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Effect Of L-Carnitine On Urinary Il-18 And Gfr In Patient Receiving Cisplatin-Based Regimen

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Background: Nephrotoxicity is a major dose-limiting side effect facing cisplatin-based chemotherapy of a wide variety of cancers. Acute kidney injury occurs after cisplatin chemotherapy in approximately 30% of patients where severe and lifelong nephrotoxicity can result regardless of the use of powerful hydration with normal saline. 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. 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. L-carnitine with their antioxidant, anti-inflammatory and to some extent antiapoptotic effects may have ameliorative effect on nephrotoxicity.

Aim: To assess the effects of L-carnitine in protection from cisplatin–induced nephrotoxicity in cancer patients.

Patients and methods: 28 patients were participated in the study and successfully completed their treatment cycles. They were randomized into two groups (N=14 in each). In group I, patients received six cycles of cisplatin based regimen with 21 days-intervals. In group II, patients received L-carnitine (500 mg oral tablet twice daily) plus cisplatin based regimen. GFR (Modification of Diet in renal Diseases formula) was measured at base line and 21 days after 1, 2, 4 and 6 cycles but IL-18 was measured at base line and 1 day after 1, 2, 4 and 6 cycles of cisplatin based regimen.

Results: In patients of group I, cisplatin-based regimen caused significant ($P<0.05$) increment in serum creatinine and urea levels, highly significant ($P<0.01$) increment in serum urinary IL-18 levels, and significant ($P<0.05$) decrement in GFR in comparison to base line levels.

Conclusions: Each of L-carnitine significantly ameliorated nephrotoxicity in patients that received cisplatin.

Keywords: Cisplatin, Renal toxicity, L-carnitine

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Introduction:

Cisplatin has proven to be of great clinical value and in 1978, the American Food and Drug Administration approved cisplatin for clinical use in management of a wide variety of cancers such as bladder, cervical, esophageal, head, neck, ovarian, and testicular [(1)]. Cisplatin form complex reaction with DNA. The DNA-cisplatin complex inhibits DNA replication and transcription and leads to breaks and miscoding, and if recognized by p53, leads to apoptosis (2). Nephrotoxicity is a dose-dependent and dose-limiting side effect of cisplatin [(3)]. Acute kidney injury (AKI) occurs after cisplatin chemotherapy in approximately 20-30% of patients [(4)]. Although relatively less toxic but equally effective substitutes were introduced, cisplatin continues to be widely involved in chemotherapy as first line antitumor agent [(5)]. The mechanisms of cisplatin-induced nephrotoxicity are complex and include various pathways [(2)]. Apoptosis and necrosis, due to DNA damage response pathways and oxidative stress in association with severe inflammatory response and caspase activation, are the major sources of acute kidney injury due to cisplatin [(2)].

Carnitine is a naturally occurring amino acid which act as carrier for the translocation of long-chain fatty acid from cytoplasmic compartment into mitochondria, where beta-oxidation enzymes are located for energy production. In humans, 25% of carnitine is synthesized endogenously from the amino acids lysine and methionine and the rest 75% of the total body carnitine found in dietary sources [(6)]. About 98% of carnitine content in the body is in muscles, while 2% of carnitine is found in the liver and other tissues [(7)]. In the heart, carnitine concentration is about 4.2 mmol/g tissue, which is nearly three times more than striated muscles (1.26 mmol/g), four times more than the liver (0.94 mmol/g), and eight times more than the kidney carnitine contents (0.52 mmol/g) [(8)]. A reduction in endogenous synthesis of L-carnitine can result from metabolic alterations due to cancer cachexia [(9)]. The decreased dietary intake and impaired endogenous synthesis of L-carnitine results in low serum levels of L-carnitine in cancer patients. These low serum L-carnitine levels in cancer patients also found to promote cachexia [(10)]. On the other hand, cisplatin alone can lead to low serum levels of L-carnitine in cancer patients. Treatment with cisplatin caused a tenfold increase in renal L-carnitine excretion in cancer patients, most likely due to inhibition of L-carnitine reabsorption by the proximal tubule

[11]. This may have additive effect on cisplatin-induced nephrotoxicity as revealed by Arafa (2008) [12] who showed that low serum carnitine level might aggravate carboplatin nephropathy. In an experimental model, L-carnitine has a considerable protective effect against cisplatin - induced nephrotoxicity in rats [13]. 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 [14]. In rats, L-carnitine attenuated the cisplatin-induced nephrotoxicity [15].

