Original Article

Evaluation of the Protective Effect of Cystone Against Cisplatin-induced Nephrotoxicity in Patients with Cancer: A Pilot Study

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Abstract

Introduction: Cisplatin is a widely used anti-cancer drug that is commonly administered for the treatment of various cancers. However, nephrotoxicity is the most important side effect of this drug which limits its use. This study aimed to investigate the protective effect of Cystone against nephrotoxicity induced by Cisplatin in patients with cancer. **Methods:** This pilot clinical trial study was conducted on 43 cancer patients treated with Cisplatin (75 mg/m^2 for a period of six months). The subjects were divided into treatment group (receiving Cystone, two per 8 hours; n = 21) and control group (n = 22). The two groups were compared with each other in terms of demographic and laboratory variables. **Results:** In the intervention group receiving Cystone, serum creatinine-based GFR level (P = 0.453) and 24-hour urine creatinine-based GFR level (P = 0.397) did not change significantly during the studied period, but in the control group, serum creatinine-based GFR level (P = 0.013) and 24-hour urine creatinine-based GFR level (P = 0.016) significantly changed. Serum creatinine-based GFR level increased by 2.3 units in the intervention group and 10.5 units in the control group (P = 0.005) in the six months of the study. At the end of the sixth month, 24-hour urine creatinine-based GFR level increased by 2.2 units in the intervention group and 0.8 unit in the control group (P = 0.008). **Conclusions:** The use of Cystone resulted in more stable kidney function indices in the intervention group, as compared with the control group. Therefore, Cystone seems to have a protective effect against nephrotoxicity induced by Cisplatin in cancer patients.

Keywords: *Cisplatin, cystone, neoplasm, nephrotoxicity*

Introduction

Acute renal failure is common in seriously ill hospitalized patients and its mortality rate has not changed significantly over the recent decades. Available reports indicate that acute renal failure has increased over the past two decades, and the rate of mortality in dialysis patients has exceeded 50%.

The progresses which have been made in understanding the nature of the disease have led to the production and testing of several medications and interventions, and the rate of mortality has slightly improved. Therefore, it has become important to take preventive measures to prevent the incidence and progress of acute renal failure. In recent years, many efforts have been made to produce drugs from traditional and herbal materials. Acute renal failure is mainly characterized by acute tubular necrosis.[1-10] On the other hand, a number of drugs can have adverse effects on kidney, resulting in acute renal failure and other abnormalities in patients. Some drugs, such as aminoglycosides, non-steroidal anti-inflammatory drugs, and chemotherapy drugs are commonly used to deal with this problem.[11-16]

Cisplatin (cis-diammine-di-chloro-platinum) is an anticancer drug that is widely used to treat various types of cancer.[17] In 1969, the results of an animal experiment showed that this drug had anti-tumor properties. In addition to eliminating carcinogenic cells, this widely used medication also has deleterious effects on healthy tissues. As one of the main mechanisms of action, Cisplatin induces cell death.[18] Cisplatin reabsorption occurs due to an increase in radical oxygen species, which results in activation of internal and external apoptotic pathways, degradation of chromosomes, and peroxidation of lipids.[19] Nephrotoxicity is the most important side effect of Cisplatin which limits it use for the treatment of diseases. Cisplatin-induced nephrotoxicity emerges in kidney tubules, especially

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proximal tubules. Several mechanisms are involved in the nephrotoxicity caused by this drug, among which the most important are the production of active oxygen species and tissue oxidative damage. Active oxygen species, especially radical hydroxyl, leads to the peroxidation of fats, degradation of cell membrane, oxidation of protein and nucleic acids, and degradation of tissue, resulting in a reduction in glomerular filtration and causing acute nephrotoxicity.[20-28] Cisplatin-induced nephropathy is the most important reason for reducing the dose of this drug.[29] Some of the patients with acute renal failure are hospitalized due to the unavoidable administration of this drug.[30] Despite the use of hydration as a factor reducing the nephrotoxicity induced by this drug, about one third of patients receiving Cisplatin would suffer from a non-reversible kidney damage.[31-35] Therefore, there is an increasing global interest in reducing the nephrotoxicity induced by Cisplatin in cancer patients, as they are highly vulnerable patients.

