

## Research Article



## Ameliorative Effect of L-Carnitine on Renal Function and Oxidative Stress in Cancer Patients with Cisplatin - Induced Nephrotoxicity

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### ABSTRACT

Nephrotoxicity is a major dose-limiting side effect facing cisplatin-based chemotherapy of a wide variety of cancers. Oxidative stress plays an important role in mechanisms responsible for nephrotoxicity. This study was to examine the antioxidant properties of L-carnitine in protection from nephrotoxicity due to cisplatin. 32 patients were enrolled in the study and were randomized into two groups. Only 28 patients were eligible and successfully completed treatment cycles. In group I, (N=14) patients received six cycles of cisplatin based regimen with 21 days-intervals. In group II, (N=14) patients received L-carnitine plus cisplatin based regimen. Serum creatinine and cystatin C were measured at base line and 21 days after 1, 2, 4 and 6 cycles while urinary malondialdehyde was measured at base line and 1 day after 1, 2, 4 and 6 cycles of cisplatin based regimen. Group I, cisplatin caused significant ( $P < 0.05$ ) increment in serum creatinine, serum cystatin C and urinary malondialdehyde in comparison to base line levels. Serum creatinine and cystatin C and urinary malondialdehyde level of group II was significantly ( $P < 0.05$ ) lower than that of group I. L-carnitine significantly ameliorated nephrotoxicity in patients receiving cisplatin primarily by inhibiting renal oxidative stress.

**Keywords:** cisplatin, nephrotoxicity, L-carnitine, oxidative stress.

### INTRODUCTION

Cisplatin, an alkylating-like agent, is a potent chemotherapeutic drug that is widely used in management of various types of cancers.<sup>1</sup> Unfortunately, cisplatin effectiveness is limited by the resulted nephrotoxicity which is a major dose-limiting side effect of cisplatin.<sup>1</sup> Acute kidney injury (AKI) occurs after cisplatin chemotherapy in approximately 20-30% of patients.<sup>2</sup> Acute kidney injury stills a significant cause of increased morbidity and mortality.<sup>3</sup> In spite of scientific efforts to find relatively less toxic but equally effective substitutes, cisplatin continues to be widely involved in chemotherapy as first line antitumor agent.<sup>4</sup> Several therapeutic approaches have been suggested to avoid cisplatin-induced nephrotoxicity, but no specific treatments are currently recommended, except for powerful hydration with normal saline.<sup>3</sup> Severe and lifelong nephrotoxicity can result regardless of the use of currently available preventive measures.<sup>5,6</sup> Apoptosis and necrosis, due to DNA damage response pathways, oxidative stress in association with severe inflammatory response and caspase activation, are the major sources of acute kidney injury due to cisplatin.<sup>1</sup> Cisplatin-induced oxidative stress involves induction of free oxygen radicals along with inactivation of anti-oxidant systems.<sup>1</sup> Cisplatin inhibited the enzymatic complexes I to IV of the respiratory chain with resultant decreased intracellular ATP levels.<sup>7,8</sup> GSH reductase activity was also inhibited leading to reduced intracellular GSH levels<sup>9</sup> which is an early and critical step in cisplatin-induced cell injury.<sup>9</sup> In

the presence of cisplatin, reactive oxygen species are highly produced<sup>10</sup> and are implicated in the pathogenesis of AKI due to cisplatin.<sup>11</sup> Superoxide anion ( $O_2^{\bullet-}$ ),<sup>12</sup> hydrogen peroxide ( $H_2O_2$ ),<sup>13</sup> and hydroxyl radical ( $\bullet OH$ )<sup>14</sup> are increased in cisplatin-treated kidneys. Antioxidant enzymes are inhibited by cisplatin, and renal activities of superoxide dismutase, glutathione peroxidase, and catalase are significantly decreased.<sup>15,16</sup> Carnitine, b-hydroxy-c-trimethyl-amino-butyric acid, is a naturally occurring quaternary ammonium compound.<sup>17</sup> Carnitine acts as a carrier for the translocation of long-chain fatty acid from cytoplasmic compartment into mitochondria, where beta-oxidation enzymes are located for energy production<sup>18</sup>. The decreased dietary intake and impaired endogenous synthesis of L-carnitine results in low serum levels of L-carnitine in cancer patients.<sup>19</sup> In addition, cisplatin can lead to low serum levels of L-carnitine in cancer patients<sup>20</sup> Arafa<sup>21</sup> reported that low serum carnitine level might aggravate carboplatin nephropathy. In an experimental model, L-carnitine has a significant protective effect against cisplatin-induced nephrotoxicity in rats.<sup>22</sup> In another experimental study, L-carnitine strongly inhibited mitochondrial dysfunction, lipid peroxidation, and apoptosis of epithelial cells in the kidney and small intestine due to cisplatin treatment without interfering with the antitumor activity of cisplatin against cancer cells.<sup>23</sup>