Glomerular Filtration Rate (GFR) provide a more accurate assessment of the kidney function than serum creatinine and in addition, chronic kidney disease (CKD) can be defined in terms of GFR as GFR lower than 60 ml/min per 1.73 m^2 for 3 months or more [16]. CKD is classified into stages according to the level of GFR, and stage-specific action strategy assist diagnosis and management of CKD [16]. For the determination of (GFR), different calculation formulas are used for which different interindividual Parameters are involved. The creatinine-based and the cystatin C-based methods of calculation are commonly used to estimate GFR. Creatinine-based calculation method of GFR was according to updated version of Modification of Diet in Renal Disease (MDRD) formula [17] and cystatin C-based methods of determining the GFR was according to Larsson [18].

IL-18 is a proinflammatory cytokine that activate the synthesis of Interferon gamma (IFN-γ) by T cells and natural killer cells in addition to the action of IL-12 [19]. IL-18 stimulates T cell and NK cell maturation and cytotoxicity and stimulates Th1 polarization [20]. IL-18 also plays an essential role in inflammation and in exact it modulates the activity of macrophages by stimulation of transcription factors such as NF-κB [21]. Therefore, IL-18 may promote immune or non–immune-mediated tissue injury via a diverse mechanisms (enhancing macrophage and neutrophil infiltration).

A Study in humans demonstrated that urine IL-18 is an early predictive biomarker of AKI where urine IL-18 was significantly elevated in patients with acute tubular necrosis in comparison to that of normal controls [22]. In the kidney-transplant patients, lower levels of urinary IL-18 were associated with a more decline in serum creatinine concentration 4 days after operation [23]. These studies in humans showed the correlation of urine IL-18 with established tubular damage and found the basis for examining urine IL-18 as early predictive biomarker of AKI. This study was design to assess the effects of L-carnitine in protection from cisplatin–induced nephrotoxicity in cancer patients.

Methods:

Patients :

A total of 28 cancer patients who attended the oncology unit in al-sadar medical city in Al-Najaf Governorate, for whom cisplatin-based therapy was a treatment option, were enrolled in the present study. All patients eligible for the study had a confirmed diagnosis of a malignant solid tumor by histopathologic and cytologic investigation. Inclusion criteria include age between 18 and 70 years and life expectancy of more than 3 months. Exclusion criteria include pregnancy or lactation, metastasis to the central nervous system, serious cardiopulmonary comorbidity that could impair participation in the study, preexisting renal impairment, prior radiotherapy or chemotherapy, and hypersensitivity to cisplatin, carboplatin or other platinum derivative. Informed consents were obtained from all participants of the study. All the demographic details such as name, sex, age, occupation, education, clinical data for example diagnosis and therapeutic data (name of the drug, dose, route, frequency and duration of therapy) were collected from patients, case notes and treatment chart. Patients' selection and samples collection had started in March 2016 and samples collections continue until the end of June 2017.

Patient grouping:

Patients included in the study were randomized into two groups:

Group I: Patients (N=14) were treated with cisplatin based regimen for 6 cycles with 21 days interval .

Group II: Patients (N=14) were treated with L- Carnitine (500 mg oral tablet twice daily) + cisplatin-based regimen therapy.

L-Carnitine: It 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.

Statistical Analysis

Statistical analyses were performed using SPSS 16.0 for windows.lnc. 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. In all tests, $P<0.05$ was considered to be statistically significant unless another level was stated.

Results:

The present study was done on 28 patients who had been diagnosed to have cancer and their treatment options included cisplatin as anticancer agent. Their characteristics data are shown in table (1) and the difference in each characteristic was insignificant.

