Original article

The effects of vitamin E and selenium on cisplatin-induced nephrotoxicity in cancer patients treated with cisplatin-based chemotherapy: A randomized, placebo-controlled study

Simin Hemati[1], Nafiseh Arbab Jolfaie[1], Abbas Gookizadeh[1], Mohammad Rafienia[2], Mohammad Reza Ghavamnasiri[3]

[1] Department of Radiation Oncology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. [2] Biosensor Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. [3] Cancer Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

BACKGROUND: Cisplatin is a chemotherapeutic agent with a wide range of anticancer effects. Two main toxicities of this drug are nephrotoxicity and myelosuppression. These toxic effects are related to free radical damage, reduction in antioxidant levels and oxidant stress. **METHODS:** In this study, 22 patients received 400 IU vitamin E and 200 µg selenium daily and 24 patients received placebo. The primary outcome was nephrotoxicity and the secondary outcome was bone marrow suppression. Glomerular filtration rate (GFR) and complete blood count with differential (CBC/diff) including of white blood cell (WBC) count, hemoglobin (Hb), and platelet counts were determined at the start of chemotherapy and before each cycle as well as one month after cessation of chemotherapy in both groups. **RESULTS:** Significant differences in GFR were observed between the two groups after the third cycle and one month after the end of chemotherapy ($p < 0.05$). WBC, Hb, and platelet counts showed significant differences between the study groups after the second and third cycles ($p < 0.05$). While after one month WBC and platelet counts demonstrated significant differences ($p < 0.05$), Hb changed insignificantly ($p > 0.05$). **CONCLUSIONS:** According to our findings, vitamin E and selenium can be used to reduce cisplatin-induced nephrotoxicity and bone marrow suppression.

KEYWORDS: Chemotherapy, Vitamin E, Selenium, Cisplatin, Nephrotoxicity, Myelosuppression, Glomerular Filtration Rate.

BACKGROUND

Cisplatin, cis-diamminedichloroplatinum (II), is a platinum compound with the broadest range of clinical activity and the most substantial toxicity profile. Cisplatin-based therapy is curative in testicular cancer and is very active in gynecologic cancers, gastrointestinal malignancies, genitourinary cancers, head and neck cancers, lung cancer, and other malignant diseases.[1] Nephrotoxicity is one of the important dose limiting side effects since 20% of patients receiving high-dose cisplatin have severe renal dysfunction.[2] These toxic effects are related with free radical damage, reduction in antioxidant levels, and oxidant stress, which are induced by cisplatin.[3]

One of the interventions to reduce oxidative stress in renal failure patients is administration of antioxidants such as alpha-tocopherol. Another way to overcome the oxidative stress is to use substances such as erythropoietin and sodium selenite with an indirect effect on oxidative stress.[4,5] With no adverse effects on therapeutic outcome, some antioxidants, such as pineal hormone melatonin (MLT) and selenium, can even increase the efficacy of chemothera py and reduce toxicity.[6-8]

Multiple animal studies support the hypothesis that vitamin E succinate (VES, alpha-tocopherol succinate) interferes with cisplatin-induced damage. These studies suggest that concurrent treatment with this supplement can be useful in protection against nephrotoxicity.[3,9-12] Ajith et al. designed a study to compare the effectiveness of single and multi doses of vitamin C (500 mg/kg), vitamin E (500 mg/kg), and vitamin C plus E (250 mg/kg each) in prevention of acute renal failure. They found that co-administration of single and multi doses of vitamins in mice caused a significant decline in glutathione level and protection from cisplatin-induced increased serum urea, creatinine levels, and renal malondialdehyde (MDA).[9] Another study showed vitamin E to be effective in preventing oxidative renal damage in mice.[12] Atasayar et al. found that aminoguanidine (an antioxidant agent) as well as vitamin C-E combination resulted in a lower incidence of nephrotoxicity in rats.[10] Another research addressed the role of ascorbic acid and alpha-tocopherol monoglucoside (TMG) in reducing cisplatin-induced higher plasma creatinine and urea levels and lipid peroxidation in mice.

Address of Correspondence: Nafiseh Arbab Jolfaie, Department of Radiation Oncology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. Email: nafiseharbab@yahoo.com
Received: 05-12-2011; **Revised:** 07-01-2012; **Accepted:** 15-02-2012

The authors suggested that ascorbic acid monoglucoside (AsAG) or TMG have implications to prevent drug-induced nephrotoxicity in humans.[11]

Interactions between selenium and platinum-containing chemotherapy agents have been extensively studied. With consumption of selenium in mice, the activity of cisplatin increased and its toxicity decreased.[8] Intraperitoneal injection of selenium and high doses of vitamin E could increase antioxidant concentrations in rats. Therefore these agents may have a protective property in cisplatin-induced nephropathy and cataract formation in cancer patient.[13] Plasma creatinine, urea, and nitrate levels were reduced clearly with sodium selenite (an exogenous source of selenium) and toxic effects of cisplatin on oxidative stress markers were neutralized in rats.[14] Some other studies on animals confirmed these findings.[15,16]

In view of the suggested protective effects of selenium and vitamin E in mentioned animal studies, this clinical trial was carried out to evaluate the effects of these antioxidant micronutrients in preventing cisplatin nephrotoxicity and bone marrow suppression.