The aim of this study was to investigate the protective effect of L-carnitine in cisplatin-induced nephrotoxicity in cancer patients.



## PATIENTS AND METHODS

### Patients

A total of 32 cancer patients who attended the oncology unit in al-sadar medical city in Al-Najaf Governorate which cisplatin-based therapy was a treatment option, were enrolled for the study. All patients eligible for the study had a confirmed diagnosis of a malignant solid tumor by histopathologic and cytologic investigation. Informed consents were obtained from all participants of the study. The study protocol was approved by the Ethical Committees of Al-Nahrain College of Medicine. Patients selection and samples collection had started in March 2013 and sample collection continue until the end of June 2014. Inclusion criteria include no prior radiotherapy or chemotherapy, age between 18 and 70 years, no serious cardiopulmonary comorbidity which could impair involvement in the study, life expectancy of more than 3 months. Exclusion criteria include pregnancy or lactation, metastasis to the central nervous system, psychiatric disorders, prior treatment with platinum derivatives, and hypersensitivity to cisplatin, carboplatin or other platinum derivatives. All the demographic details such as name, sex, age, occupation, education, clinical data such as diagnosis and therapeutic data such as name of the drug, dose, route, frequency and duration of therapy were collected from patients, case notes and treatment chart.

### Study treatment

Only 28 patients still eligible to criteria of present study because some patient either changed or discontinued their cisplatin treatment or due to any cause that affect study design. Patients included in the study were randomized into two groups: *Group I*: Patients (N=14) received cisplatin based regimen for 6 cycles with 21 days interval. *Group II*: Patients (N=14) received L- Carnitine (500 mg oral tablet twice daily) + cisplatin-based regimen therapy. Cisplatin in a dose of 75 mg/m<sup>2</sup> was administered in combination with other chemotherapeutic agents which don't have overlapping kidney toxicity and/or could not affect cisplatin-induced nephrotoxicity, such as docetaxel, etoposide, 5-flourouracil and gemcitabine, (Takimoto, de Jongh)<sup>24,25</sup> every 21 days for 6 cycles. L-Carnitine was given as an oral tablet in a dose of 500 mg twice daily for all patients included in group II. It was manufactured by VALUPAC BR Pharmaceuticals Ltd Leeds UK. Batch NO. L11334.

### Collection of blood and urine samples

5 ml of blood were collected from patients included in the current study before 1<sup>st</sup> dose (base line) and 21 days after 1<sup>st</sup>, 2<sup>nd</sup>, 4<sup>th</sup> and 6<sup>th</sup> dose of chemotherapy for evaluation of Cisplatin-induced nephrotoxicity based on changes of the biomarkers of renal function, serum creatinine and cystatin C. Each blood sample was left for 15 minutes and centrifuged at 2500 rpm for 15 minutes, and then serum was collected and frozen. Urine was collected from patients included in the current study before 1<sup>st</sup> dose

(base line) and one days after 1<sup>st</sup>, 2<sup>nd</sup>, 4<sup>th</sup> and 6<sup>th</sup> dose of chemotherapy for evaluation of Cisplatin-induced kidney injury based on changes of MDA levels in urine. Each urine sample was centrifuged at 1500 rpm for 10 minutes and then supernatant was collected and frozen. Serum and urine samples were stored in deep freeze at -80 °C.

### Assessment of kidney function

Serum creatinine concentration was measured by colorimetric assay using commercially available Creatinine (serum) Colorimetric Assay Kit (Catalog Number. 700460) from Cayman Chemical Co. Serum cystatin C concentration was measured by enzyme-linked immunosorbent assay using commercially available human cystatin C (Cys C) ELISA kit (Catalog Number CSB-E08384h) from Cusabio Biotech Co., LTD.