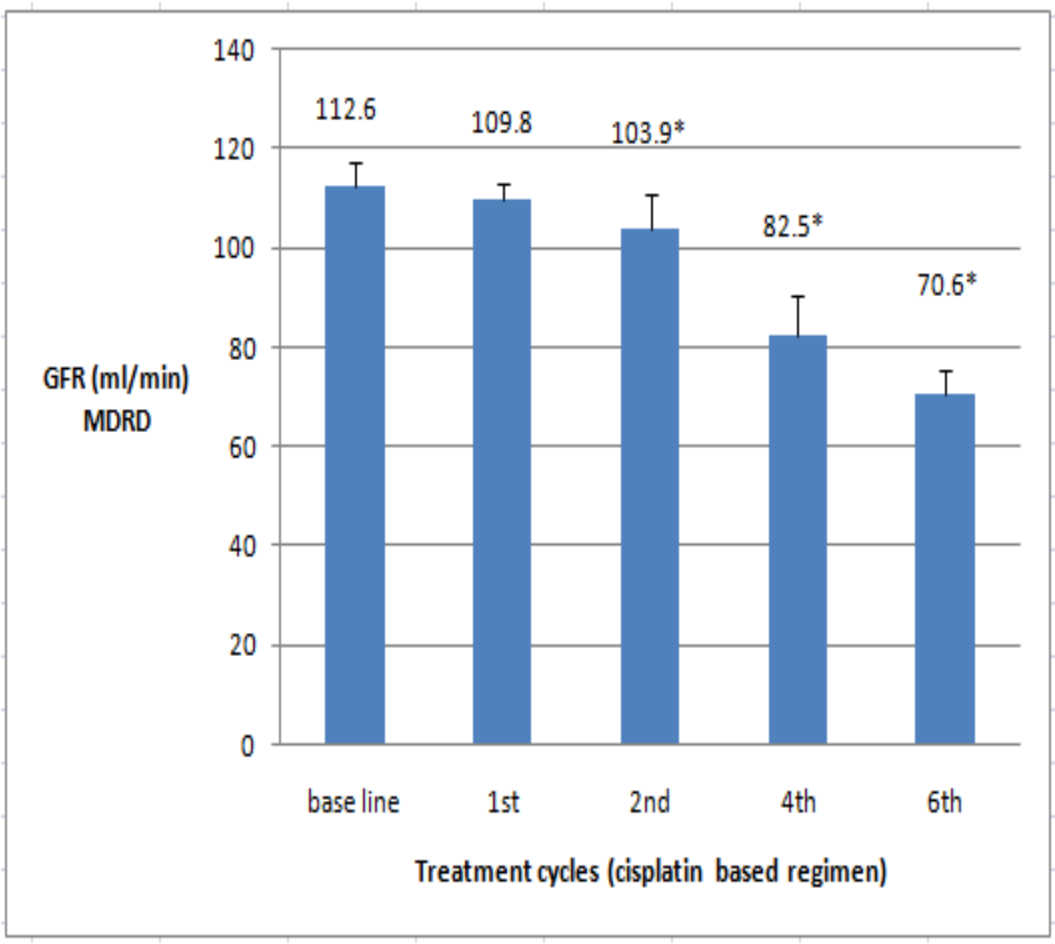
Table (1): Characteristics data for all patients included in the present study.

Characteristics	Group I	Group II	P values
Number of patients	14	14	NS
Sex (male/female)	10/4	11/3	NS
Age (yr) Mean ± SEM	51.9± 6.78	53.44± 1.51	NS
Weight (kg) Mean ± SEM	76.31± 0.94	75.6±1.76	NS
Height (cm) Mean ± SEM	162.3±3.48	157.4±2.46	NS
Body Surface Area (m^2) Mean ± SEM	1.74±2.06	1.72±0.57	NS
no. of Diabetic patients	2	2	NS
no. of Hypertensive patient	1	0	NS
Cisplatin based regimens received by patients:			
Cisplatin + gemcitabine	7	7	NS
Cisplatin + 5-flourouracil + docetaxel	3	4	NS
Cisplatin + 5-flourouracil	1	1	NS
Cisplatin + etoposide	3	2	NS

*P<0.05.

Effect of cisplatin based regimen on GFR estimated by MDRD formula

In comparison with baseline level, there was insignificant decreasing (p> 0.05) in MDRD-GFR (ml/min) after 1 cycle and significant decreasing (p<0.05) after 2, 4 and 6 cycles in cisplatin based regimen group as shown in figure (1).