METHODS

Patient Selection

This study was performed in the department of radiation oncology in Seyed-al-Shohada Hospital (Isfahan, Iran), during April 2010 to August 2011. Patients who were indicated for cisplatin-based chemotherapy were divided into two groups. In order to perform a randomized study, the supplement and placebo were administrated alternatively among the qualified patients. Group 1 received selenium and vitamin E (target group) and group 2 received placebos (control group).

Inclusion criteria were aging ≥ 18 years, having glomerular filtration rate (GFR) > 80 ml/min, and scoring > 60 on Karnofsky Performance Status (KPS) scale. Exclusion criteria were comorbidity that affected renal function (such as diabetes mellitus, hypertension, and past history of renal dysfunction), previous chemotherapy, and treatment with other supplementation. The proposal was approved by the adjunct research center of Isfahan University of Medical Sciences (IUMS). IUMS has two informed consent forms for all medical studies. We chose the second form for this research. All patients thoroughly read and signed the informed consent form.

Drug administration

Cisplatin was administered intravenously (IV) on days 1-2 of each chemotherapy cycle for 4 cycles every 21 days. We endeavored to choose the chemotherapy regimens as uniform as possible to match the study groups. Therefore, patients undergoing treatments out of this protocol (every 21 days to 4 cycles), such as weekly chemoradiation, 3 or 6 treatment cycles, starting radiotherapy 3 weeks after chemotherapy (because patients should not receive any treatment in the first month of chemotherapy), and previous chemotherapy, were not enrolled in the study. In four patients with testicular cancer, the bleomycin, etoposide, and cisplatin (BEP) regimen was applied. Cisplatin administrations were on days 1-5 in this regimen. Despite the differences in cisplatin doses between testicular cancers and other cancers, we recruited the patients due to the similar number of patients with these cancers in the two groups. Prior to cisplatin administration, one liter of normal saline plus 20 mEq of potassium chloride (KCl) and 2 g of magnesium sulfate over three hours, and thereafter 500 ml normal saline over two hours were used for all patients to reduce cisplatin nephrotoxicity.

The target group included 22 patients who received one pearl tablet containing 400 IU vitamin E (as dl-α-tocopherol-acetate) and one tablet containing 200 μg selenium (as sodium selenite) daily. We recommended all patients to use the supplements after lunch. The drugs were prescribed from one week before the initiation of chemotherapy and continued along chemotherapy cycles until three weeks after the end of the treatment. On the other hand, the 24 patients in the control group received two placebo tablets daily. The vitamin E placebo tablet contained water, glycerin, gelatin, and maintaining substances. Another placebo tablet consisted of paraffin. Appearance, color, and weight of both placebo tablets were similar to main drugs.

Laboratory tests

Blood urea nitrogen (BUN), creatinine, and complete blood count with differential (CBC/diff) including hemoglobin (Hb), and white blood cell (WBC) and platelet counts were determined before each chemotherapy cycle and one month after the cessation of the cycles. Then, GFR, as an estimation of creatinine clearance, was calculated using Cockcroft-Gault formula:[17]

$$\text{creatinine clearance}\left(\frac{\text{ml}}{\text{min}}\right) = \frac{(140 - \text{age}) \times \text{lean body weight (kg)}}{\text{plasma creatinine (mg/dl)} \times 72}.$$

The obtained value was multiplied by 0.85 for women.

Statistical analysis

To evaluate the parameters, we used independent t-test, repeated measures analysis of variance (ANOVA), and Fisher's exact test. P values less than 0.05 indicated significant differences. SPSS18 (SPSS Inc., Chicago, IL, USA) was used as the statistical software.

The primary outcome was evaluation of nephrotoxicity and was estimated by GFR. The secondary outcome was assessment of myelosuppression that was estimated by WBC, Hb, and platelet counts.

RESULTS

Patient Information

Both the target and placebo groups included 25 patients. However, 3 patients were excluded from the target group (one patient due to early death, one left the study and did not use the supplements because of dyspepsia, and one moved to another city and was not in access for follow-up). In the placebo group, one patient left the chemotherapy. Therefore, 22 and 24 patients remained in the target and control groups, respectively.

Patients in the target group had bladder cancer (n = 6), gastric cancer (n = 4), esophageal cancer (n = 3), head and neck cancer (n = 2), lung cancer (n = 2), testicular cancer (n = 2), cervical cancer (n = 2), and thymic carcinoma (n = 1). The youngest patient was 18 and the oldest was 72 years old. The mean age of patients was 53 ± 13 years. In this group, body mass index (BMI) and male to female (M/F) ratio were 25.8 ± 4.6 kg/m^2 and 19/3, respectively. One patient with gastric cancer and two patients with cervical cancer were female. The control group suffered from bladder cancer (n = 6), gastric cancer (n = 5), head and neck cancer (n = 4), esophageal cancer (n = 3), lung cancer (n = 2), testicular cancer (n = 2), cervical cancer (n = 1), and malignant mesothelioma (n = 1). In this group, the youngest patient was 20 and the oldest was 71 years old (mean age: 55 ± 11 years). BMI and M/F ratio were 26.8 ± 3.0 kg/m^2 and 20/4, respectively. One patient with gastric cancer, one patient with cervical cancer, one patient with head and neck cancer, and one patient with esophageal cancer were female. Table 1 shows the information of the participants. Independent t-test showed no significant differences in mean age and mean BMI between the two groups. Moreover, the study groups did not show significant differences in gender according to Fisher's exact test ($p > 0.05$).

Tumor types in each group are shown in table 2. There were no significant differences regarding tumor types and their numbers between the two groups. Table 3 summarizes the pathology, stages, and treatment of patients.

