (treated by SM) and placebo, and DN4 (Douleur neuropathique 4 questions) and CIPNAT (chemotherapy-induced peripheral neuropathy assessment tool) were completed for patients in the before and after intervention groups and compared between the two groups.

Results: The mean of DN4 score in the before and after study in the intervention group was in 1.76 ± 1.24 and 2.07 ± 2.03, respectively ($P = 0.38$), and in the control group was 1.41 ± 1.28 ± 3.11 ± 2.86, respectively ($P = 0.012$). The mean CIPNAT score in the intervention groups was 5.93 ± 3.65 and 4.20 ± 3.23 ($P = 0.01$), and in the control group was 4.20 ± 4.22 and 4.16 ± 4.03 ($P = 0.39$).

Conclusion: Based on our data, SM is an effective agent in reducing peripheral neuropathy. The use of SM was associated with decreased scores of peripheral neuropathy and was helpful in patients undergoing chemotherapy with cisplatin.

Keywords: Cisplatin, drug therapy, milk thistle, neoplasms, peripheral nervous system diseases

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Introduction

Cancer is one of the leading causes of mortality among populations, especially with the increasing trend due to changes in lifestyle and environmental factors.[1] The incidence and mortality of 27 major cancers in the world were 14.1 million new cases and 8.2 million deaths in 2012.[2,3] Cancer statistics among Iranians also show that the number of cancers is more than 110 per 100,000 people.[4,5]

One of the most important treatment methods for cancer is chemotherapy, which is commonly used for lung, breast, bladder, colorectal, cervical, ovarian, and prostate cancers. The main complications of chemotherapy include vomiting, nausea and hair loss, fatigue, sleep disturbance, weight gain, mouth ulcers, numbness, tingling, pain (peripheral neuropathy), eye problems, diarrhea, constipation, urinary problems, etc.[6-8]

Chemotherapy-induced peripheral neurotoxicity (CIPN) is one of the major complications of chemotherapy regimens commonly used in the treatment of cancers. Cisplatin, carboplatin, oxaliplatin, and vincristine are drugs that cause neurotoxicity more than any other drug, and the incidence of this type of neurotoxicity is between 10 and 100 percent.[9-11] Cisplatin is a chemotherapy medication used to treat many

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cancers. These include testicular cancer, ovarian cancer, cervical cancer, breast cancer, bladder cancer, head and neck cancer, esophageal cancer, lung cancer, mesothelioma, brain tumors, and neuroblastoma. The side effects of cisplatin include black, tarry stools, blood in urine or stools, burning, numbness, tingling, or painful sensations, change in frequency of urination or amount of urine, cough or hoarseness, difficulty in breathing, feeling of fullness in the ears, and fever or chills.

Neuropathy may increase following diabetes, malnutrition, previous neurotoxic treatments, alcohol usage, or hereditary neuropathies.[12-14] Disruption of axonal transport or neuronal metabolism may increase nerve damage. Neuropathic disorders may persist for months or years and even worsen after treatment, and in a few cases, sensory and motor disorders may remain constant.[15,16] The mechanisms of CIPN induced by epothilones are as follows: Epothilones cause microtubule disruption, which impairs axonal transport and leads to Wallerian degeneration, the altered activity of ion channels, and the hyperexcitability of peripheral neurons.

Overall, CIPN shows itself with sensory symptoms that include numbness, seen in more than 90%, and pain in 26% of patients. The distribution of these signals is mostly gloves or stocking patterns and double-sided.[17,18] Firstly, long myelinated fibers are involved which eliminates the feeling of proprioceptive and increases sensitivity to the fingertips, palms, and soles of the feet. Other damage to small non-mineralized fibers reduces sensitivity to needle tip testing. Transient muscle cramps are also commonly seen in cisplatin treatment and autonomic neuropathy is the result of treatment with vincristine.[19]

The Silybum marianum (SM) plant contains flavonolignan. It is available as a medicinal compound and is routinely used to treat chronic inflammatory liver disease and cirrhosis and is a hepatoprotective drug.[20] SM prevents lipid peroxidation and prevents the oxidation of light lipoproteins and destroys reactive oxygen species.[21] It has been involved in increasing antioxidant enzymes and limiting lipid peroxidation and improving superoxide dismutase activity.[22,23] Animal studies have shown that SM can prevent and treat neuropathy and improve nerve conduction velocity, antioxidant enzyme levels, and decrease hyperalgesia and lipid peroxidation.[24]

Considering the lack of a human-focused clinical trial on the potential effect of SM to reduce the onset and exacerbation of CIPN, and given the attention to the inconsistency of the results of existing retrospective studies, conducting a clinical trial on this issue seemed necessary. As a result, here we aimed to investigate the effect of SM on the management of CIPN in cancer patients treated with cisplatin.