The use of herbal medicines has a long history and it can be said that the basis of modern medicine. Many conventional drugs originate from plant sources. In many literatures has been mentioned that effectiveness of herbal medicines is resulted from antioxidants. Antioxidants are effective in prevention and treatment of many diseases, as well as the side effects of some medications.[36-46]

Cystone, as an herbal drug, is one of the medications that have recently been tested on the patients and, as reported, it has had satisfactory results. Cystone is a well-known herbal medicine used for many years for the treatment of kidney stones and urinary tract infections.[47] This herbal mix contains nine different types of plant extracts.[48] Cystone has shown anti-carcinogenic effects against sarcoma in mice.[49] The results of a study has shown that Cystone protects kidney against the toxicity induced by Cisplatin and it acts through inhibiting fat peroxidation.[50] Therefore, several studies have investigated the effect of Cystone on the prevention of the toxic effects of Cisplatin and other factors that cause nephrotoxicity; however, not only the results have been controversial, but also many of these studies are conducted on animals.[1,11,51-54] Overall, in spite of extensive studies on the factors affecting the nephrotoxicity induced by Cisplatin which have been conducted over the past few decades, there is still insufficient knowledge about the cause and pathogenesis of this complex disorder; thus, there is not adequate knowledge basis for designing and targeting interventions for the effective prevention and treatment of this disorder. Therefore, it is of great importance to identify and assess its current status and conduct further studies to control this disorder, in order to prevent clinical symptoms or prevent the transfer from mild to severe cases. As a consequence, as the pathogenesis of Cisplatin-induced nephrotoxicity in cancer has not been clearly defined yet, and since a limited number of studies have investigated the effects of Cystone on nephrotoxicity induced by Cisplatin, it seems necessary to carry out further studies in order to clarify the relationship between the nephrotoxicity induced by Cisplatin drug and investigate the positive effects of Cystone. Hence, based on what has been mentioned so far, the study of the effects of Cystone on Cisplatin-induced nephrotoxicity in cancer patients have been assessed in a small number of studies, mainly on animal samples; even, the small number of studies, which have been conducted so far, have presented contradictory results. In addition, the impact of race, ethnicity, and geographical area on the results of studies is undeniable. Therefore, it is of great importance to conduct more clinical trials in different communities using different methods.[55-61] The present study aimed to investigate the effect of Cystone on nephrotoxicity induced by Cisplatin in cancer patients.

Methods

This study was a clinical trial which was conducted as a pilot study because the majority of previous studies have often been performed as animal experiments and very few human studies are found in this field.

The study sample included all patients with cancer who referred to Kosar Hospital in Semnan from spring 2015 to summer 2016 to start their treatment using Cisplatin. After confirming the preliminary proposal of the project in the research council of Kosar Educational, Research, and Therapeutic Center, in Semnan, it received an ethics approval code from the Ethics Committee of the university. After explaining the details about the method and importance of this study and giving a full description of the process of study, a written consent from was given to the patients or their relatives to consent participating in the study.

Exclusion criteria were the followings:

- Previous history of kidney disease
- Concurrent use of drugs or materials inducing nephrotoxicity
- Previous history of treatment with Cisplatin
- Incidence of Cisplatin-induced complications that require discontinuation of the drug.

Primary data were collected using a checklist containing questions about demographic features, type of cancer, clinical examination, para-clinical data (white blood cell count (WBC), hemoglobin, platelet, BUN, creatinine, creatinine-based GFR, 24-hourine-based GFR, AST, ALT, alkaline phosphatase, INR, albumin, direct bilirubin (DBil), and total bilirubin (TBil)). Then, the subjects were randomly divided into two intervention and control groups using six-member blocks, in which the members were matched in terms of age and sex.

- Intervention group: Treated with Cisplatin 75 mg/m^2 in six rounds each lasting 21 days plus Cystone tablet (manufactured by the Himalayan

Pharmaceutical Company, India) administered as two pills every 8 hours for 21 days
- Control group: Treated with Cisplatin 75 mg/m^2 in six rounds each lasting 21 days.