### Assessment of kidney oxidative stress by measurement of urinary malondialdehyde (MDA) Level

Malondialdehyde, the end product of lipid peroxidation, was analyzed according to the method of Buege and Aust<sup>26</sup> which based on the reaction of MDA with thiobarbituric acid (TBA) to form MDA-TBA complex, a red chromophore, which can be quantitated spectrophotometrically according to this method. We selected the TBA test in this study since this method is popular and clinically used to measure MDA.<sup>27</sup>

### Statistical Analysis

Statistical analyses were performed using SPSS 16.0 for windows Inc. Data of quantitative variables were expressed as Mean ± SEM. Differences in each variable through treatment cycles in the same group were compared using paired-sample Student's t-test. Chi-Square test or (independent) unpaired-sample Student's t-test were used for the comparisons between the two groups variables. In all tests, P<0.05 was considered to be statistically significant unless another level was stated.

## RESULTS

### Patients characteristics

The patients characteristics data are shown in Table 1 and the difference in each characteristic was insignificant (p>0.05) in comparisons between the two randomization groups.

### Changes in serum creatinine level

In comparison with baseline level, there was significant increment (P < 0.05) after 2, 4 and 6 cycles in serum creatinine (mg/dl) level in cisplatin based regimen group as shown in Figure 1. In comparisons between treatment groups, there is no significant difference (P > 0.05) in serum creatinine level at base line and after 1 and 2 cycles of treatment as shown in Figure 1.

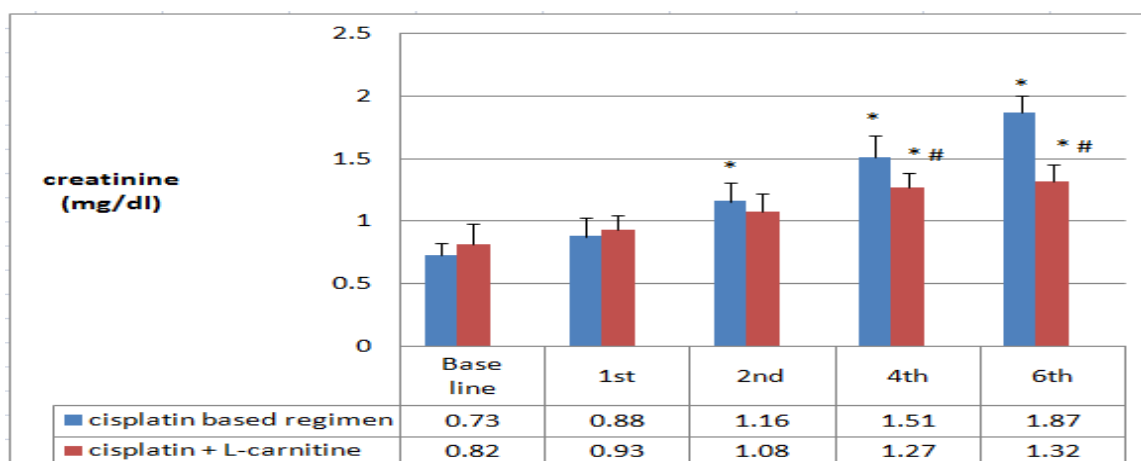
After 4 and 6 cycles of treatment, serum creatinine level of group II was significantly lower (P < 0.05) than that of group I as shown in Figure 1.