Materials and Methods

This is a double-blinded controlled clinical trial that was performed in 2019–2020 in Seyed-al-Shohada Hospital affiliated to Isfahan University of Medical Sciences. The current study was conducted on 60 patients with cancer who underwent treatment with cisplatin after chemotherapy. The study protocol was approved by the Research Committee of Isfahan University of Medical Sciences and the ethics committee has confirmed it (Ethics code: IR.MUI.REC.1398.3.114, Iranian Registry of Clinical Trial Study (IRCT) code: IRCT20200825048515N29).

Inclusion criteria were age over 18 years, patients with solid and hematological cancer who underwent treatment with cisplatin chemotherapy, ability to take oral medication, no previous neurological disorders, avoid diseases that cause peripheral neuropathy such as diabetes, no pregnancy and lactation, newly diagnosed cancer, and informed consent to participation in the study. Exclusion criteria were incidence of side effects caused by SM consumption (such as severe skin allergies, eczema, headache and nausea, impaired taste, sweating, weakness, and hypoglycemia), and withdrawal from continuing intervention.

The sample size of the study was calculated using a standard formula, so 95% confidence interval and 80% power test were considered to sample size; in addition, standard deviations for neuropathy score in the recent study[25] were S1 = 6.3 and S2 = 10.6 and also the means of neuropathy score were M1 = 3.4 and M2 = 11.5, then the sample size was considered 30 patients in each group.

Sixty cancer patients undergoing chemotherapy with cisplatin were selected. At first, the study was explained to the patients and if the patients were satisfied, the informed consent form was completed. Both patients and physicians were unaware of the types of drugs. The data collectors and data analysts were also blinded to the types of drugs. The drug types were decoded at the end of the analysis.

Based on convenient sampling methods, patients were selected from those referring to oncology outpatient clinics of Seyed-al-Shohada Hospital. Initially, demographic information (age, sex) and disease information (type of cancer, duration of diagnosis, type of used drugs) were extracted from the patient's record and entered into the special checklists. Also, DN4 (Douleur neuropathique 4 questions) and CIPNAT (chemotherapy-induced peripheral neuropathy assessment tool) checklists were completed.

The patients were randomly distributed into two groups of intervention and control groups by using Random Allocation the Statistical Package for the Social Sciences software, version 26 (SAS Institute, Inc., N.C., USA). Patients in the SM group received cisplatin plus SM (Livergol manufactured by Goldaru company, Iran) with a dosage of 140 mg three times daily for 90 days and patients in the placebo group received the same amount of cisplatin with placebo (They received placebo made by Livergol's drug maker in the same form and size). Doses are usually 80 mg/m^2 and usually 4 to 6 doses, meaning we give about 300 to 500 mg per square meter. According to the other literature, the minimum doses of cisplatin for neuropathy was 300–500 (417 ± 132 mg/m^2).[19] At the end of the treatment period, the patients again completed the DN4 and CIPNAT checklists. We excluded patients with a complication of such

anaphylactic shock or other types of hypersensitivity due to the usage of SM. The incidence of neuropathy also was evaluated in patients of two groups during the study.

DN4 and CIPNAT checklists are two checklists that are used to evaluate peripheral neuropathy. The validity and reliability of this questionnaire have been studied in different studies.[16] The higher the score of these two questionnaires is indicated, the higher the severity of neuropathy, and also the DN4 questionnaire contains four questions with a total score of 0 to 10. On the other hand, the CIPNAT questionnaire contains 11 questions each with a score of 0 to 4 and the total score of the questionnaire is from 0 to 44.[26]

Finally, information about patients was entered and analyzed using Statistical Package for Social Sciences (SPSS) version 24. The quantitative data were shown based on mean and standard deviation, and the qualitative data were reported based on frequency and percentage. Chi-square test and independent t-test were used to assess the variables between the two groups. The changes of quantitative variables before and after were evaluated using the repeated measures analysis of variance (ANOVA) test. A *P* value less than 0.05 was considered a significant level. Also, a binary logistic regression test was used for evaluating neuropathy chance in the two groups.