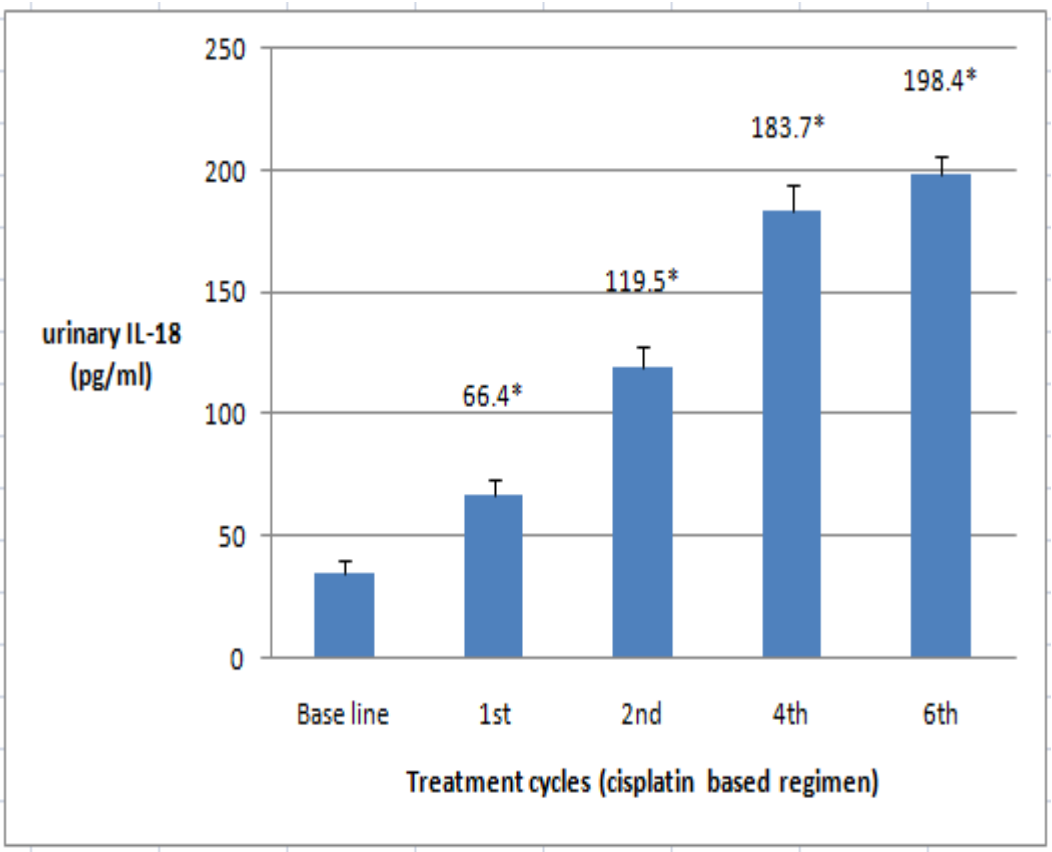


* Significant difference compared to baseline values (P < 0.05)

Figure (1): The differences in mean ± SEM in MDRD-GFR at baseline and after 1, 2, 4 and 6 cycles among patients in group I.

Effect of cisplatin based regimen on urinary IL-18 level

In comparison with baseline level, there was high significant increment (p< 0.01) in urinary IL-18 (pg/ml) level after 1, 2, 4 and 6 cycles in cisplatin based regimen group as shown in figure (2).