Cisplatin dose in each cycle and total doses of cisplatin in two groups are presented in Table 4. If GFR value was between 30-60 ml/min, the cisplatin dose was reduced to half of the prior dose and if GFR < 30 ml/min, cisplatin was not continued. Independent t-test showed no significant differences between the study groups regarding the mean cisplatin dose in one cycle and total cisplatin dose. Although the total cisplatin dose was modified in the control group because of GFR reduction in some patients, independent t-test showed no significant differences between the two groups ($p > 0.05$).

GFR values before each chemotherapy cycle and one month after the end of chemotherapy in the study groups are shown in Table 5 and Figure 1. Independent t-test showed no significant differences between the two groups in GFR scores before the first, second, and third chemotherapy cycles ($p > 0.05$). However, the results showed significant differences in GFR values before the fourth cycle and one month after the end of chemotherapy between the two groups ($p < 0.05$). Repeated measures ANOVA suggested significant differences in mean GFR values between chemotherapy cycles in each group ($p < 0.001$).

The results after the end of chemotherapy are compared in Table 6 and Figure 2. Although WBC count did not show significant differences before the first and second cycles ($p > 0.05$), independent t-test indicated significant differences between the two groups before the third and fourth cycles and one month after the cessation of chemotherapy ($p < 0.05$). According to repeated measures ANOVA, there were significant differences in mean WBC count between chemotherapy cycles in each group ($p < 0.001$).

Blood Hb levels in the target and control groups before each chemotherapy cycle and one month after the end of chemotherapy are shown in Table 7 and Figure 3. Independent t-test did not reveal any significant differences in Hb levels before the first and second cycles and one month after the termination of chemotherapy ($p > 0.05$). However, significant differences were present before the third and fourth cycles ($p < 0.05$). Repeated measures ANOVA showed significant differences in blood Hb levels between chemotherapy cycles in each group ($p < 0.001$).

Table 1. Characteristics of patients

	Target (n = 22)	Control (n = 24)	P-value
Age (years) (mean ± SD; range)	53.0 ± 13.0 (18-72)	55.0 ± 11.0 (20-71)	0.648 (NS)
Male/female	19/3 (86.4%/13.6%)	20/4 (83.3%/16.7%)	0.550 (NS)
Body mass index (kg/m^2)	25.8 ± 4.6	26.8 ± 3.0	0.360 (NS)

NS: Not Significant

SD: Standard deviation

Table 2. Tumor types

Tumor types	Target (n = 22)	Control (n = 24)
Bladder cancer	6	6
Gastric cancer	4	5
Esophageal cancer	3	3
Head and neck cancer	2	4
Lung cancer	2	2
Testicular cancer	2	2
Cervical cancer	2	1
Thymic carcinoma	1	-
Malignant mesothelioma	-	1

Table 3. Pathology, stages, and treatments in the studied patients

Cancer type	Pathology	Stage	Treatment	Chemotherapy regimen
Bladder cancer	TCC	T3, T4, N+	CT for 4 cycles followed by CRT	GC
Gastric cancer	Adenocarcinoma	M+	CT	DCF
Esophageal cancer	SCC/ Adenocarcinoma	I-IIA	Esophagectomy followed by adjuvant CT	Cisplatin-Paclitaxel
Head and neck cancer	Vocal cord carcinoma (SCC) (n = 2)	T3	Total laryngectomy + PORT	DCF
	Supraglottic carcinoma (SCC) (n = 1)	T3	Supraglottic laryngectomy + PORT	DCF
	Adenoid cystic carcinoma of parotid (n = 1)	T3	Surgery + PORT	DCF
	SCC of maxillary sinus (n = 1)	T3	Surgery + PORT	DCF
	SCC of tongue (n = 1)	T3	Surgery + PORT + CT	Cisplatin-Paclitaxel
Lung cancer	NSCLC (n = 2)	IV	CT	Cisplatin-Paclitaxel
	NSCLC (n = 2)	T2b N0	Surgery + adjuvant CT	Cisplatin-Paclitaxel
Testicular cancer	NSGCT	M1a S3 (IIIc)	CT	BEP
	NSGCT	M1b S2 (IIIc)		
	NSGCT	N3 S2 (IIc)		
	NSGCT	N3 S2 (IIc)		
Cervical cancer	SCC	IVB	CT then palliative RT	Cisplatin-Paclitaxel
Thymic carcinoma	SCC	T2N0M0 (I)	Surgery+ PORT+ CT	EP
Malignant mesothelioma	Epithelial type	T4N1	RT and CT	Doxorubicin -cisplatin

TCC: Transitional cell carcinoma; SCC: Squamous cell carcinoma; NSCLC: Non-small cell lung carcinoma; CT: Chemotherapy; CRT: chemo-radiation; RT: Radiation therapy; PORT: Postoperative radiation therapy; G: Gemcitabine; C: Cisplatin; D: Docetaxel; BEP, Bleomycin, etoposide, cisplatin; EP: Etoposide, cisplatin

Table 4. Cisplatin dosage

	Target (n = 22)		Control (n = 24)		p
Cisplatin dose/cycle (mg/m^2)					
(Mean ± SD)	76 ± 8		76 ± 7		0.956
	Dose/cycle (mg/m^2)	No. of patients	Dose/cycle (mg/m^2)	No. of patients	
	60	1	60	1	
	75	19	75	21	
	100	2	100	2	
Total dose of cisplatin (mg/m^2)					
(Mean ± SD)	306 ± 32		296 ± 43		0.387
	Total dose (mg/m^2)	No. of patients	Total dose (mg/m^2)	No. of patients	
	240	1	187	1	
	300	19	224	1	
	400	2	262	1	
			240	1	
			300	18	
			400	2	