**Table 1:** Characteristics data for all included patients.

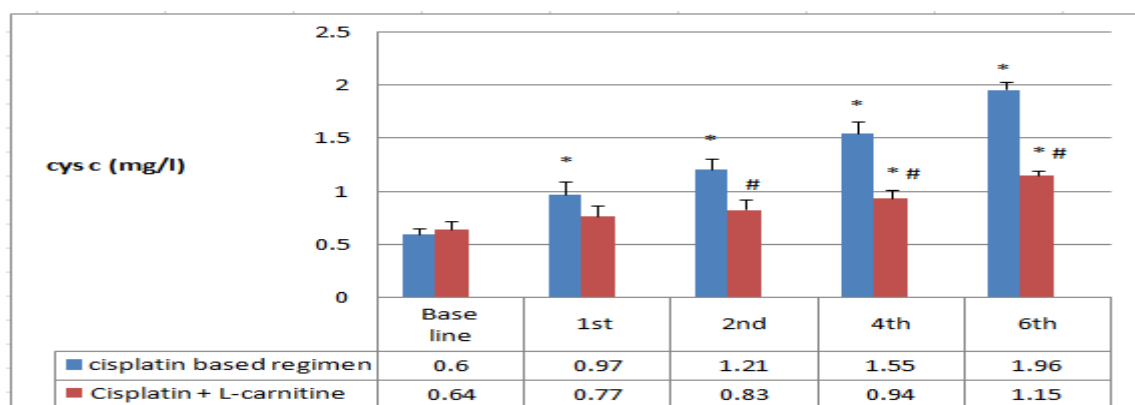
Characteristics	Group I	Group II
Number of patients	14	14
Sex (male/female)	10/4	11/3
Age (yr) Mean ± SEM	51.8 ± 6.78	53.34 ± 1.51
Weight (kg) Mean ± SEM	76.21 ± 0.94	75.5 ± 1.76
Height (cm) Mean ± SEM	161.3 ± 3.48	156.4 ± 2.46
Body Surface Area (m <sup>2</sup> ) Mean ± SEM	1.73 ± 2.06	1.71 ± 0.57
no. of Diabetic patients	1	1
no. of Hypertensive patient	2	1
Cisplatin based regimens received by patients:		
Cisplatin + gemcitabine	6	8
Cisplatin + 5-flourouracil + docetaxel	3	4
Cisplatin + 5-flourouracil	2	2
Cisplatin + etoposide	3	0

P > 0.05 (unpaired-sample t-test or Chi-Square test were used as appropriate).



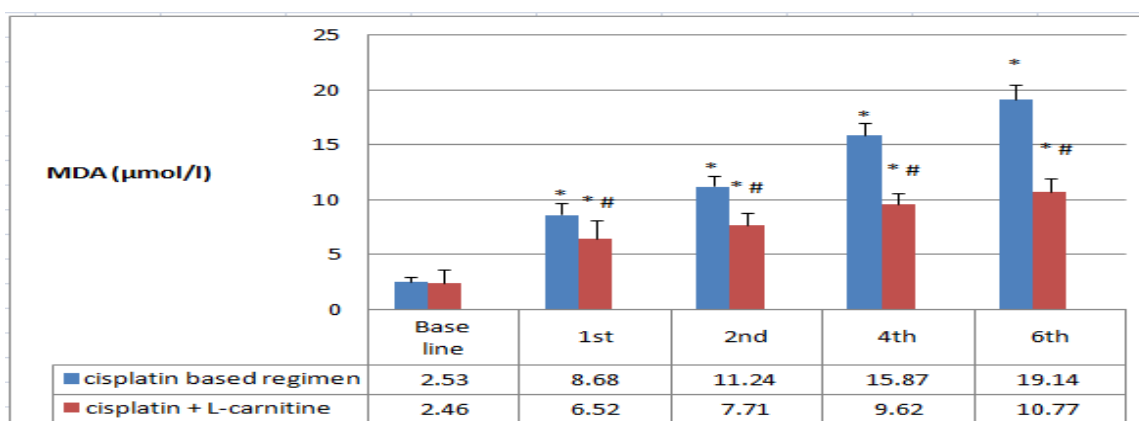
\* P < 0.05 compared to baseline values of the same treatment group.  
# p < 0.05 compared to group I.

**Figure 1:** Mean ± SEM values of serum creatinine (mg/dl) at baseline and after 1, 2, 4 and 6 cycles in both group I (cisplatin based regimen, n=14) and group II (cisplatin + L-carnitine, n= 14).



\* P < 0.05 compared to baseline values of the same treatment group.  
# p < 0.05 compared to group I.

**Figure 2:** Mean ± SEM values of serum cystatin C (mg/l) at baseline and after 1, 2, 4 and 6 cycles in both group I (cisplatin based regimen, n=14) and group II (cisplatin + L-carnitine, n= 14).



