Mild Hypomagnesemia as the Most Common Cisplatin Nephropathy in Iran

Mohammad Ali Mashhadi,[1] Zahra Heidari,[2] Zahra Zakeri[3]

[1]Genetics of Non-commucable Disease Research Center, Zahedan University of Medical Sciences, Zahedan, Iran
[2]Division of Endocrinology, Department of Internal Medicine, Zahedan University of Medical Sciences, Zahedan, Iran
[3]Division of Rheumatology, Department of Internal Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

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Introduction. Cisplatin still has a central role in cancer chemotherapy, but is associated with the risk of toxicities, the most common of which is nephrotoxicity. The aim of the present study is evaluation of cisplatin nephrotoxicity in Iranian population of cancer patients.
Materials and Methods. All admitted patients to the oncology service who received cisplatin were included in a prospective study from 2004 to 2010. Clinical and laboratory data including kidney function tests were recorded at baseline and during follow-up visits.
Results. One hundred patients (56% men) were included. Their mean age was 44 years. Common adverse events were nausea (85%) and vomiting (78%), followed by anorexia and fatigue (20%), taste change (10%), hearing loss (8%), cramping abdominal pain (8%), and tinnitus (5%). The most important finding was normal kidney function, except for mild hypomagnesemia (grade 1 toxicity) in 18%, without any symptoms or other electrolyte abnormalities. None of the patients with hypomagnesemia had significant serum electrolyte imbalances, diarrhea, severe allergic reactions, difficulty in walking, or chest pain.
Conclusions. Cisplatin has the potential to produce both mild and severe side effects. Although the neurologic and gastrointestinal toxicities were observed, renal toxicity (rising blood urea and creatinine or electrolyte abnormality) was not observed, and the only toxicity was grade 1 hypomagnesaemia.

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INTRODUCTION

Cisplatin is one of the most important chemotherapeutic agents, which still has a central role in cancer chemotherapy despite its toxicity. Efforts should be focused on attenuation and resolution of the side effects. One of the most common and serious toxicities is nephrotoxicity, and the results of multiple pathogenic renal abnormality are causes of renal cell death and apoptosis.[1-3] The Iranian population showed different degrees and range of toxicity to every chemotherapeutic agent.[4-7] These findings and results should be confirmed with others large multicenter studies in the Iranian population.

Cisplatin and other platinum-containing agents are used as chemotherapeutic drugs for many cancers, such as testicular, head and neck, lung, ovary, and gastro-esophageal cancers.[8-11] Cisplatin mainly has renal excretion and the maximum excretion is during the first hour after its administration.[12] The major causes of cisplatin discontinuation are 2-fold: toxicity and resistance.[13-16] Cisplatin nephrotoxicity occurred in one third of patients that received cisplatin,[17] and usually, in 10 days of administration and revealed with a decrease in glomerular filtration rate (GFR), rising in creatinine level, and hypomagnesemia, and hypokalemia.[17,18] Acute kidney failure with

cisplatin administration could occur in the majority of cases in intensive care unit.[19]

The aim of this study is the evaluation of cisplatin nephrotoxicity in Iranian population.

MATERIALS AND METHODS

This prospective study was done on all admitted patients to the Hematology-Oncology units that received cisplatin for chemotherapy. Physical examination and necessary paraclinical tests were done for all of the patients during admission and in follow-up visits. Patients with all malignancies who were candidates for cisplatin therapy included those with esophageal, gastric, head and neck, lung, and cervix cancers, as well as sarcoma and primitive neuroectodermal tumor. The inclusion criteria were normal kidney function, normal serum electrolytes levels (sodium, potassium, phosphorus, calcium, and magnesium levels), normal urinalysis, and performance status 0 or 1. All patients had acceptable nutritional status and had normal nutritional profile (serum albumin, iron, and ferritin levels). Exclusion criteria were leukopenia, thrombocytopenia, alcohol use, pregnancy, hepatitis, positive hepatitis B and C virus markers, abnormal liver function test or liver involvement secondary to primary disease, abnormal feeding and severe nutritional status, and use of nephrotoxic drugs such as aminoglycoside. Patients were examined prior to the start of the treatment protocol and then prior to every cycle of cisplatin therapy for renal toxicities. Kidney dysfunction definition was according to the acute kidney injury criteria, and the Cockroft-Gault formula was used for estimation of GFR. Paraclinic parameters included electrocardiography, urinalysis, complete blood count, and serum sodium, potassium, calcium, magnesium, phosphorus, albumin, urea nitrogen, creatinine, uric acid, alanine aminotransferase, aspartate aminotransferase, and bilirubin. The Cancer Therapy Evaluation Program criteria (version 3) were used for assessment of laboratory findings (Tables 1 and 2).[20]