Table 5. Glomerular filtration rate (GFR) in the target and control groups before each chemotherapy cycle and one month after the end of chemotherapy

GFR (ml/min)	Target (n = 22)	Control (n = 24)	p*
GFR 1	112 ± 17	116 ± 13	0.353 (NS)
GFR 2	108 ± 17	108 ± 16	0.985 (NS)
GFR 3	102 ± 16	97 ± 21	0.425 (NS)
GFR 4	98 ± 17	88 ± 23	0.048
GFR 1 month	94 ± 14	84 ± 23	0.049
p**	< 0.001	< 0.001	

NS: Not significant

* Independent t-test

** Repeated measures analysis of variance

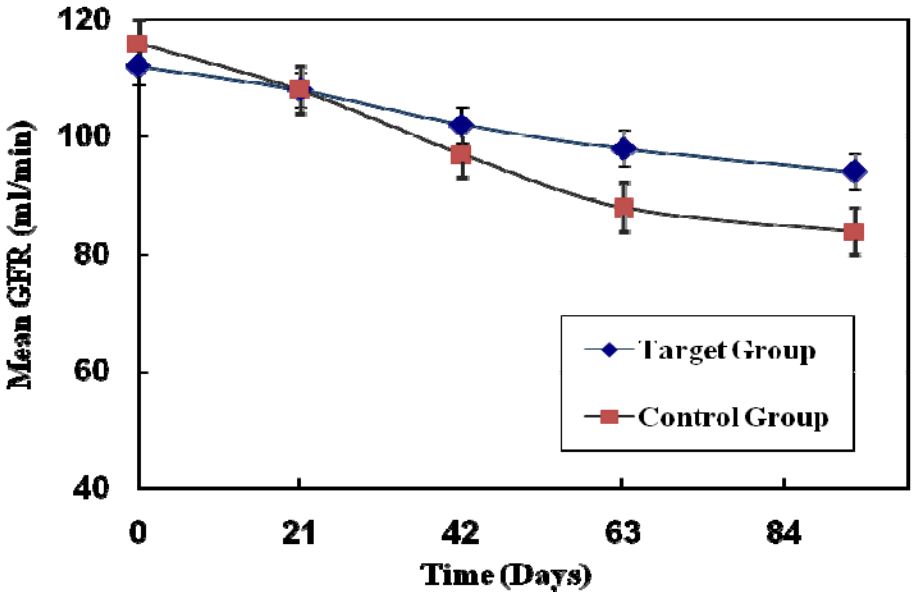

Figure 1. Mean changes of glomerular filtration rate (GFR) during and one month after chemotherapy in the target and control groups

Table 6. White blood cell (WBC) count in the target and control groups before each chemotherapy cycle and 1 month after the end of chemotherapy

WBC (10^9 cells/l)	Target (n = 22)	Control (n = 24)	p*
WBC 1	7.5 ± 0.8	7.6 ± 1.3	0.771 (NS)
WBC 2	7.4 ± 0.8	7.3 ± 1.2	0.652 (NS)
WBC 3	7.1 ± 1.0	5.9 ± 1.5	0.007
WBC 4	6.6 ± 0.9	4.2 ± 1.7	< 0.001
WBC 1 month	6.9 ± 0.6	5.6 ± 1.5	0.001
p**	< 0.001	< 0.001	

NS: Not significant
* Independent t-test
** Repeated measures analysis of variance

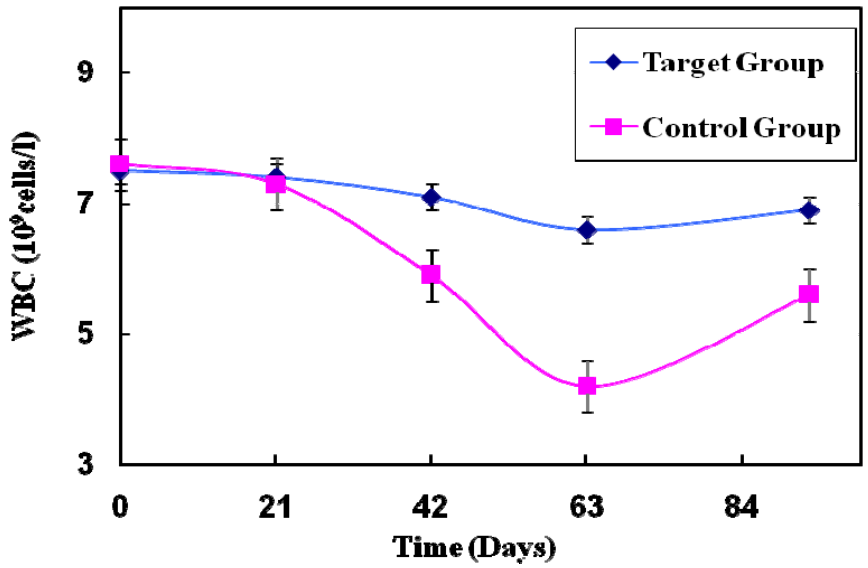

Figure 2. Changes in white blood cell (WBC) count during and one month after chemotherapy in the target and control groups

Table 7. Blood hemoglobin (Hb) in the target and control groups before each chemotherapy cycle and 1 month after the end of chemotherapy

