Reducing the Side-Effects of Cisplatin to Improve the Social Acceptance of Chemotherapy as CAM Adjunct in Cancer Treatment

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Abstract

*Background:*In sociology, the prevalence of cancer is interpreted as a broken social contract that requires behaviour change. Complementary and alternative medicine (CAM) is a vital social phenomenon, whose usage is socially patterned out. Perceptions of the limitations of chemotherapy and radiotherapy among cancer patients have contributed to the preference for CAM use, particularly plant-derived polysaccharides like HemoHIM, which contain cisplatin. This research was undertaken to show whether co-administration of vitamin C with cisplatin in chemotherapy can prevent or reduce the side-effects of cisplatin nephrotoxicity.

*Objectives:*The objective of this study was to overturn social perceptions of conventional therapy as associated with nephrotoxicity. It investigates the renoprotective effects of high-dose vitamin C by performing an animal experiment to determine body weight, organ weight, and biochemical blood parameters; as well as to measure inflammatory cytokines.

*Design:*Mice were randomly divided into five groups (control; and 500, 1000, and 2000 mg/kg of vitamin C with cisplatin). All groups except for the control group were intraperitoneally injected with 5- mg/kg cisplatin for 10 days, and the mice in the respective groups were orally administered each 500-, 1000-, 2000- mg/kg vitamin C 2 h prior to cisplatin treatment. After 10 days, the mice were sacrificed, and their blood samples and kidney tissues were obtainedfor further analysis.

*Setting and location:*Republic of Korea

*Methods:*Blood samples from animal experiments and tissue preparation were analyzed using real-time quantitative polymerase chain reaction.

*Results:*The intraperitoneal injection of cisplatinreduced body weight, and elevated levels of blood urea nitrogen, serum creatinine, and uric acid. It also triggered an inflammatory response in the mouse kidney by inducing the pro-inflammatory cytokines TNFα, IL-6, and IL-1β and increasing in the expression of iNOS, and IL-4. Renal injury was decreased by the administration of vitamin C; the oral administration of vitamin C (500, 1000, 2000 mg/kg) decreased or normalized the renal function through the attenuation of cisplatin-induced inflammatory cytokines and the modulation of biochemical parameters (ALT, AST, cholesterol, TG, HDL, LDL, blood urea nitrogen, creatinine, and Uric acid) following the intraperitoneal injection of cisplatin.

*Conclusion:*The results of our present study suggest that the co-administration of vitamin C with cisplatin chemotherapy is a promising method to prevent or reduce the side effects of cisplatin nephrotoxicity. These findings can remodel how the Korean society thinks, approaches and fights cancer by showing how nephrotoxicity can be counteracted to ensure social acceptance of CAM as an adjunctive to cisplatin therapy.

*Keywords:*Complementary and alternative medicine, CAM, Vitamin C, Renoprotective therapy, Cisplatin, Nephrotoxicity, High-dose vitamin C

Introduction

Complementary and alternative medicine (CAM) is a vital social phenomenon in South Korea. A high usage of CAM has been observed particularly among elderly South Koreans with cancer.[1] There are also indications that CAM can be a primary interconnected source of stability and support for health care delivery in remote and rural regions.[2] Such phenomenon is socially patterned out across South Korea. In effect, CAM refers to a combination of socially diverse therapeutic and patient care systems that normally considered as an alternative to conventional medicine.[3] They are culturally diverse, and their administration may depend on the social dynamics of people in certain cultures. While the growing popularity of CAM has become certain in South Korea in recent decades, it is unclear to what extent it is effective when used as standalone therapeutic modality, in comparison to conventional medicine like radiotherapy or chemotherapy.