Table 2. Hypomagnesaemia Based on Cancer Therapy Evaluation Program Grading of the National Cancer Institute[30]

Grade	Serum Magnesium, mg/dL
0	Within normal limit
1	≥ 1.2
2	< 1.2 to 0.9
3	< 0.9 to 0.7
4	< 0.7

After establishing an appropriate intravenous line, maintenance fluid therapy and granisetron, 3 mg, were initiated 30 minutes before initiation of cisplatin therapy. The dose of cisplatin was 50 mg/m^2 to 100 mg/m^2 in 1 liter of normal saline, which was infused in 1000 mL of isotonic saline within 2 hours. Other drugs administered were doxorubicin and fluorouracil, which do not have nephrotoxic effects. The patients did not receive any other nephrotoxic agents or diuretics prior to the start of treatment and during therapy and follow-up.

Other toxicities such as liver, gastrointestinal, or neurologic abnormalities were evaluated and documented.

RESULTS

One hundred patients (56 men and 44 women) were included in the study during the period between 2008 and 2011 at Ali-Ebne-Abitaleb Hospital of Zahedan, Iran. The mean age was 44 years (range, 17 to 65 years; Table 3). All of the participants received cisplatin at a dose of 50 mg/m^2 to 100 mg/m^2. All courses of cisplatin administration were 3 to 6 cycles, and all of them received at least 3 courses of cisplatin therapy.

The patients had no other underlying diseases (renal, hepatic, cardiac disorders). Laboratory profile prior to treatment and after cisplatin administration is summarized in Table 4. None of the patients had significant changes in GFR or rising in blood urea nitrogen and creatinine as markers of kidney dysfunction after cisplatin administration. Renal toxicity was limited to hypomagnesemia (18%), which was minimal, and all of the patients had grade

Table 1. Kidney Function Based on Cancer Therapy Evaluation Program Grading of the National Cancer Institute[30]

	Adverse Event				
Parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Serum creatinine, mg/dL	≤ 1.5	> 1.5 to 3.0	> 3.0 to 6.0	> 6.0	Death
Glomerular filtration rate, %	50 to < 75	25 to < 50	< 25, Chronic dialysis, no indication of kidney transplant	Chronic dialysis or Kidney transplant	Death

Table 3. Patients' Characteristics

Characteristic	Value
Mean age, y	44 (17 to 65)
Male sex, %	56
Site of tumor, %	
Esophagus	20
Head and neck	10
Stomach	27
Lung	27
Sarcoma	12
PNET and cervix	4
Performance status, %	
0	80
1	20
Dose of cisplatin, mg/m^2	50 to 100
Total courses of cisplatin administration, %	
3	15
6	85

Table 4. Laboratory Studies at Baseline and After Cisplatin Therapy

Parameter	Baseline	After Cisplatin
Blood urea nitrogen, mg/dL	14 ± 4.5	15 ± 3.8
Creatinine, mg/dL	0.82 ± 0.20	0.85 ± 0.22
Potassium, mg/dL	4.1 ± 0.4	3.9 ± 0.4
Phosphorus, mg/dL	4.4 ± 0.4	4.2 ± 0.4
Calcium, mg/dL	8.8 ± 0.9	8.6 ± 1.1
Magnesium, mg/dL	2.2 ± 0.6	1.4 ± 0.4

1 hypomagnesaemia. The method for magnesium measurement was spectrophotometric assay. This finding was the most common major side effect.