Then, we compared and analyzed the measured levels of white blood cells (WBC), hemoglobin, platelets, BUN, and creatinine at the end of each round and the measured levels of creatinine-based GFR, 24-hour urine-based GFR, AST, ALT, alkaline phosphatase, INR, albumin, total bilirubin, and direct bilirubin, just at the end of the first, third, and sixth rounds of chemotherapy with Cisplatin.

Using Kolmogorov-Smirnov test, T-Student test (or Mann-Whitney test), analysis of variance with repeated measurements, and Friedman test, the collected data were analyzed at a significance level of 5%, using SPSS software version 18.

In this study, the following ethical issues were observed. The checklists were anonymous and only included figures and raw data. In addition, the subject were ensured about the confidentiality of the data. On the other hand, a written informed consent was obtained from all the subjects and they were allowed to withdraw and quit the study, at any stage, if they wished to do not participate anymore.

Results

Of the 44 patients (aged 18 to 75 years), two patients were excluded from the study due to overexpression of creatinine and one patient due to skin rash and the probable allergy to Cystone. The other patients were divided into two groups of Cystone and control groups. There was no significant difference between the two groups in terms of age, sex, and body mass index (respectively, $P = 0.443$, $P = 0.193$, $P = 0.118$). Gastric cancer was the most common malignancy observed in patients.

Mean and standard deviation of the level of creatinine-based GFR after the intervention, as compared with the time before the intervention, was increased by an average of 2.3 ml/min/m2in the intervention group receiving Cystone; however, it decreased by an average of 10.5 ml/min/m2in the control group. Thus, the difference was significant ($P = 0.005$) [Table 1].

In the group treated with Cystone, the level of creatinine-based GFR did not change significantly in the six stages ($P = 0.453$); however, in the control group, the level of creatinine-based GFR level was significantly changed in the six stages ($P = 0.013$).

The mean and standard deviation of the level of 24-hour urine creatinine-based GFR at the end of the sixth month, as compared with the first month, was increased by an average of 2.2 ml/min/m2in the group treated with Cystone, while it decreased by an average of 8.0 ml/min/m2in the control group, and the difference was significant ($P = 0.008$) [Table 2].

In the group treated with Cystone, the level of 24-hour urine creatinine-based GFR did not change significantly in the three stages ($P = 0.397$), but in the control group, the changes were significant ($P = 0.016$).

The changes in BUN level and the difference between the two groups were not significant in the studied stages, as compared with the time before the intervention [Table 1]. In the intervention group treated with Cystone, BUN level did not change significantly in the six stages ($P = 0.186$); however, in the control group, BUN levels significantly changed in the six stages ($P = 0.006$).

The comparison of mean and standard deviation of hemoglobin level at the end of the sixth month, as compared with the first month, showed that the mean hemoglobin level in the group treated Cystone and in the non-Cystone group (control group) decreased by an average of 0.22 g/dL and1.70 g/dl, respectively. Thus, the difference was significant ($P = 0.10$).

Table 1: Mean and standard deviation of glomerular filtration rate, creatinine and blood urea nitrogen levels in different stages of study in two groups

Stage	GFR			Creatinine			BUN		
	Mean±SD		*P*	Mean±SD		*P*	Mean±SD		*P*
	Case	Control		Case	Control		Case	Control	
1	87.7±26.3	83.0±29.5	0.591	0.96±0.15	0.94±0.16	0.662	17.1±4.7	18.4±5.2	0.394
2	91.2±23.0	78.0±25.3	0.105	0.91±0.10	0.99±0.15	0.074	16.8±3.2	17.8±3.8	0.372
3	89.8±26.6	77.9±26.3	0.158	0.93±0.09	1.02±0.29	0.176	15.9±3.9	18.3±6.8	0.175
4	87.8±27.0	75.5±21.0	0.120	0.95±0.10	1.05±0.39	0.279	18.6±2.8	20.1±8.0	0.425
5	85.1±27.9	87.1±26.2	0.427	0.96±0.12	0.99±0.13	0.530	17.2±3.8	18.6±3.8	0.246
6	90.0±28.5	75.4±26.3	0.106	0.94±0.13	1.03±0.14	0.05	17.7±4.1	19.9±4.4	0.126
1 and 2 difference	−3.5±9.5	50.0±17.1	0.056	0.05±0.12	−0.05±0.17	0.042	0.25±4.8	0.61±3.9	0.793
1 and 3 difference	−2.1±15.2	5.1±15.6	0.145	0.03±0.16	−0.08±0.20	0.049	1.17±5.6	0.10±3.9	0.475
1 and 4 difference	0.03±15.9	9.1±16.5	0.084	0.01±0.19	−0.13±0.31	0.096	−1.51±4.8	−2.58±7.8	0.607
1 and 5 difference	1.5±12.5	7.9±13.2	0.129	0±0.16	−0.09±0.12	0.70	−0.12±4.5	−1.17±3.9	0.449
1 and 6 difference	−2.3±12.5	10.5±14.6	0.005	0.02±0.14	−0.13±0.14	0.002	−0.68±4.3	−2.42±5.0	0.248