Hb (mmol/l)	Target (n = 22)	Control (n = 24)	p*
Hb 1	12.2 ± 1.2	12.8 ± 1.2	0.135 (NS)
Hb 2	11.8 ± 1.5	12.1 ± 1.4	0.493 (NS)
Hb 3	11.2 ± 1.3	10.3 ± 1.4	0.035
Hb 4	10. 8 ± 1.1	9.8 ± 1.5	0.012
Hb 1 month	11.5 ± 1.2	11.6 ± 1.2	0.739 (NS)
p**	< 0.001	< 0.001	

NS: Not significant
* Independent t-test
** Repeated measures analysis of variance

Table 8. Platelet (Plt) count in the target and control groups before each chemotherapy cycle and 1 month after the end of chemotherapy

Plt (10^9cells/l)	Target (n = 22)	Control (n = 24)	p*
Plt 1	338 ± 86	331 ± 85	0.775 (NS)
Plt 2	324 ± 79	304 ± 90	0.436 (NS)
Plt 3	286 ± 78	217 ± 90	0.008
Plt 4	220 ± 79	122 ± 54	< 0.001
Plt 1 month	284 ± 77	121 ± 56	< 0.001
p**	< 0.001	< 0.001	

NS: Not significant
* Independent t-test
** Repeated measures analysis of variance

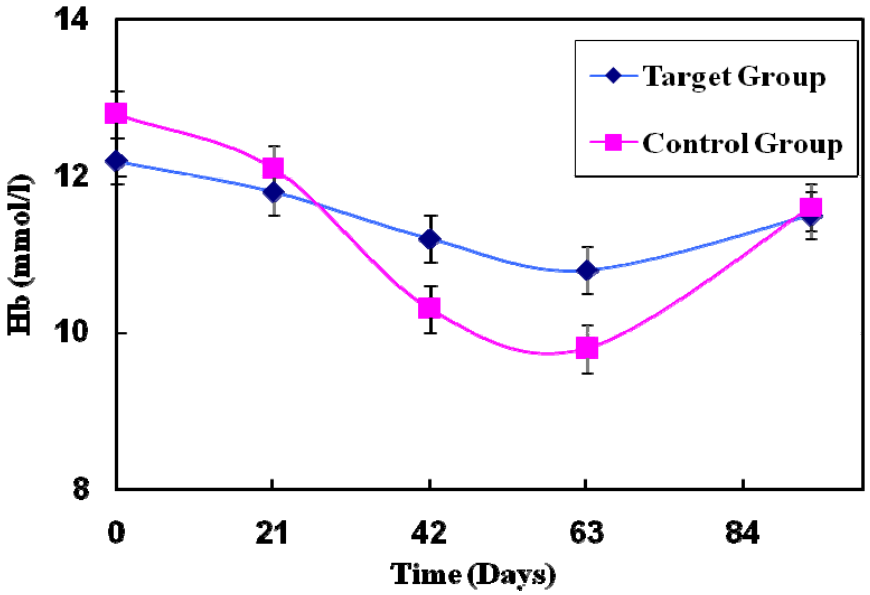

Figure 3. Hemoglobin (Hb) changes during and one month after chemotherapy in the target and control groups

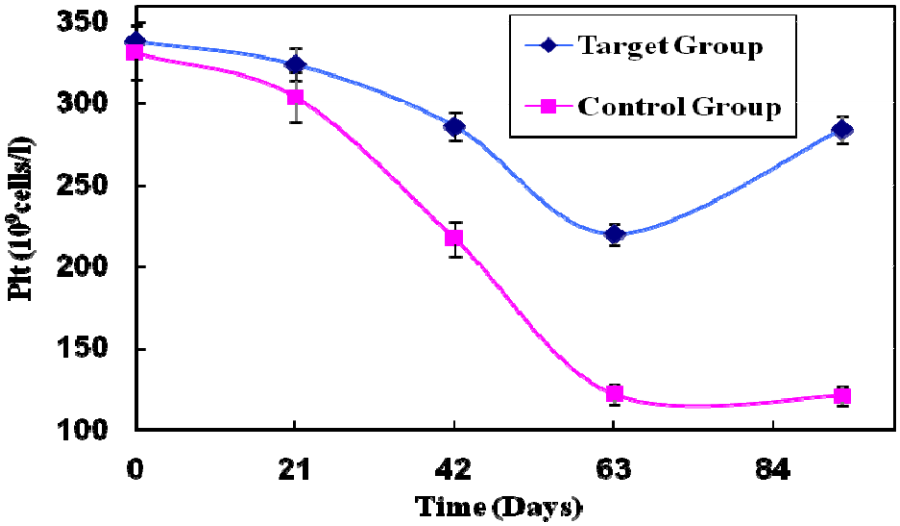

Figure 4. Platelet (Plt) changes during and one month after chemotherapy in the target and control groups

Platelet counts in the target and control groups before each chemotherapy cycle and one month after the end of chemotherapy are presented in Table 8 and Figure 4. Independent t-test was not suggestive of significant differences regarding platelet count before the first and second cycles ($p > 0.05$). This test demonstrated significant differences before the third and fourth cycles and one month after the course of chemotherapy ($p < 0.05$). Repeated measures ANOVA showed significant differences in platelet count between chemotherapy cycles in each group ($p < 0.001$).