    A growing body of research is continuing to demonstrate that perceptions of the limitations of

chemotherapy and radiotherapy among cancer patients have contributed to the preference for CAM use, or the desire for natural and holistic therapies.[4] In spite of this, clinicians have argued that this is because of a lack of clear information on the real efficacies and limitations of conventional treatment, the increasing advertisements for CAM, or the desire for holistic or natural treatments.[5] Although clinicians care for many cancer patients using CAM in everyday clinics, little information is available regarding CAM, and there are, as yet, no available and definitive practical guidelines for CAM usage in Korea. Studies that have examine usage of CAM among Korean cancer patients have identified some of the parameters for using the therapy – other than social factors - as including the cost, prevalence, side-effects and subjective-effects.[6] Additional parameters are the clinical attributes of users in comparison to non-users and patients and doctor's expectations. Among the findings made in research undertaken in Korea is that use of CAM is highly prevalent, with 78.5% of cancer patients having used on form of CAM or the other because of its social prevalence. While such findings may not truly reflect the accurate prevalence of CAM use, many of the participants were in advanced cancer stages. This could be linked to the high prevalence of CAM use rather than conventional therapy.This indicates that the prevalence of CAM is a cause for concern. For this reason, critical action is necessary to remodel how the Korean society thinks, approaches and fights cancer. In sociology, the prevalence of cancer could be interpreted as a broken social contract requiring conceptual frameworks that can inspire behaviour change. For this reason, there is a need for researches that can push forward discussions to rethink the manner in which conventional therapy is approached and communicated.[7] Approaching the prevalence of cancer as a consequence of broken social contract is one way in which this can be achieved. Equally, this undertaking calls for a combination of ideas drawn from biology, biochemistry, computational medicine, and physics. An infusion of ideas from these fields of study is expected to illuminate aspects of cancer biology that could be applied to inspire consideration of conventional therapy as an adjunctive of CAM.

While it has been posited across some conventional medicine research that CAM may not inhibit the growth of tumours when used in place of conventional treatments.[6,7,8] A number of studies undertaken across some societies in Asia – such as China, Japan and Korea, have showed that plant-derived polysaccharides – which are used as CAM - have some anticancer elements like Cisplatin.[8] For instance, studies on the efficacy of an herbal combination of CAM known as HemoHIM have indicated that has immunotherapy properties.[9] HemoHIM is designed to safeguard the self-renewal tissues and to encourage the recovery of the immune system. It is made by adding polysaccharides to a hot water extract of an herbal mixture of Paeonia Radix, Cnidium Rhizoma, and Angelica Radix. In their study, Park et al. examined the use of HemoHIM to augment the anticancer effects of cisplatin and to restore immune functions.[10] They found HemoHIM to enhance antitumor efficacies of cisplatin. While this gives some hope in the use of CAM, cisplatin has objectionable side-effects like severe nephrotoxicity.

In the context of this research, there is significant rationale to carry out a research that can overturn social perceptions of conventional therapy as associated with nephrotoxicity – a common side effect in patients with cancer receiving cisplatin therapy. Fundamentally, oxidative stress, production of inflammatory cytokines, and cell death are the major pathological mechanisms underlying cisplatin-induced nephrotoxicity. Therefore, undertaking a research to show how nephrotoxicity can be reduced could be beneficial in changing the prevalent social perceptions regarding side-effects of conventional therapy such as chemotherapy.

Against this backdrop, a study was undertaken to show whether co-administration of vitamin C with cisplatin chemotherapy can prevent or reduce the side-effects of cisplatin nephrotoxicity. The present study investigated the renoprotective effects of high-dose vitamin C by carrying out an animal experiment to determine body weight, organ weight, and biochemical blood parameters; as well as to measure inflammatory cytokines.

Literature review

Cancer therapy has traditionally been driven by the conception of eradicating proliferating cancer cells by inducing cell death of the dividing tumour cells using chemotherapeutic, or radiotherapy. Over the years, chemotherapy has become the foremost therapeutic modality universally used in the treatment various cancers. Research evidence has also showed that, use of chemotherapy or radiotherapy as standalone therapeutic modalities cannot attain acceptable therapeutic outcomes, including attaining a complete remission of tumours.[11] They have also been found to contribute to serious side-effects in spite of being administered at therapeutically acceptable doses, leading to a preference for CAM.[2]

The growing prevalence of CAM usage differs across countries depending on diverse social, demographic, and cultural attributes of particular population, such as age, ethnicity, gender, income, and level of education.[12] Compared to many Western or Asian countries, use of traditional medicine is prevalent even in the South Korean national healthcare system. This could be attributed to the reality that the popularity of traditional medicine has witnessed a sharp rise since the early 1990s.[13] Among the demographic patterns of the preference of CAM use is the perception of their efficacy depending on age. Already, some studies have indicated that the patterns of preferences of CAM use differs substantially among the young and older adults in South Korea, with the latter showing a greater inclination. Kim et al. also explored whether reasons for CAM use differ among young adults

depending on their physical fitness and found that use of CAM tended to be higher among patients who use nonsurgical and nonpharmacological approaches.[14]