SD=Standard deviation, GFR=Glomerular filtration rate, BUN=Blood urea nitrogen

Table 2: Mean and standard deviation of glomerular filtration rate level based on 24-hour urine creatinine in different stages of study in two groups

Stage	GFR		
	Mean±SD		*P*
	Case	Control	
End of the 1st month	81.1±20.2	78.3±19.0	0.661
End of the 3rd month	80.0±16.9	73.6±24.4	0.337
End of the 6th month	83.3±18.9	73.4±18.7	0.113
End of 1st and 3rd months difference	1.1±11.9	4.8±12.0	0.332
End of 1st and 6th months difference	−2.2±10.2	8.0±12.2	0.008

GFR=Glomerular filtration rate

The changes in hemoglobin level were significant in the six stages both in the Cystone group ($P = 0.009$) and in the control group ($P \leq 0.001$).

The comparison of mean and standard deviation of creatinine level at the end of the second month, as compared with the time before the intervention, showed that the creatinine level in the intervention group treated with Cystone decreased by an average of 0.05 mg/dL, while in the group that did not receive Cystone (control group) it was increased by an average of 0.05 mg/dL, and the difference was significant ($P = 0.42$) [Table 1]. The changes in creatinine level in 6 stages in the Cystone group were not significant ($P = 0.408$), but in the control group, the changes in creatinine level were significant in the six stages ($P = 0.004$).

The mean and standard deviation of WBC levels in the second to sixth stages of the study, as compared with the time before the intervention (stage one), did not change significantly. Changes in WBC levels were not significant in the Cystone intervention group in the six stages ($P = 0.127$), but the changes in WBC levels in the control group in the six stages were significant ($P = 0.046$).

There was no significant change in mean and standard deviation of platelet level from the second to the sixth stage of the study, as compared with the time before the intervention (stage one). Platelet level changes were significantly different in the Cystone group ($P < 0.001$) and the control group ($P = 0.026$) in all the six stages.

The changes in AST level in the two groups were not significant in the studied months, as compared with the end of the first month. There was no significant difference between the levels of AST in the group treated Cystone ($P = 0.223$) and the group that did not receive Cystone ($P = 0.399$) in the three stages.

The changes in ALT level in the two groups were not significant in the studied months, as compared with the end of the first month. There was no significant difference in ALT levels in the group treated with Cystone ($P = 0.520$); however, in the group that did not receive Cystone, there was a significant difference in the three stages ($P = 0.399$).

The changes in ALKP level in the two groups were not significant in the studied months, as compared with the end of the first month. In the group treated with Cystone ($P = 0.990$) and in the group that did not receive Cystone ($P = 0.119$), ALKP level was significantly different in the three stages.

The changes in INR level in the two groups were not significant in the studied months, as compared with the end of the first month. In the intervention group treated with Cystone ($P = 0.128$) and in the group that did not receive Cystone ($P = 0.066$), the level of INR was significantly different in the three stages.

The changes in albumin level in the two groups were not significant in the studied months, as compared with the end of the first month. In the group treated with Cystone, the level of albumin was not significantly different in the three stages ($P = 0.831$); however, in the group that did not receive Cystone, the level of albumin was significantly different in the three stages ($P = 0.007$).