Results

In this study, 69 patients who underwent chemotherapy were interviewed. Nine patients (six due to not meeting inclusion criteria and three due to declined to participate) were not included in the study. During the intervention, four patients were excluded (one in the intervention group and three in the control group) due to death (one in the control group) and withdrawal from continuing to study, and data analysis was done on 29 patients in the intervention and 27 patients from the control group [Figure 1].

There was no significant difference between the two groups based on gender, age, and type of cancer and received doses of cisplatin ($P > 0.05$) [Table 1].

According to Table 2, there was no statistical difference between intervention and control groups I in the before and after intervention, but the DN4 score was statistically increased in the control group ($P = 0.012$). Also, the CIPNAT score in the intervention group was statistically decreased ($P = 0.01$). According to repeated measures ANOVA, the mean changes of DN4 and CIPNAT are not statistically different between the two groups ($P = 0.37$, $P = 0.09$).

Table 3 shows the frequency distribution of neuropathic pain symptoms according to the DN4 questionnaire before and after the intervention in the two groups. According to the table, the frequency of pain associated with one or more itching in the intervention and control groups was significantly different ($P = 0.029$) but other items were not significantly different between the two groups. In the after intervention, the three items of electric shock ($P = 0.016$), pins, and needles ($P = 0.001$), and hypesthesia to touch are statistically different between the two groups. According to the results of the study, the mean doses of received cisplatin in patients with and without neuropathy were 539.7 ± 35.9 and 537.7 ± 45.6 mg/m^2, and no statistical difference between the two groups were seen ($P = 0.86$).

The incidence of neuropathy in the intervention group was 7 (24.1%) and in the control group was 10 (37%) and no significant difference between the two groups was seen ($P = 0.29$). According to Table 4, the frequency distribution of peripheral neuropathy did not differ significantly according to the intervention group and demographic and clinical characteristics. We also observed no side effects in the present study. Also applying logistic regression with backward conditional method showed that only using SM can statistically decrease the chance of peripheral neuropathy (OR = 0.8, 95% CI: 0.11–0.91, $P = 0.042$).

Discussion

In the current study, we investigated and evaluated the therapeutic effects of SM on CIPN with cisplatin. Here, we showed that usage of SM is associated with a decrease in

Table 1: The demographics of study based on groups

Variables	Groups		*P*
	Intervention (*n*=29)	Placebo (*n*=27)	
Gender			
Male	15 (51.7)	17 (63)	0.396
Female	14 (48.3)	10 (37)	
Mean of age (year)	43.51±15.67	45.70±11.60	0.59
Type of cancer			
Solid	25 (86.2)	26 (96.3)	0.19
Hematologic	4 (13.8)	1 (3.7)	
Mean received cisplatin (mg/m^2)	532.9±36.47	545.8±41.2	0.22

*Chi-square, **Independent *t*-test

Table 2: The changing of DN4 and CIPNAT before and after intervention in both groups

Variables	Intervention	Placebo	*P* (95% Confidence level)*
DN4			
Before	1.76±1.24	1.41±1.28	0.3 (-0.99-0.49)
After	2.07±2.03	3.11±2.86	0.12 (-4.27-1.86)
*P***	0.38	0.012	0.37***
CIPNAT			
Before	5.93±3.65	4.20±4.22	0.10 (2.43-6.61)
After	4.20±3.23	4.16±4.03	0.97 (0.83-4.0)
*P***	0.01	0.39	0.09***

*Significant level of difference between the two groups in each time period according to independent *t*-test. **Significant level of difference within each group in each time period according to repeated measures ANOVA test. ***The trend of changes between the two groups according to the repeated measures ANOVA test