In the wider Korean society, medical practitioners have questioned the efficacy of CAM. It may tempt sociologists to demonstrate indifference to answer that question as they consider CAM to be a fundamental social phenomenon, which is widely considered by users to be effective and necessary. Nevertheless, sociologists have, in recent decades, demonstrated the readiness to engage more critically with technical questions that require medical expertise by falling back on science studies and sociology to understand how CAM works in relation to conventional biomedical therapies like chemotherapy or radiotherapy.[15] Of particular interest to sociologists is the realization the efficacy of chemotherapy and radiotherapy cannot guaranteed without CAM.

In the case of South Korea, studies have showed that the primary reason for preferring CAM therapies among, 31.6% of participants surveyed was to prevent diseases and promote health, and that this was largely influenced by the popularity of Korean Oriental Medicine (KOM). An estimated 75% of adults in Korea were found to have also used a form of CAM in the last year.[16] The prevalence rate of CAM usage in South Korea is higher than that of Western countries. This prevalence rates were based on social, economic, demographic and gender factors. For instance, preference for CAM to cisplatin therapy tends be higher among men than women. In relation to socioeconomic and demographic factors, Koreans in the age bracket of 50-29 years old with lower educational attainment, higher religious values, higher family income, and higher marital experience were found to be more likely to prefer CAM.[13] In the past, some significant empirical developments have been made in the forms of qualitative and quantitative studies that have explored experiences of cancer patients when they use CAM. Such studies have made a fine contribution to knowledge on the use of CAM in different social contexts, such as ethnicity, gender, and cultural backgrounds in relation to health practices and beliefs.[17] In one such study, Shippee et al. established that Black Americans tend to prefer CAM to cisplatin therapy because of high perceptions of racial discrimination in medical context.[18]

While more social researchers are currently throwing their weight behind CAM, it is not clear how social dynamics affect the decision to use cisplatin due to its side-effects like severe nephrotoxicity.[19] Typically, social phenomena that generate significant controversy in the larger society appeal to sociologists. Early sociological research concentrated on users of CAM with explanations for this including the degree of discontent with the health outcomes of conventional medicine, cultural norms and practices that have tended to prefer use of alternative medicine, and the social approval of the level in which alternative therapists understand ingrained cultural practices. This has presented challenges to usage of conventional medicine. In spite of this, there is a growing understanding in research of the potential of combining conventional medicine and CAM. It is expected that a more sophisticated quantitative research is necessary to demonstrate how nephrotoxicity can be counteracted to ensure social acceptance of CAM as an adjunctive to cisplatin therapy.

Cisplatin (cis-diamminedichloroplatinum II) has been widely used in the treatment of various cancers,[20] such as those of the brain, ovary, bladder, and colon cancer,[21] and is one of the most effective anticancer agents available. The anticancer mechanism of cisplatin involves binding to DNA, the formation of inter- and intra-strand crosslinks that can activate several signal transduction pathways, and the activation of apoptosis.[22] However, it is limited by associated toxicities, which include nephrotoxicity, ototoxicity, gastrointestinal disorders, and allergic reactions.[23]

Cisplatin can cause the accumulation of platinum within the kidney and thus inhibit renal tubular tissue and function. The pathophysiology of cisplatin nephrotoxicity is a complicated process and involves vascular, tubular, glomerular and interstitial destruction that can lead to chronic renal disease.[1] Moreover, it causes dose-dependent toxicity and cumulative nephrotoxicity which causes severe symptoms. The mechanism underlying cisplatin nephrotoxicity in the kidney involves: decreased renal blood flow,[2] tubular necrosis/apoptosis,[3] increased lipid peroxidation and decreased antioxidant system,[4] increased inflammation markers, and increased apoptotic activity (caspase-3).[24] Nephrotoxicity caused by platinum-based anticancer drugs, such as cisplatin results from free radical generation, and oxidative stress and can be relieved by antioxidants.[25] Oxidation reactions can produce free radicals, which start from chain reactions and cause severe disease in humans. Consequently, it leads to a decrease in natural cell antioxidant capacity or an increase in reactive oxygen species (ROS) in the kidney. Antioxidants are a potential therapeutic method to detoxify ROS in the kidney.[5] Antioxidants are bioactive molecules that have the ability to decrease or prevent the oxidation of substrate molecules[26]. In other words, the use of antioxidants in combination with cancer drugs can decrease the risk of cisplatin induced nephrotoxicity by reducing oxidative stress.[27]