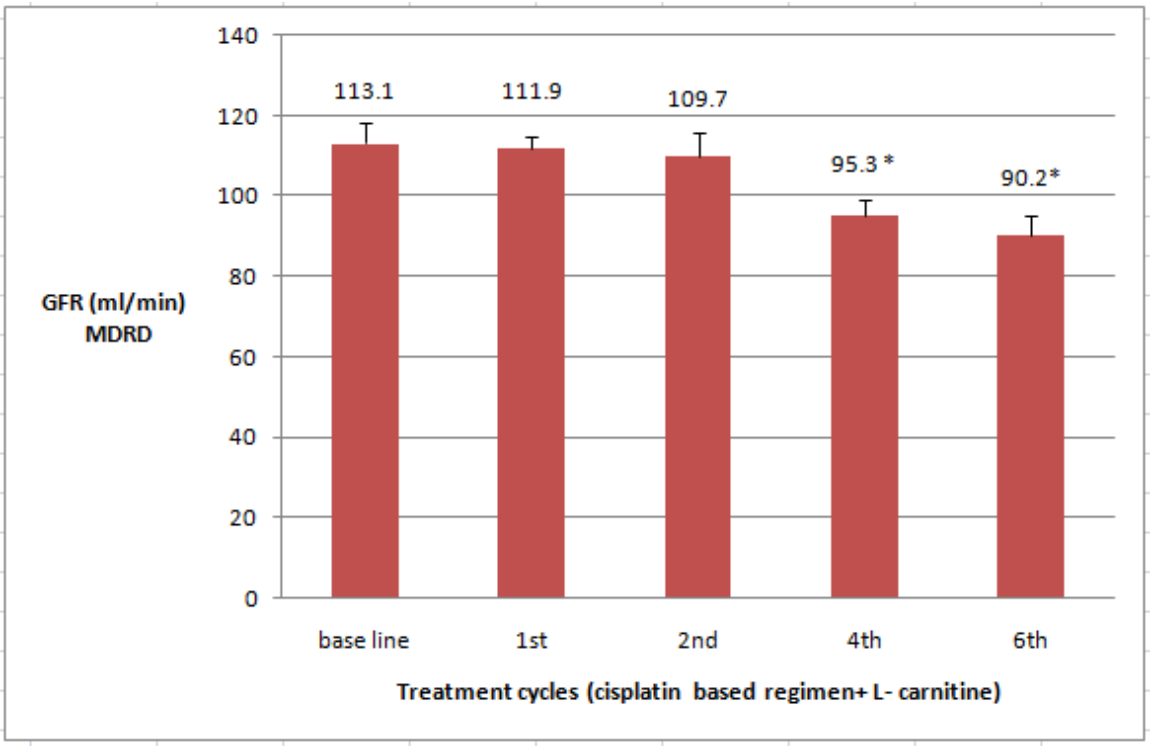


* Significant difference compared to baseline values (P < 0.01)

Figure (2): The differences in mean ± SEM in urinary IL-18 levels at baseline and after 1, 2, 4 and 6 cycles among patients in group I.

Effect of cisplatin based regimen + L-carnitine on GFR estimated by MDRD formula

In comparison with baseline level, there was insignificant decreasing (p> 0.05) in MDRD-GFR (ml/min) after 1 and 2 cycles and significant decreasing (p<0.05) after 4 and 6 cycles in cisplatin based regimen + L-carnitine (500 mg × 2) group as shown in figure (3).

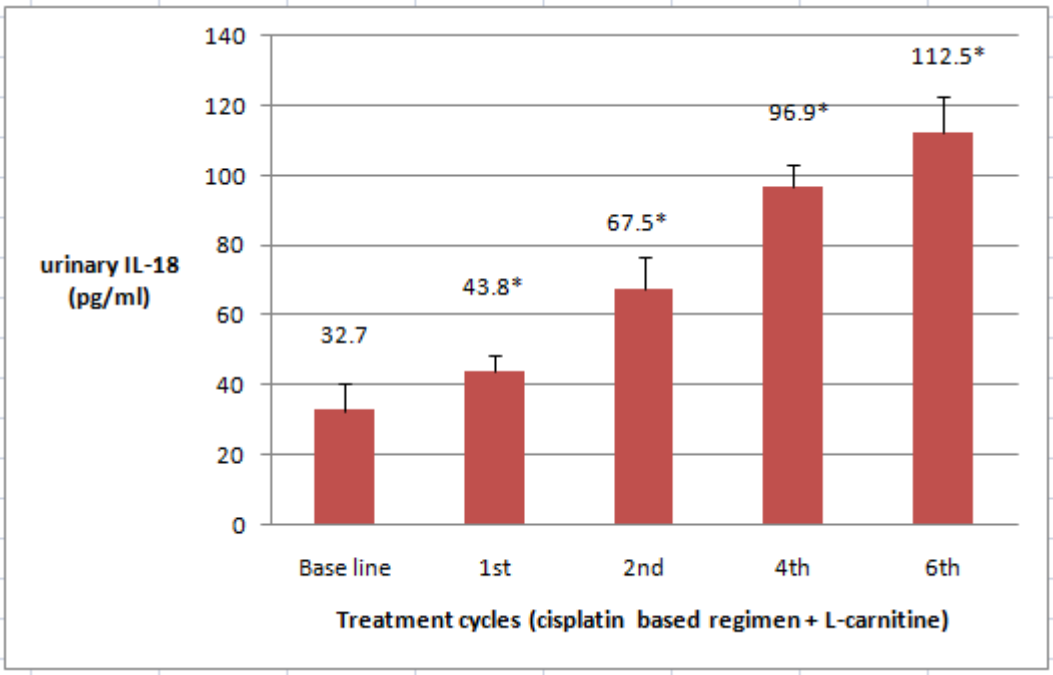


* Significant difference compared to baseline values (P < 0.05)