The changes in total bilirubin level in the two groups were not significant in the studied months, as compared with the end of the first month. In the Cystone group ($P = 0.805$) and in the group that did not receive Cystone ($P = 0.77$), total bilirubin levels were not significantly different in the three stages.

At the end of the sixth month, as compared with the end of the first month, direct bilirubin level in the Cystone group decreased by an average of 0.6 mg/dL and while in the control group it increased by an average of 0.60 mg/dL, and the difference was significant ($P = 0.049$). There was no significant difference in the level of direct bilirubin between the intervention group treated with Cystone ($P = 0.607$) and the group that did not receive Cystone ($P = 0.078$).

Discussion

The present study was one of the first studies examining and evaluating the protective effect of Cystone against nephrotoxicity induced by Cisplatin in human subjects. Based on the results of a search, of all previous studies in this field, only two studies were conducted on human subjects and the other studies were carried out on animals. On the other hand, based on the results of a study conducted by El-Ghiaty *et al*. in 2014, it was stated that Cystone had a protective effect against Cisplatin; they also reported that the kidney function was significantly better in patients receiving Cystone than in those who did not receive this medication.[48]

Based on the results of this study, no significant difference in the results of renal pelvic tests was not observed in the intervention group treated with Cystone during the different stages of the study. Other studies have shown

that kidney failure is observed several days after Cisplatin administration with a decrease in glomerular filtration rate, an increase in blood urea nitrogen, and an increase in serum creatinine.[62] The results of other studies have also shown that the use of Cisplatin alone for chemotherapy, without the use of protective drugs, resulted in abnormal renal test results, especially in creatinine[63] and BUN level.[64] The results of our study showed no significant change in the level of creatinine-based GFR in the group treated with Cystone in the six stages of the study. However, the level of creatinine-based GFR had significant changes in the control group in the six stages of the study. The results showed that at the end of the sixth month, as compared with the first month, the mean hemoglobin level was reduced by an average of 0.22 g/dl in the group treated Cystone and by an average of 1.70 g/dl in the non-Cystone group (control group) and the difference was significant. These findings are in line with the results of a study by El-Ghiaty *et al*., 2014.[48] Other studies have suggested that the administration of Cisplatin without protective drugs causes direct tubular damage, which in turn results in a reduction in glomerular filtration and, ultimately leads to acute nephrotoxicity.[20] Several studies have shown that some symptoms such as proteinuria, glycosuria, and increased plasma urea and creatinine level are observed after the incidence of acute nephrotoxicity,[65] and the results of this study also confirmed such a finding. El-ghiaty *et al*. investigated kidney function in 49 patients with cancer who were under treatment through taking six rounds of Cisplatin; in that study, kidney function was measured through calculating serum creatinine, creatinine clearance, and blood urea. At the end of the study it was observed that kidney function in patients receiving Cystone was far better than that in patients who did not receive this drug,[48] which is consistent with the results of this study. Other studies are often performed on animal subjects. In a study conducted in 2004, researchers had injected Cisplatin and Cystone into the peritoneum of male rats; at the end of the study, the results showed that the changes in kidney function in mice receiving Cystone was much lower than that in the control group.[52] The results of a study in 2011 showed that the administration of Cystone reduced kidney dysfunction in rats treated with Cisplatin and resulted in a better level of serum creatinine at the end of treatment.[53] However, there are other studies that used other criteria for assessing renal function and had similar results. Raom *et al*. showed that cats receiving Cisplatin together with Cystone had better urine output. At the end, the researchers concluded that patients receiving Cystone had better urine output and, consequently, had better kidney function after receiving Cisplatin.[47] The induction of cell death, the activation of internal and external apoptotic pathways, chromosomal degradation and lipid peroxidation are among the main mechanisms of actions of Cisplatin. This drug, which is a commonly used drug in the chemotherapy of cancer patients, plays a special role in the development of toxicity in kidney tubules, and in particular in proximal tubule.[18,19] Several other mechanisms are involved in the nephrotoxicity induced by this drug, among which the most important are the production of active oxygen species and tissue oxidative damage. Active oxygen species, especially radical hydroxyl, lead to fat peroxidation, cell membrane degradation, protein and nucleic acid oxidation, and tissue degradation, resulting in decreased glomerular filtration and acute nephrotoxicity.[20] A number of studies have also suggested that nephropathy induced by this drug may be due to the direct effect of the drug on different stages of tubular or mitochondrial transmission,[66] alteration in cellular structure,[67] or the release of free radicals.[50] Moreover, Cystone not only has anticancer effects in mice,[49] but also protects the kidney against the toxicity induced by Cisplatin through its ability to inhibit lipid peroxidation.[50] A number of studies has investigated the role of Cystone's components on the nephrotoxicity of the drug; for example, in a study in 2008, the effect of Rubiacardifolia, a component of Cystone, on the nephrotoxicity induced by Cisplatin was investigated. The results of the mentioned study showed that the glomerular filtration rate in mice that received this compound was significantly lower than that in the group that did not receive that component;[51] this finings is in line with the results of our study. Nonetheless, free oxygen radicals play an important role in causing acute renal failure induced by Cisplatin.[68] Therefore, it is not surprising to observe that Cystone, as an herbal medicine and effective antioxidant, like many other antioxidants such as vitamins C and E can reduce the nephrotoxicity induced by Cisplatin.[69] Other studies have also indicated that other antioxidants, such as N-acetyl cysteine (NAC), can reduce the severity of Cisplatin-induced renal damage in both animals and humans.[70] It highlights the importance of the antioxidant effect of drugs (especially Cystone which is a drug with low complications) against toxicity induced by Cisplatin. The renal damage induced by Cisplatin is caused by reactive oxygen species, and in particular hydroxyl, which lead to lipid peroxidation and protein degradation, causing tubular damage and acute nephrotoxicity; thus, one of the most important prevention factors is the amount of intracellular glutathione storage which is reduced as the result of the formation of oxidative stress induced by Cisplatin, as it reduces cellular glutathione level, and increases the activity of reactive oxygen species, and ultimately, results in tubular degeneration and acute nephrotoxicity.[71] However, Cystone has some indirect effects which emerge through various components and paths and improve the outcomes.