Recent studies have focused on the function of antioxidants in cisplatin toxicity because cisplatin-induced nephrotoxicity occurs through the induction of oxidative stress, and is inhibited by antioxidant therapies, such as vitamin C.[28] Given that vitamin C is a powerful antioxidant, it can protect cells from oxidative damage by blocking free radicals [29]. These antioxidants may detoxify ROS in the kidney without altering the anticancer efficacy of cisplatin. Therefore, antioxidants are a promising therapeutic method. Vitamin C largely prevents the

functional and structural lesions in the tubules of the kidney. Cisplatin-induced mitochondrial production of oxidants was inhibited by vitamin C which is the key to its ability to injure mitochondria[30]. In a previous study, the improvement in renal function following the oral administration, of a combination of different vitamins or of vitamins with other agents effectively protected against oxidative organ damages.[31] The dosage of vitamin C was lower than that in the present research and was not considered as high dose. A previous study has reported that high dose vitamin C (1000 mg/kg) can aggravate renal injury as vitamin C enhances oxalate excretion.[32] Ascorbate radicals and hydrogen peroxide are correlated with the oxidative damage observed in renal epithelial cells[33]. However, the administration of high-dose vitamin C alone had no side effects on renal function although oxalate nephrotoxicity has been reported with its administration.[34] The effects of high-dose vitamin C remain controversial.

Methods

1) Animal experiments

Eight-week-old, male ICR mice were purchased from Raonbio (Yongin, Korea) and were housed for acclimatization for 7 days prior to the experiment. The mice were randomly divided into five groups each containing six mice: control, cisplatin, and cisplatin with 500-, 1000-, and 2000 mg/kg vitamin C. All groups except the control group were administered 5-mg/kg cisplatin intraperitoneally for 10 days and mice in respective groups were orally administered each 500-, 1000-, and 2000- mg/kg vitamin C diluted in water 2 h before cisplatin treatment.The mice were housed at 25ºC ± 2ºCin a humidity of 55% ± 5% under a 12 h light/dark cycle. After 10 days, all mice were humanely killed. Blood samples and kidney tissue were collected for further analysis. The Institutional Animal Care and Use Committee of Kyung Hee University approved the experimental animal facility and protocols. All experimental procedures were performed in compliance with the NIH Guide for the Care and Use of Laboratory Animals and National Animal Welfare Law in Korea.

2) Analysis of blood samples

Blood samples were collected in test tubes containing EDTA as an anticoagulant. These tubes were placed in an icebox and transferred to the laboratory within 1 h of collection. In the laboratory, these samples were centrifuged at 3000 rpm for 10 min. The plasma was separated and stored at –4 °C for further analysis. Serum creatinine, uric acid and blood urea nitrogen (BUN) were measured using a colorimetric assay kit accordance with the manufacturer's instructions. BUN, uric acid and serum creatinine levels were measured as the indicators of kidney function.

3) Tissue preparation

Mice in the control group, cisplatin control group, and cisplatin vitamin C (500, 1000, 2000 mg/kg) groups were deeply anesthetized using diethyl ether. Subsequently, blood samples werecollected. Thekidney was frozen immediately in liquid nitrogen, and stored at –80°C until use.