Figure (3): The differences in mean ± SEM in MDRD-GFR at baseline and after 1, 2, 4 and 6 cycles among patients in group II.

Effect of cisplatin based regimen + L-carnitine on urinary IL-18 level

In comparison with baseline level, there was high significant increment (p< 0.01) in urinary IL-18 (pg/ml) level after 1, 2, 4 and 6 cycles in cisplatin based regimen + L-carnitine (500 mg × 2) group as shown in figure (4).



* Significant difference compared to baseline values (P < 0.01)

Figure (4): The differences in mean ± SEM in urinary IL-18 levels at baseline and after 1, 2, 4 and 6 cycles among patients in group II.

Discussion

Cisplatin based regimen caused insignificant decreasing (p> 0.05) in MDRD-GFR after 1 cycle and significant decreasing (p<0.05) after 2 cycles and highly significant decreasing (p<0.01) after 4 and 6 cycles in comparison to base line level. These results are consistent with that showed by Bodnar and colleagues (2008) [24] where they recorded significant decrease in GFR estimated from MDRD formula after 1, 3, 4, 5 and 6 cycles of treatment with cisplatin in patients with ovarian cancer.

In the present study, cisplatin based regimen caused highly significant increment (p< 0.01) in urinary IL-18 (pg/ml) level after 1, 2, 4 and 6 cycles in comparison to base line level. These data indicated the presence of AKI after the first cycle of cisplatin treatment which could not be diagnosed by the normal levels of serum urea and creatinine after the first cycle. An explanation is that cisplatin administration significantly upregulated several cytokines and chemokines and the most important of them are TNF-α, monocyte chemoattractant protein-1 (MCP-1) and intercellular adhesion molecule (ICAM) [25]. This leads to the recruitment and accumulation of inflammatory cells. IL-18 is produced in the kidney predominantly by recruited inflammatory cells, probably

macrophages but also by activated injured renal parenchymal cells [26].

Up to our knowledge, there is no similar study that measured urinary or even serum level of IL-18 in patient receiving cisplatin. On the other hand, there are some reports of measuring urinary IL-18 in patients with AKI. A case-control study on patients with the acute respiratory distress syndrome was performed to determine whether urinary IL-18 is an early diagnostic marker for AKI in critically ill patients in the ICU. On multivariable analysis, urine IL-18 values predicted development of AKI (defined as a 50% increase in serum creatinine) 24 and 48 hours later [27].

After 4 and 6 cycles of treatment, GFR, estimated by MDRD formula, of L-carnitine treated group was significantly higher ($P < 0.05$) than that of cisplatin based regimen only group (which is comparable to L-carnitine effect on serum creatinine). Best to our knowledge, no previous related studies supported the result of present study. Since cisplatin-induced tubular injury share many pathophysiological features with ischemic damage [4], positive results of L-carnitine in protection against ischemia/ reperfusion might be useful to be compared with that of present study. In an experimental model of ischemia/reperfusion injury propionyl-L-carnitine is of value in preventing decline of renal function that occurs during ischemia/reperfusion where infusion of propionyl-L-carnitine starting at the beginning of reperfusion resulted in marked increase of GFR. The beneficial effect of propionyl-L-carnitine possibly relates to lowering lipid peroxidation and free radical generation that eventually results in the preservation of tubular cell structure [28].