DISCUSSION

The role of vitamin E and selenium in protecting against cisplatin nephrotoxicity and bone marrow suppression was investigated in this study. The main limitation of this research was applying different cisplatin-based chemotherapy regimens with variable doses in patients. Therefore, it was difficult to match the studied groups. Moreover, although we had recommended all patients not to use any drugs without our consultation, some patients may have used nephrotoxic drugs without informing us. In addition, the antioxidant values of dietary regimens were different among the patients that may confound the results.

Renal Toxicity

We used the RIFLE criteria (risk, injury, failure, loss, and end-stage kidney disease) including three graded levels of injury (risk, injury, and failure) based on either the magnitude of elevation in serum creatinine or reduction in GFR values. The RIFLE classifications are as follows:

- Risk: 1.5-fold increase in serum creatinine or 25% reduction in GFR
- Injury: Twofold increase in serum creatinine or 50% reduction in GFR
- Failure: Threefold increase in serum creatinine or 75% reduction in GFR.[18]

If GFR decreased for 30-60 ml/min, the dose of cisplatin dose was halved. Chemotherapy was not continued if GFR was under 30 ml/min.[19]

In the placebo group, GFR of three patients decreased by 40, 41, and 47%. These patients were placed in the injury category. GFR varied from a primary value of 115 ml/min to 57 ml/min in the fourth cycle (57% reduction) in one patient and cisplatin dose was hence halved (37 mg/m², total dose 262 mg/m²). In a patient, GFR reduced from 96 ml/min to 57 ml/min and 48 ml/min in the third and fourth cycles, respectively (55% reduction). Therefore, 37 mg/m² of cisplatin was administered in these courses (total dose 224 mg/m²). In another patient, GFR changed from 98 ml/min to 53 ml/min and 25 ml/min in the third and fourth cycles, respectively (74% reduction). Dose limitation was hence performed in the third cycle. This patient was not treated longer since his GFR was under 30 ml/min at the beginning of the fourth cycle (total dose 187 mg/m²). These three patients were included in the failure category. Overall, renal dysfunction was observed in 25% of the placebo group whereas it occurred only in 9% of the target group. In the target group, two patients were allocated to the injury category. GFR of these patients decreased from primary values of 146 and 104 to 102 and 72, respectively (30% and 31% reductions). Dose limitation was not carried out for these patients.

The mean GFR values in all cycles were calculated in the two groups. In the beginning of the first, second, and third cycles, the values did not show significant differences between the two groups ($p > 0.05$). However, the results showed significant differences between the two groups after three cycles (98 ± 17 vs. 88 ± 23 ml/min; $p = 0.048$) and one month after the end of chemotherapy (94 ± 14 vs. 84 ± 23 ml/min; $p = 0.049$). Therefore, nephrotoxicity was lower in the target group after the third cycle and one month after the chemotherapy. Moreover, there were significant differences in mean GFR values between chemotherapy cycles in each group ($p < 0.001$).

Our results suggest that co-administration of selenium and vitamin E is effective in reducing renal injury induced by cisplatin-based chemotherapy. Perhaps administration of these supplements from almost two months before starting chemotherapy could increase their nephroprotective effects. However, this subject needs further research.

Bone Marrow Suppression

CBC/diff was measured before starting chemotherapy cycles in all patients. WBC count of the target and control groups at the beginning of chemotherapy (7.5 ± 0.8 vs. 7.6 ± 1.3; $p = 0.771$) and before the second cycle (7.5 ± 0.8 vs. 7.6 ± 1.3; $p = 0.771$) did not show significant differences.

There were significant differences in WBC count between the target and control groups before the third (7.1 ± 1.0 vs. 5.9 ± 1.5; $p = 0.007$) and fourth (6.6 ± 0.9 vs. 4.2 ± 1.7; $p < 0.001$) cycles and one month after the end of chemotherapy (6.9 ± 0.6 vs. 5.6 ± 1.5; $p = 0.001$). As a result, co-administration of selenium and vitamin E is effective in reducing leucopenia induced by cisplatin-based chemotherapy. This effect was apparent from the third course.

Hb in the target and control groups did not show significant differences before the first (12.2 ± 1.2 vs. 12.8 ± 1.2; $p = 0.135$) and second (11.8 ± 1.5 vs. 12.1 ± 1.4; $p = 0.493$) cycles and one month after chemotherapy (11.5 ± 1.2 vs. 11.6 ± 1.2; $p = 0.739$). However, there were significant differences before the third (11.2 ± 1.3 vs. 10.3 ± 1.4; $p = 0.035$) and fourth (10. 8 ± 1.1 vs. 9.8 ± 1.5; $p = 0.012$) cycles between two groups. Data analysis indicated that chemotherapy-induced anemia could be clearly reduced by these micronutrient supplementations. The protective effect was noticeable from the third course just like the results of WBC. It is ambiguous for us why while WBC and platelet counts were obviously higher in the target group compared to the control group after one month, Hb values were not.

There were no significant differences in platelet count between the target and control groups before the first (338 ± 86 vs. 331 ± 85; $p = 0.775$) and second (324 ± 79 vs. 304 ± 90; $p = 0.436$) cycles. However, platelet counts indicated significant differences between the two groups before the third (286 ± 78 vs. 217 ± 90; $p = 0.008$) and fourth (220 ± 79 vs. 122 ± 54; $p < 0.001$) cycles and one month after chemotherapy (284 ± 77 vs. 121 ± 56; $p < 0.001$). It can be concluded that selenium and vitamin E may reduce cisplatin-induced thrombocytopenia.