4) Real-time quantitative (qRT)-PCR

In accordance with the manufacturer's protocol, total RNA was extracted using Trizol reagent from the kidney tissues isolated from mice that were orally administered vitamin C.A The qRT-PCR was performed using a previously described procedure with minor modifications. Briefly, RNase-Free DNase (QIAGEN, Venlo, Netherlands) was added to RNA samplesto eliminate DNA contamination. The verification of RNA purity and integrity was performed by measuring the 260/280 nm absorbance ratio using NanoDrop (ND-1000; NanoDrop Technologies, DE).cDNA was synthesized using only RNA samples with an absorbance ratio between 1.8 and 2.1.qRT-PCR was conducted using a light cycler system (STRATAGENE. CA) with cDNA mixed with SYBR Green (TAKARA Co., Ltd., Shiga, and TECAN, Männedorf, Switzerland, Japan). Relative gene expression was calculated according to the comparative Ct method using β-actin as the internal standard.

5) Statistical analysis

Each result is reported as the mean ± standard error of mean.The statistical significance of differences between the control and experimental values was calculated by two-way analysis of variance, which was performed using GraphPad Prism5.

Results

1) Body weight graph

No mortality related to vitamin C administration after treatment with cisplatin was observed in mice for 10 days at any dose. There was a decreasing trend in body weight following cisplatin/ vitamin C (500, 1000, and 2000 mg/kg) treatment at 4-8 days after cisplatin injection. However, there was an increasing trend in body weight in the cisplatin/vitamin C (500, 1000 mg/kg) groups after cisplatin injection for 10 days. Thecisplatin control group showed a significant change in the animal physiology, as manifested by a decrease in body weight, compared with the normal control group. Thecisplatin control group showed a prolonged decrease (Fig. 1). Vitamin C at doses (of 500-, and 1000 mg/kg) resulted in significant relief of these manifestations.

2)Organ weight

The effect of cisplatin and vitamin C on renal function in the experimental groups was examined by usingorgan weight. After 10 days of vitamin C administration (500, 1000,and 2000 mg/kg) treatment after cisplatin injection, there was no significant changes in the weight of the kidneys and the liver (Table 1). In other words, there were no significant changes in the kidney, and liver weight between groups.

3) Biochemical analysis of blood:Effect on renal function

Statistically significant differences were observed for a number of parameters (AST, ALT, cholesterol, TG, HDL, LDL, creatinine, BUN, anduric acid), particularly in the vitamin C (500, 1000, and 2000 mg/kg) and cisplatin treated groups. It is thought that these events were related to vitamin C exposure, but they did not occur in a dose responsive manner (Fig. 2). The effects of cisplatin and vitamin C on renal function in the experimental groups was evaluated by AST, ALT, cholesterol, TG, HDL, and LDL in this study (Fig. 2). Cisplatin administration decreased AST, ALT, cholesterol, TG, and LDL and increased HDL compared with the normal control group.

In particular, cisplatin nephrotoxicity is shown by a clinical increase in the elevation of BUN, serum creatinine, proteinuria, and hyperuricemia[4]. The effect of cisplatin and vitamin C on renal function in the experimental groups was evaluated through creatinine, BUN, and uric acid (Fig. 2). Cisplatin administration increased creatinine, BUN, and uric acid in the cisplatin control group compared with the normal control group. Animals treated with vitamin 500, 1000, and 2000 mg/kg showed differences compared with cisplatin control group but no dose-response relationship was observed.

In the vitamin C treatment groups, biochemical parameters were normalized compared with the cisplatin controlgroup.

4) qRT-PCR : Effect on renal inflammatory cytokines

The levels of pro-inflammatory cytokines, IL-1β, TNFα, and IL-6 in the kidney homogenate of the experimental groups were estimated byqRT-PCR in accordance with the manufacturer's protocols. The effects of cisplatin and vitamin C on the level of renal pro-inflammatory cytokinesin the experimental groups are shown in Fig. 3.Cisplatin administration resulted in a significant increase in IL-1β, TNFα, and IL-6 compared with the normal control group. Vitamin C administration at a doses of 500, 1000, and 2000 mg/kg attenuated the increase in IL-1β, TNFα, and IL-6 compared with the cisplatin control group, but no dose-response relationship was observed.