\* P < 0.01 compared to baseline values of the same treatment group.  
# p < 0.05 compared to group I.

**Figure 3:** Mean  $\pm$  SEM values of MDRD-GFR (ml/min) at baseline and after 1, 2, 4 and 6 cycles in both group I (cisplatin based regimen, n=14) and group II (cisplatin + L-carnitine, n= 14).

### Changes in serum cystatin C level

In comparison with baseline level, there was significant increment ( $P < 0.05$ ) after 1, 2, 4 and 6 cycles in serum cystatin C (mg/l) level in cisplatin based regimen group as shown in Figure 2. Incomparisons between treatment groups, there is no significant difference ( $P > 0.05$ ) in serum cystatin C level at base line and after 1 cycle of treatment as shown in Figure 2. After 2, 4 and 6 cycles of treatment, serum cystatin C level of group II was significantly lower ( $P < 0.05$ ) than that of group I as shown in Figure 2.

### Changes in urinary MDA level

In comparison with baseline level, there was high significant increment ( $p < 0.01$ ) in urinary MDA ( $\mu\text{mol/l}$ ) level after 1, 2, 4 and 6 cycles in cisplatin based regimen group as shown in Figure 3. Incomparisons between treatment groups, there is no significant difference ( $P > 0.05$ ) in urinary MDA ( $\mu\text{mol/l}$ ) level at base line before treatment as shown in Figure 3. After 1, 2, 4 and 6 cycles of treatment, urinary MDA ( $\mu\text{mol/l}$ ) level of group II was significantly lower ( $P < 0.05$ ) than that of group I as shown in Figure 3.

## DISCUSSION

### Effects of cisplatin based regimen on kidney function parameters

In the present study, although insignificant increment ( $P > 0.05$ ) in serum creatinine was observed after first cycle, cisplatin-based regimen caused significant increment ( $P < 0.05$ ) after 2 cycles and highly significant increment ( $P < 0.01$ ) in serum creatinine after 4 and 6 treatment cycles in comparison to baseline values. These results are in good agreement with that showed by Kumara<sup>28</sup> in that there is significant increment in serum creatinine level in patients after 2 and 4 cycle of cisplatin chemotherapy in comparison to base line levels. Also Arunkumar<sup>29</sup> revealed that serum creatinine level was significantly higher than base line level after 5 cycles of cisplatin treatment.

In the present study, unlike serum creatinine, significant increment ( $P < 0.05$ ) in serum cystatin C in comparison to base line level had started from the first cycle and highly significant increment ( $P < 0.01$ ) after 2, 4 and 6 cycles was observed. These results are in good agreement with that showed by Benohr<sup>30</sup> and Zhang and Zhou<sup>31</sup>.

However, non-significant changes of serum creatinine after first cycle might be due to the poor sensitivity and specificity of serum creatinine.<sup>32,33</sup> In contrast, cystatin C has recently been proposed as a more sensitive clinical marker than serum creatinine for the early assessment of GFR disturbance caused by cisplatin. Changes in cystatin C serum level correlated well to GFR decrease as measured by insulin clearance, which was recognized as gold standards to estimate the GFR.<sup>30</sup> The reason why cystatin C rises before serum creatinine is not clear. A possible explanation is that cystatin C represents the ideal endogenous marker of GFR; it is produced by all nucleated cells at a constant rate, is not affected by changes in body mass, nutrition or sex, and is not degraded or secreted by the renal tubules. In contrast, serum creatinine is affected by many non-renal factors that affect generation of creatinine and tubular secretion.<sup>34</sup>

An explanation of the significant decline in GFR and then the significant increase in serum kidney parameters in the present study is that renal blood flow can decrease within 3 hours after cisplatin infusion, GFR falls after the decrease in renal blood flow.<sup>35</sup> The changes in renal blood flow probably reflect increased renal vascular resistance secondary to tubular-glomerular feedback from increased sodium chloride delivery to the macula densa.<sup>35</sup>