In the present study, urinary IL-18 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 or even on experimental model that assess the effect of L-carnitine on renal IL-18 as marker for inflammation but rather many reports studied the effects of L-carnitine on renal inflammation. Chapela et al (2009) [29] revealed the strong anti-inflammatory effect in addition to anti-oxidative and anti-apoptotic effects. Tufekci and colleagues (2009) [30] revealed the protective effects of acetyl L-carnitine on cisplatin-induced nephrotoxicity in rats. Renal caspase-3, 8 and 9 activities were decreased in acetyl L-carnitine treated group where caspase-3 activation resulted from the interaction of TNF-α with TNF-α receptor [30]. Juan-Pablo et al (2012) showed that combination of acetyl L-carnitine and L-carnitine caused significant decrement in renal TNF-α level after renal ischemia- reperfusion injury. According to these results, L-carnitine might inhibited cisplatin -induced upregulation of TNF-α, [25] and so inhibition of the recruitment and accumulation of inflammatory cells

that are responsible for IL-18 production [26].

Conclusions

According to the results of the present study, the following conclusions can be stated:

1- Cisplatin-based regimen caused highly significant decline in kidney function in the cancer patients approved by the highly significant GFR.

2- Cisplatin-based regimen caused acute kidney injury revealed by highly significant increment in urinary injury parameter (IL-18).

3- Addition of L-carnitine to Cisplatin-based regimen caused highly significant amelioration on kidney injury parameter that is accompanied by the significant improvement in kidney function parameters.

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تأثير ال-كارنيتين على انترلوكين 18 في الادراروmعدل الترشيح الكبيبي في المرضى الذين يتلقون علاج السيسبلاتين

احسان صلاح ربيع احمد جلال محمد فاضل عبد الجبار رزج

الخلفية: السمية الكلوية هي تأثير جانبي كبير يحد من جرعة السيسبلاتين ويعرقل العلاج الكيميائي القائم على السيسبلاتين لمجموعة واسعة من أنواع السرطان. بعد العلاج الكيميائي بالسيسبلاتين تحدث الإصابة الكلوية الحادة في ما يقرب من ٣٠ ٪ من المرضى حيث ان هذه السمية الكلوية الحادة يمكن أن تنتج بغض النظر عن استخدام الارواء الجيد مع المحلول الملحي المتعادل. على الرغم من الجهود العلمية المبذولة لإيجاد بدائل أقل سمية ولكنها فعالة بنفس القدر، لا يزال السيسبلاتين يستخدم في الخط الأول وعلى نطاق واسع في العلاج الكيميائي كعامل مضاد للورم. يعتبر كل من موت الخلايا المبرمج والغير مبرمج ، بسبب تلف الحمض النووي ، والإجهاد التأكسدي المرتبط بالاستجابة الالتهابية الحادة وتفعيل مسار كاسباس ، من المصادر الرئيسية للسسبلاتين لإصابة الكلى بالسمية الحادة. ال- كارنيتيني مع آثارها المضادة للأكسدة ، المضادة للالتهابات وإلى حد ما مضادات موت الخلايا قد يكون لها تأثير تحسين على السمية الكلوية.

الهدف: تقييم آثار ال- كارنيتيني في الحماية من السمية الكلوية التي يسببها السيسبلاتين في مرضى السرطان.

المرضى والطرق: شارك ٢٨ مريضا في الدراسة وأكملت دوراتهم العلاجية بنجاح. تم توزيعهم بصورة عشوائية إلى مجموعتين (N = 14 في كل منهما). في المجموعة الأولى ، تلقى المرضى ست دورات من نظام السيسبلاتين القائم على فترات ٢١ يوما. في المجموعة الثانية ، تلقى المرضى ال- كارنيتيني (قرص ٥٠٠ ملغ عن طريق الفم مرتين يوميًا) بالإضافة إلى نظام السيسبلاتين. تم قياس GFR في خط الأساس و ٢١ يومًا بعد الدورة الاولى والثانية والرابعة والسادسة وكذلك تم قياس IL-18 عند خط الأساس وبعد يوم واحد من دورات السيسبلاتين العلاجية الاولى والثانية والسادسة.

النتائج: في مرضى المجموعة الأولى ، تسبب النظام المعتمد على السيسبلاتين في زيادة ملحوظة (P <0.05) في مستويات الكرياتينين واليوريا في الدم ، زيادة كبيرة (P <0.01) في مستويات IL-18 في المصل ، وكذلك انخفاض ملحوظ (P <0.05) في GFR بالمقارنة مع مستويات خط الأساس.

الاستنتاجات: ال كارنيتيني اظهر تحسن ملحوظ في منع السمية الكلوية في المرضى الذين تلقوا العلاج بالسيسبلاتين.