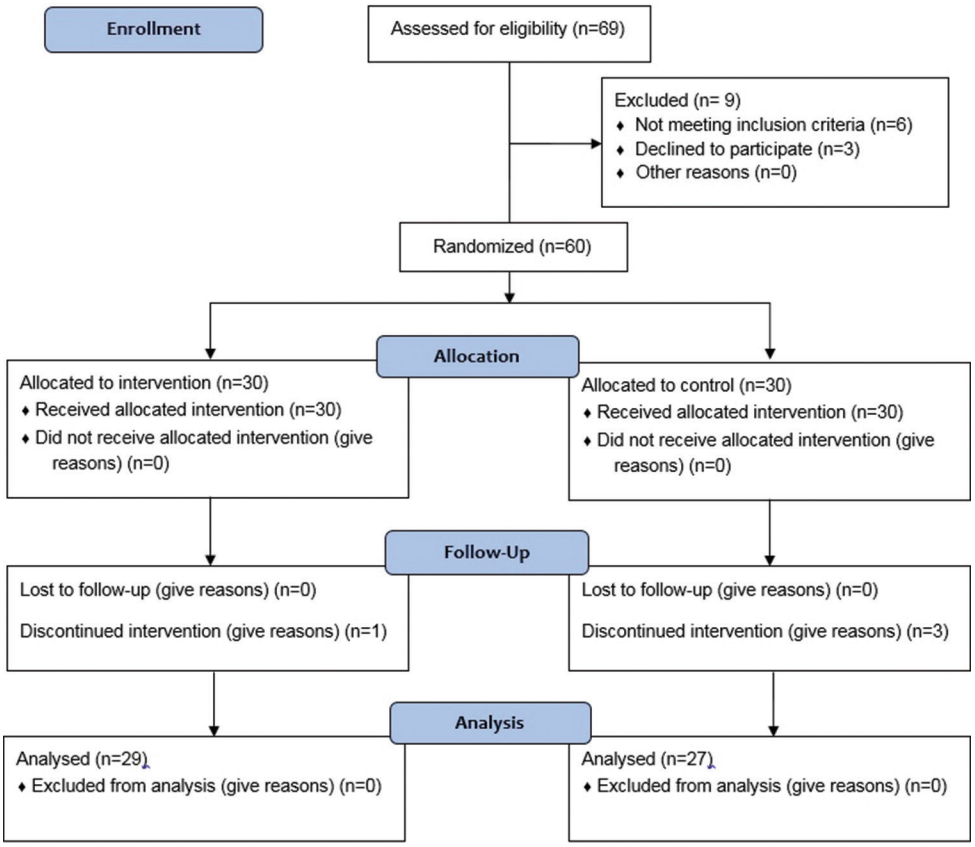

Figure 1: The Consolidated Standards of Reporting Trials flow chart of the study population

Table 3: Frequency distribution of DN4 items in the before and after intervention

Question	Before intervention			After intervention		
	Intervention	Control	*P*	Intervention	Control	*P*
Pain has one or more of the following characteristics						
Burning	8 (27.6)	11 (40.7)	0.3	9 (31)	13 (48.1)	0.19
Painful cold	8 (27.6)	9 (33.3)	0.64	8 (27.6)	10 (37)	0.45
Electric shocks	0 (0)	2 (7.4)	0.14	1 (3.4)	7 (25.9)	0.016
Pain associated with one or more of the following						
Tingling	15 (51.7)	7 (25.9)	0.05	14 (48.3)	12 (44.4)	0.77
Pins and needles	2 (6.9)	2 (7.4)	0.94	2 (6.9)	12 (44.4)	0.001
Numbness	12 (41.4)	9 (33.3)	0.53	14 (48.3)	12 (44.4)	0.77
Itching	7 (24.1)	1 (3.7)	0.029	8 (27.6)	5 (18.5)	0.42
Physical examination						
Hypesthesia to touch	2 (6.9)	1 (3.7)	0.6	1 (3.4)	8 (29.6)	0.008
Hypesthesia to pinprick	0 (0)	0 (0)	1	1 (3.4)	3 (11.1)	0.27
Pain increased by brushing	0 (0)	2 (7.4)	0.14	1 (3.4)	3 (11.1)	0.27

the intensity of peripheral neurotoxicity. These emphasize the beneficial effects of SM in patients undergoing chemotherapy. Previous studies have also evaluated different agents for treatments of CIPN.