### Effects of cisplatin based regimen on renal oxidative stress parameter

In the present study, cisplatin based regimen caused highly significant increment ( $p < 0.01$ ) in urinary MDA ( $\mu\text{mol/l}$ ) level after 1, 2, 4 and 6 cycles in comparison to base line level. Zhou<sup>36</sup> reported a preliminary observation in 8 patients with cancer who presented an increase in

urinary MDA excretion, 24 h after cisplatin treatment. On experimental level, a single dose of cisplatin (6 mg/kg) yielded a significant increase of MDA in kidneys and urine of rats at day 1 and then rapidly decreased to the basal level which preceded the significant rise in serum creatinine and BUN concentrations and tubular damage which was not noticed until day 5 after cisplatin treatment.<sup>36</sup> The use of spot urine sample collection instead of 24-hour collection was a limitation of the present study. However, according to a previous study, 24 hours urine was not necessary for measurement of biomarkers and there was no statistically significant difference between spot and 24 hours urines.<sup>37</sup>

Higher urinary MDA level may be due to formation of GSH-cisplatin adduct which decreases availability of GSH and increase calcium concentration and lead to over production of ROS<sup>11</sup> along with inactivation of antioxidant enzymes as superoxide dismutase, glutathione peroxidase, and catalase.<sup>15,16</sup> The excess ROS damages the lipid components of the cell membrane by peroxidation (increased renal MDA) and denature proteins, which lead to enzymatic inactivation.

#### Effects of cisplatin based regimen + L-carnitine on kidney function parameters

In the present study, serum creatinine level of L-carnitine treated group was significantly lower ( $P < 0.05$ ) than that of cisplatin based regimen only treated group after 4 and 6 cycles of treatment. Up to our knowledge, there is no similar study on cancer patient but on experimental level, Aleisa and colleagues<sup>38</sup> reported the progression of cisplatin-induced nephrotoxicity in carnitine-depleted rat model. They concluded that carnitine supplementation attenuates cisplatin-induced nephrotoxicity. L-carnitine, attenuated cisplatin-induced nephrotoxicity (inhibited the enhancement in serum creatinine).<sup>38</sup>

The results of the present study demonstrated that there is significant ( $P < 0.05$ ) attenuation of the increased cystatin C level after 2, 4 and 6 treatment cycles in L-carnitine treated group in comparison to that of cisplatin only treated group. Up to our knowledge, there is no similar study on cancer patients or any experimental models that studied the effect of L-carnitine on serum cystatin C.

#### Effects of cisplatin based regimen + L-carnitine on renal oxidative stress parameter

In the present study, urinary MDA level of L-carnitine treated group was significantly lower ( $P < 0.05$ ) than that of cisplatin based regimen treated group after 1, 2, 4 and 6 cycles of treatment. Up to our knowledge there is no similar study on cancer patient but on experimental level Sayed-Ahmed and colleagues<sup>39</sup> reported that L-carnitine, attenuated cisplatin-induced increase in MDA and the decrease in total L-carnitine, GSH, and ATP content in kidney tissues. Yürekli<sup>40</sup> revealed that L-carnitine significantly ( $p < 0.05$ ) attenuated the cisplatin-induced

nephrotoxicity and significantly ( $p < 0.05$ ) inhibited MDA elevation and GH depletion induced by cisplatin.

The administered L-carnitine preferentially accumulates in the kidney and facilitates the  $\beta$ -oxidation to generate ATP, thereby minimizing the toxic effects of free forms of long-chain fatty acids in and around mitochondria.<sup>41,42</sup> Furthermore, L-carnitine strongly inhibited mitochondrial membrane permeability transition and cytochrome c release from mitochondria that is responsible for induction of caspases and then apoptosis of various types of cells.<sup>43,44</sup> Although L-carnitine lacks activity to scavenge free radicals, this amino acid shows properties similar to that of antioxidants.<sup>41,42</sup> The protective effects of L-carnitine might reflect their activities to improve energy metabolism and repair oxidized membrane/lipid bilayers<sup>42</sup>, thereby suppressing the release of free electrons from mitochondrial electron transport systems, a required reaction to the generation of free radicals.<sup>41</sup>

#### CONCLUSION

L-carnitine had a significant ameliorative effect on cisplatin-induced nephrotoxicity in cancer patients that reflected by the significant improvement of kidney function parameters.

This protective effect might be primarily through antioxidant action as demonstrated by significant lowering of urinary MDA level in patients treated with L-carnitine plus cisplatin.

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