Eighty-five patients (85%) had nausea and 78% had vomiting, which began within the first hours of cisplatin administration and lasted up to 24 hours. In 19 patients, the symptoms continued up to 72 hours after the end of treatment, requiring more anti-emetic therapies. Eight patients (8%) had hearing loss, 2 of whom were women with bilateral hearing loss who had ovarian cancer, receiving cisplatin at a dose of 75 mg/m^2. The other cases were in the men with nasopharyngeal cancer and germ cell tumor, who had unilateral hearing loss. Five patients (5%) experienced tinnitus. Taste change was observed in 10% of the patients, but all of them were minimal and resolved spontaneously. Twenty patients (20%) had anorexia and fatigue, and 8% had cramping abdominal pain. Hepatotoxicity, serum electrolyte imbalances (except for hypomagnesaemia), diarrhea, severe allergic reactions, difficulty in walking, and chest pain were not observed.

DISCUSSIONS

Reviewing the literature for renal toxicity due to cisplatin administration, the majority of reports were different from our findings. In an Indian study, cisplatin nephropathy was observed with a high prevalence.[20] Hypokalemia (95%) and hypocalcaemia (89%) were the most common findings followed by hypomagnesaemia (60%), hypophsphatemia (57%), and significant elevation of serum creatinine level. In comparison to our study, the number of patients were limited (18 cases), and in our study, the only renal toxicity was hypomagnesemia. Another study reported a high prevalence of hypomagnesaemia due to cisplatin administration up to 90% of the patients, which was completely different from our result.[22] In the study of Zekri and coworkers, the most common renal toxicity was hypomagnesemia in 40% of the cases, which were severe and needed replacement therapy, but hypocalcaemia and hypokalemia were minimal and did not need supplement therapy.[23] The study of Skinner and coworkers showed a decrease in GFR of 58% of the patients, hypomagnesaemia in 32%, and hypocalcaemia in 16%.[24] Acute kidney failure occurred in 2 cases, and one patient needed peritoneal dialysis and cisplatin discontinued. Tetany does not occur in any patients and there is no need for long-term supplement administration of magnesium.[25]

In another study, the rate of renal toxicity with high-dose (120 mg/m^2) cisplatin therapy was 36% and with moderate-dose (60 mg/m^2), it was 19%.[26] Panichpisal and colleagues showed cisplatin-induced nephrotoxcity in 3 groups of patients regarding hydration before cisplatin administration: normal saline alone, normal saline plus furosemide, and normal saline plus manitol. The 24-hour creatinine clearance was measured before and on day 6 after cisplatin infusion. The toxicity was more prominent in patients who were hydrated with normal saline plus manitol.[26] A case report and review of 13 cases with cisplatin administration demonstrated a rare renal toxicity of hypokalemic metabolic alkalosis with hypomagnesemia and hypocalcemia.[27] In this report, permanent nephrotoxicity after many years of cisplatin administration was observed.

One of the less common renal toxicities is renal salt wasting syndrome, seen in 1% to 10 %.[28,29] In one study, the salt wasting syndrome involved 10

of 17 patients, all of whom had symptoms such as volume depletion and hyponatremia, mental confusion (2 cases), and seizure (1 case).[30]

In our study, the toxicity scoring system was the use of Cancer Therapy Evaluation Program grading system (version 3.0) of the National Cancer Institute (Tables 1 and 2).[20] In the study of Stohr and coworkers, the rate of hypomagnesemia was 14.4 %, and elevation of serum creatinine and decreased GFR were seen in none of the patients.[31] However, our study revealed the low prevalence of nephrotoxicity and nephropathy was limited to hypomagnesemia, and all of which were grade 1 toxicity without any magnesium replacement therapy required. We did not have any significant abnormality in GFR or rising in creatinine.

The limitations of our study were small number of patients, investigating different types of malignancy, and short duration of follow-up. Larger studies are needed to understand the renal side effects of cisplatin among the Iranian cancer patients treated with cisplatin.

CONCLUSIONS

This study showed that renal toxicity associated with cisplatin administration was limited to hypomagnesaemia among the Iranian patients with cancer. This study and other studies in similar populations documented different side effects in different settings.

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CONFLICT OF INTEREST

None declared.

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Correspondence to:
Mohammadali Mashhadi, MD
Hematology- Oncology Department, Zahedan University of Medical Sciences, Zahedan, Iran
Tel: +98 915 341 1445
E-mail: dralimashhadi@yahoo.com

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