Discussion

The platinum derivative cisplatin has limited therapeutic efficacy owing to its nephrotoxicity which primarily affects the S3 segment of the proximal renal tubule[35]. It is known thatthe release of pro-inflammatory cytokines, the recruitment of inflammatory cells and mitochondrial dysfunction leads to the formation of ROS and damage to renal tissue[36]. Oxidative stress and inflammation are two of the most important causes of cisplatin-induced nephrotoxicity[37]. Therefore, the enhancement of antioxidant defenses in renal tissue by antioxidants may be a beneficial strategy for protection against cisplatin nephrotoxicity. In this context, a strategy that targets multiple mechanisms including the suppression of free radical production and from pro-inflammatory cytokines and the amelioration of blood biochemical parameters in the kidney may offer meaningful prevention against nephrotoxicity by using high-dose vitamin C therapy because the antioxidant effect of vitamin C can be beneficial when co-administered with cisplatin.

In other studies, cisplatin significantly increased the total ROS, MDA, oxidative stress, and protein carbonyl levels in the kidney tissues[38]. In addition, the antioxidants glutathione (GSH) and vitamin C were significantly reduced in cisplatin control group.

A single dose of cisplatin (5 mg/kg) to the mice resulted in nephrotoxicity in the cisplatin control group. BUN, creatinine, and uric acid are the kidney function biomarkers associated with kidney pathologies, and a significant increase in BUN, creatinine, anduric acid levels were observed in the cisplatin control group (Fig. 2). This was further supported by a decrease in body weight in the cisplatin control group compared with that in the normal group (Fig. 1). These results support earlier findings on cisplatin nephrotoxicity. The doses of vitamin C (500, 1000, and 2000 mg/kg) reduced levels of uric acid, AST, ALT, cholesterol, triglyceride, LDL, and increased HDL levels.

Non-enzymatic antioxidants, such as vitamin C have immunomodulatory effects. It is an antioxidant, and therefore protects important biomolecules from damage by scavenging free radicals or by converting the toxic radicals to non-toxic products[39]. These outcomes indicate the antioxidant activity of vitamin C and the possible mechanisms underlyingrenoprotective activity.

Several reports have suggested that vitamin C exerts anti-inflammatory activity through the inhibition of inflammatory cytokines[40]. Inflammation plays an important role in the pathogenesis of cisplatin-induced nephrotoxicity. TNFα, IL-1β, and IL-6 has been reported asimportant pathogenic factors in cisplatin-induced nephrotoxicity. As vitamin C can systemically modulate cytokines in a complex manner, the addition of vitamin C decreased the generation of the pro-inflammatory cytokines TNFα, IL-1β, and IL-6 (Fig. 3). Vitamin C (500, 1000, 2000 mg/kg) significantly decreased the level of inflammatory cytokines, implying that itprotects the

kidney from inflammatory insulation.[41] This is indicative of the anti-inflammatory action.

Furthermore, vitamin C enhanced or normalized the levels of the antiviral cytokine IFNγ. Moreover, the product of iNOS catalysis, nitric oxide (NO), is an important regulator of COX-2 expression, and can also influence iNOS expression (Dolores and Santiago, 2004). Cisplatin significantly reduced the renal tissue nitrite levels, the extent of NO, in the kidney tissues of the cisplatin group.[42] In other words,NO augmentation exerts a renoprotective effects against cisplatin nephrotoxicity. In this study, iNOSlevels were increased in the vitamin C treatment group.

Conclusion

As a result of its antioxidant, immunomodulatory, and anti-inflammatory activity, vitamin C can protect the kidney from cisplatin-induced kidneys damage. Our findings suggest that high-dose vitamin C can be used the prevention of nephrotoxicity in cisplatin-based cancer chemotherapy. The capacity of this research to demonstrate that nephrotoxicity can be reduced is indeed beneficial in changing the prevalent social perceptions regarding side-effects of conventional therapy such as chemotherapy. By demonstrating how nephrotoxicity can be counteracted, the results of this research overturn negative attitudes towards conventional therapy. It is expected to promote a high social acceptance of CAM as an adjunctive to cisplatin therapy. Future studies involving a selection of patients could help confirm whether high-dose vitamin C prevents nephrotoxicity in cisplatin-based cancer chemotherapy. It is possible that the type of adaptability and resilience enabled by vitamin C buffers adverse effects of nephrotoxicity. Future research is needed to investigate this relationship, at the population level and how it affects societal attitudes towards use of chemotherapy and radiotherapy.

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