In this study, there was no significant difference between the two groups treated with Cystone and the control group in terms of the underlying variables such as age, gender, and body mass index. It indicates that the subjects are

homogeneous and, as a result, the effect of confounding variables (including age, gender, and body mass index) on the findings of this study are controlled. It improves the judgment and comparison between the two groups. This finding is similar to the results of a number of other valid studies;[72,73] as a number of studies have emphasized the effectiveness of age and sex on the increase in nephrotoxicity.[74] Therefore, the homogeneity of the two studied groups in terms of these variables can be considered as one of the strengths of this study which was achieved through the selection of the subjects and implementation of the research plan.

Along with the strengths of this study, our study, like any other study, had a number of limitations. One of the most important limitations of this study was the low sample size. In addition, we analyzed the protective effects of Cystone against Cisplatin-induced nephrotoxicity only within a six-month period of treatment, which was due to lack of cooperation in patients and the limited financial resources for carrying out periodic tests. Thus, it was not possible to conduct longer-term studies, and, consequently, assess the benefits or complications of long-term use of Cystone intervention.

In order to achieve better results and operationalize the findings of the study, it might be helpful to investigate the effects of higher doses of Cystone, and assess the effects of prolonged treatment using this drug, and even the prophylactic effects of the administration of the drug long before the start of chemotherapy. Other clinical trials can help generalize the results of this study by examining the protective effects of Cystone against nephrotoxicity induced by other nephrotoxic drugs. They might also assess other groups of patients, and even those who met the exclusion criteria in our study. As our study was not a blinded trial and the control group did not receive any specific placebo, it is recommended to conduct further blinded trials using placebo for the control group to achieve better results.

Conclusions

Overall, the results of this study showed that the use of Cystone resulted in more stable kidney function indices in the intervention group, as compared with the control group. Therefore, Cystone seems to have a protective effect against nephrotoxicity induced by Cisplatin in cancer patients. It is recommended to conduct further studies to clarify the mechanism of the effect of Cystone on kidney, and also to investigate its protective effect against other nephrotoxic drugs.

Limitations of our study

Given the contradicting results of this and other studies, future studies are recommended to be conducted on the long-term effects of contrast agents on renal function.

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Conflicts of interest

There are no conflicts of interest.

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