Based on the results of this study, vitamin E and selenium could reduce bone marrow suppression.

To the best of our knowledge, there have been few studies about this subject in humans and the results of the available studies are controversial. Hu et al. investigated the effects of selenium on the toxicity of cisplatin. Selenium was administered 4000 μg/day from four days before until four days after chemotherapy. WBC counts were higher in patients who received selenium. Administration of granulocyte stimulating factor and blood infusion were lower in these patients. Nephrotoxicity, evaluated by urine enzymes, was also significantly less in the patients who received selenium. The effects of selenium intake on the therapeutic activity of cisplatin was not discussed by the researchers.[20]

A randomized, double-blind, placebo-controlled study by Weijl et al. showed that patients who were supplemented with 400 mg vitamin E (as dl-α-tocopherol-acetate), 100 μg selenium, and 1000 mg vitamin C did not have a significant reduction in renal and bone marrow damage. In this study, 64% of the intervention group and 26% of the placebo group were non-compliant because of gastrointestinal problems caused by the consumed beverage in the intervention group. The authors suggested that the lack of compliance may have been an important reason for failure to prevent the oxidative damage caused by chemotherapy. They proposed that a higher daily dose or longer period of supplementation and accumulation of other antioxidants can lead to prevent organ damages by free radicals.[3]

Other agents that have been investigated to reduce cisplatin nephrotoxicity are amifostine,[21,22] N-acetylcysteine (NAC),[23,24] cimetidine,[25,26] sulfa-containing amino acid,[27] procainamide,[28,29] allopurinol, ebselen,[30] interleukin 10 (IL-10),[31] salicylates,[32,33] L-arginine,[34]and fibrates.[35]

Our study showed that antioxidant agents such as vitamin E and selenium are effective in reducing oxidative toxicity of cisplatin. We suggest designing a study with a larger number of patients to compare all of the promising protective agents with each other and placebo.

We believe that using a nephroprotective agent, like the routinely administered mesna, with cisplatin-based chemotherapy regimens, might protect from cystitis in chemotherapy with ifosfamide [e.g. in mesna, doxorubicin, ifosfamide, dacarbazine (MAID) regimen].

ACKNOWLEDGMENTS

This study was supported by the adjunct research center of Isfahan University of Medical Sciences, Isfahan, Iran (research project number: 289264). We thank Zahravi Pharmaceutical Company (Iran) for providing vitamin E placebo.

REFERENCES

1. DeVita VT, Lawrence TS, Rosenberg SA. Cancer principles & practice of oncology: Annual advances in oncology. New York: Lippincott Williams & Wilkins; 2011.
2. Yao X, Panichpisal K, Kurtzman N, Nugent K. Cisplatin nephrotoxicity: a review. Am J Med Sci 2007; 334(2): 115-24.
3. Weijl NI, Elsendoorn TJ, Lentjes EG, Hopman GD, Wipkink-Bakker A, Zwinderman AH, et al. Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomised, double-blind, placebo-controlled study. Eur J Cancer 2004; 40(11): 1713-23.
4. Tilgner S. The contented kidney. Medical Herbalism 1998; 10(3): 5-13.
5. Luciak M. Antioxidants in the treatment of patients with renal failure .Rocz Akad Med Bialymst 2004; 49: 157-61.
6. Galland L. Drug-supplement interactions in Lyme disease. [Online]. 2006; Available from URL: http://www.mdheal.org/healthprofessionals/pdf/lymedrugInteractions.pdf
7. Messina G ,Lissoni P, Marchiori P, Bartolacelli E, Brivio F, Magotti L. Enhancement of the efficacy of cancer chemotherapy by the pineal hormone melatonin and its relation with the psychospiritual status of cancer patients. J Res Med Sci 2010; 15(4): 225-8.
8. Lamson DW, Brignall MS. Antioxidants in cancer therapy; their actions and interactions with oncologic therapies. Altern Med Rev 1999; 4(5): 304-29.
9. Ajith TA, Abhishek G, Roshny D, Sudheesh NP. Co-supplementation of single and multi doses of vitamins C and E ameliorates cisplatin-induced acute renal failure in mice. Exp Toxicol Pathol 2009; 61(6): 565-71.
10. Atasayar S, Gurer-Orhan H, Orhan H, Gurel B, Girgin G, Ozgunes H. Preventive effect of aminoguanidine compared to vitamin E and C on cisplatin-induced nephrotoxicity in rats. Exp Toxicol Pathol 2009; 61(1): 23-32.
11. Maliakel DM, Kagiya TV, Nair CK. Prevention of cisplatin-induced nephrotoxicity by glucosides of ascorbic acid and alpha-tocopherol. Exp Toxicol Pathol 2008; 60(6): 521-7.
12. Ajith TA, Usha S, Nivitha V. Ascorbic acid and alpha-tocopherol protect anticancer drug cisplatin induced nephrotoxicity in mice: a comparative study. Clin Chim Acta 2007; 375(1-2): 82-6.
13. Naziroglu M, Karaoglu A, Aksoy AO. Selenium and high dose vitamin E administration protects cisplatin-induced oxidative damage to renal, liver and lens tissues in rats. Toxicology 2004; 195(2-3): 221-30.
14. Noori S, Mahboob T. Protective role of sodium selenite on cisplatin induced oxidative and renal stress. Journal of Basic and Applied Sciences 2008; 4(1): 5-12.
15. Berry JP, Pauwells C, Tlouzeau S, Lespinats G. Effect of selenium in combination with cis-diamminedichloroplatinum(II) in the treatment of murine fibrosarcoma. Cancer Res 1984; 44(7): 2864-8.
16. Ohkawa K, Tsukada Y, Dohzono H, Koike K, Terashima Y. The effects of co-administration of selenium and cis-platin (CDDP) on CDDP-induced toxicity and antitumour activity. Br J Cancer 1988; 58(1): 38-41.
17. Fauci AS. Harrison's principles of internal medicine. 17th ed. New York: McGraw-Hill Medical; 2008.
18. Palevsky PM. Definition of acute kidney injury (acute renal