In a review study by Carvalho and others in 2017, the use of antioxidants and other agents was evaluated in CIPN. In this article, they showed that the usage of anticonvulsants, antispastic agents, and other drugs could not provide evidence on their effectiveness against CIPN but antioxidants including SM could be a better choice in this issue.[9] In comparison with our findings, these results are in line with ours. We showed that treatments with SM are associated with decreased neuropathy in patients under cisplatin chemotherapy. Bahmani and colleagues also had a study on the therapeutic effects of SM in 2015. They showed that SM has a wide range of effects in patients especially patients undergoing chemotherapy. However, its effects are beyond hepatoprotection, which requires further evaluation. They showed that the main

Table 4: Frequency distribution of peripheral neuropathy based on intervention, demographic, and clinical characteristics

Variables	Peripheral neuropathy		*P*
	No	Yes	
Groups			
Intervention	22 (75.9)	7 (24.1)	0.29
Control	17 (63)	10 (37)	
Mean of age (year)	44.21±14.7	45.41±11.75	0.77
Sex			
Male	25 (78.1)	7 (21.9)	0.11
Female	14 (58.3)	10 (41.7)	
Type of cancer			
Solid	36 (70.6)	15 (29.4)	0.62
	3 (60)	2 (40)	

mechanism of SM therapeutic effects is via antioxidant and anti-inflammatory activities, cell permeability regulation, and membrane stabilization.[27] These mechanisms could explain the effectiveness of this drug in patients with CIPN. Here, in the current study, we showed that the means of DN4 and CIPNAT in the intervention group were significantly lower than the placebo group after intervention. We believe that these effects could be mediated through antioxidant and anti-inflammatory activities of SM. Zimmerman and Yernell performed a recent study in 2019 investigating the roles of herbal medicine as adjuvant therapy to cancer. They showed that SM is an effective drug with very few side effects between other herbal medicines and a wide range of documented beneficial effects in different aspects. They also showed that SM might have beneficial effects on CIPN.[28-30] Compared to our results, the results of Zimmerman and colleagues were also in line with our findings, showing the effectiveness of SM in treatments of CIPN. We assume that these effects are mediated through the antioxidant characteristics of SM.

In a study by Greenlee and colleagues in 2007, therapeutic effects of SM were evaluated in patients undergoing chemotherapy. They explained that SM could be used in both adult and pediatric populations to prevent cardiovascular and hepatic side effects of chemotherapy. They also showed that SM has beneficial effects in cleansing and detoxification after chemotherapy, preventing hepatotoxicity during chemotherapy, treating hepatotoxicity after chemotherapy, and potentiating chemotherapy and radiation therapy as an adjuvant treatment.[31,32] Our results are in line with this report, showing the importance of SM usage in preventing or treating chemotherapy side effects. Bone and colleagues also indicated that SM is safe and effective in preventing chemotherapy side effects but there are also concerns that SM could increase the hepatic clearance of chemotherapy drugs.[33,34] Santabarbara and others evaluated pharmacotherapeutic options for treatments of cisplatin chemotherapy and declared that antioxidant agents are beneficial and effective in this regard and could bring important therapeutic effects. They also showed that amifostine, vitamin E, SM, and NK-1 receptor antagonists could prevent cisplatin-induced DNA damage and the production of reactive oxygen species.[35,36] These findings are also in line with our study. Another study was conducted by Zhang and colleagues in 2018. In this study, they reviewed variable natural products for chemotherapy- and radiotherapy-induced side effects and indicated that SM might not reduce peripheral neuropathy, and suggested that further studies should be performed in this regard.[37,38] They also showed that the anti-inflammatory effects of SM could be utilized in liver function diseases. These results are not in line with our findings. We showed that SM is an effective agent in CIPN. Furthermore, in another study by Madani and others in 2008, hepatoprotective effects of SM were investigated. They indicated that SM was not effective in hepatotoxicity and other chemotherapy-associated diseases and further studies might be required.[39,40] These results are not the same as our study, because we believe that changes of intensity of neuropathy were not different between the two groups, and finally, the effectiveness of SM on CIPN was not statistically significant.

Conclusion

Here, we evaluated the therapeutic effects of SM in CIPN and showed that SM is an effective agent in reducing peripheral neuropathy. It is believed that SM could have beneficial clinical effects in patients undergoing chemotherapy with cisplatin.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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