failure). [Online]. 2012 [cited 11 Apr 2012]; Available from URL: http://www.uptodate.com/contents/definition-of-acute-kidney-injury-acute-renal fai ure?source=search_result & search= definition+of+acute+ kidney+injury&selected Title=1~150. 2012 .
19. Chu E. Physicians' cancer chemotherapy drug manual 2010. 10th ed. Canada: Jones & Bartlett Publishers; 2011.
20. Hu YJ, Chen Y, Zhang YQ, Zhou MZ, Song XM, Zhang BZ, et al. The protective role of selenium on the toxicity of cisplatin-contained chemotherapy regimen in cancer patients. Biol Trace Elem Res 1997; 56(3): 331-41.
21. Castiglione F, Dalla MA, Porcile G. Protection of normal tissues from radiation and cytotoxic therapy: the development of amifostine. Tumori 1999; 85(2): 85-91.
22. Capizzi RL. Amifostine reduces the incidence of cumulative nephrotoxicity from cisplatin: laboratory and clinical aspects. Semin Oncol 1999; 26(2 Suppl 7): 72-81.
23. Nisar S, Feinfeld DA. N-acetylcysteine as salvage therapy in cisplatin nephrotoxicity. Ren Fail 2002; 24(4): 529-33.
24. Dickey DT, Wu YJ, Muldoon LL, Neuwelt EA. Protection against cisplatin-induced toxicities by N-acetylcysteine and sodium thiosulfate as assessed at the molecular, cellular, and in vivo levels. J Pharmacol Exp Ther 2005; 314(3): 1052-8.
25. Ciarimboli G, Ludwig T, Lang D, Pavenstadt H, Koepsell H, Piechota HJ, et al. Cisplatin nephrotoxicity is critically mediated via the human organic cation transporter 2. Am J Pathol 2005; 167(6): 1477-84.
26. Ludwig T, Riethmuller C, Gekle M, Schwerdt G, Oberleithner H. Nephrotoxicity of platinum complexes is related to basolateral organic cation transport. Kidney Int 2004; 66(1): 196-202.
27. Kroning R, Lichtenstein AK, Nagami GT. Sulfur-containing amino acids decrease cisplatin cytotoxicity and uptake in renal tubule epithelial cell lines. Cancer Chemother Pharmacol 2000; 45(1): 43-9.
28. Esposito M, Viale M, Vannozzi MO, Zicca A, Cadoni A, Merlo F, et al. Effect of the antiarrhythmic drug procainamide on the toxicity and antitumor activity of cis-diamminedichloroplatinum(II). Toxicol Appl Pharmacol 1996; 140(2): 370-7.
29. Viale M, Vannozzi MO, Pastrone I, Mariggio MA, Zicca A, Cadoni A, et al. Reduction of cisplatin nephrotoxicity by procainamide: does the formation of a cisplatin-procainamide complex play a role? J Pharmacol Exp Ther 2000; 293(3): 829-36.
30. Lynch ED, Gu R, Pierce C, Kil J. Reduction of acute cisplatin ototoxicity and nephrotoxicity in rats by oral administration of allopurinol and ebselen. Hear Res 2005; 201(1-2): 81-9.
31. Deng J, Kohda Y, Chiao H, Wang Y, Hu X, Hewitt SM, et al. Interleukin-10 inhibits ischemic and cisplatin-induced acute renal injury. Kidney Int 2001; 60(6): 2118-28.
32. Ramesh G, Reeves WB. Salicylate reduces cisplatin nephrotoxicity by inhibition of tumor necrosis factor-alpha. Kidney Int 2004; 65(2): 490-9.
33. Li G, Sha SH, Zotova E, Arezzo J, Van de Water T, Schacht J. Salicylate protects hearing and kidney function from cisplatin toxicity without compromising its oncolytic action. Lab Invest 2002; 82(5): 585-96.
34. Eshraghi-Jazi F, Nematbakhsh M, Nasri H, Talebi A ,Haghighi M, Pezeshki Z, et al. The protective role of endogenous nitric oxide donor (l -arginine) in cisplatin-induced nephrotoxicity: Gender related differences in rat model. J Res Med Sci 2011; 16(11): 1389-96.
35. Nagothu KK, Bhatt R, Kaushal GP ,Portilla D. Fibrate prevents cisplatin-induced proximal tubule cell death. Kidney Int 2005; 68(6): 2680-93.

How to cite this article: Hemati S, Arbab Jolfaie N, Rafienia M, Ghavamnasiri M. The effects of vitamin E and selenium on cisplatin-induced nephrotoxicity in cancer patients treated with cisplatin-based chemotherapy: A randomized, placebo-controlled study. J Res Med Sci 2012; 17(Spec 1): S49-S58.

Source of Support: This study was supported by the adjunct research center of Isfahan University of Medical Sciences, Isfahan, Iran (research project number: 289264), **Conflict of Interest**: None declared.