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Ifosfamide Nephropathy in Patients With Sarcoma

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Introduction. Ifosfamide is an alkylating agent, frequently used in the treatment of sarcoma. Major side effects of ifosfamide are classified as nephropathy, neuropathy, and hematologic complications. The aim of present study was to determine the frequency and severity of ifosfamide nephropathy in patients with various types of sarcoma.
Materials and Methods. Ninety patients (52 males and 38 females) who had received ifosfamide chemotherapy for sarcoma were included in this study. Data on physical examination, laboratory studies, and estimation of glomerular filtration rate were collected. The median duration of follow-up was 6 to 12 months. Records of documented nephropathy were identified in these patients.
Results. The age range of patients on ifosfamide was 5 to 59 years. Thirty-four of the patients were children and 56 were adults. The most common renal side effects were proteinuria (15.5%), glycosuria (7.8%), elevation of serum creatinine (2.2%), hematuria (14.4%), and combination of proteinuria and glycosuria (5.5%). None of the patients had gross hematuria, but microscopic hematuria was present in 14.4%.
Conclusions. Ifosfamide nephropathy was seen with different degrees of severity in patients with sarcoma. Monitoring of the side effects of ifosfamide should be revised in different populations.

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INTRODUCTION

Ifosfamide is an alkylating agent frequently used in the treatment of sarcoma and hematologic malignancy.[1] Important renal side effects of ifosfamide are hemorrhagic cystitis, Fanconi syndrome, proximal tubular damage, and decreased glomerular filtration rate.[2-5] Assessment of nephropathy during ifosfamide therapy is based on conventional tests of kidney function such as measurement of blood urea nitrogen, plasma electrolyte, urinalysis, and serum creatinine.[6] The incidence of ifosfamide nephrotoxicity has been estimated by various authors as ranging from 1.4% to 60%.[7]

The aim of the present study was to determine the frequency of renal side effects of ifosfamide in a large group of Iranians patients with various types of sarcoma. In the review of the literature, such reports were discrepant and vary from minimal toxicity up to major toxicity.[7]

MATERIALS AND METHODS

In a prospective study from 2007 to 2009, we enrolled 90 patients of various types of sarcoma including rhabdomyosarcoma, osteogenic sarcoma, and soft tissue sarcoma. All of the patients were assessed before and then monthly after initiation of treatment with ifosfamide. Other administered drugs were adriamycin, vincristine, and etoposide. These drugs do not cause any major renal toxicity.

Complete blood count, blood urea nitrogen, serum creatinine, serum calcium, serum phosphorus,

serum sodium, serum potassium, serum uric acid, and urinalysis were measured at baseline and during the follow-up studies. The method for determination of proteinuria was the use of sulfasalicylic acid.

After establishment of an intravenous line and pretreatment medication (maintenance fluid and electrolyte/age + 1 L/m^2 saline solution per 24 hours), granisetron was administered 30 to 60 minutes before initiation of chemotherapy. Ifosfamide therapeutic dose was 10 g/m^2 per course in adults and 8 g/m^2 to 10 g/m2 per course in children. An equal dose of Mesna was used in all of the patients. Laboratory evaluation after chemotherapy sessions included measurement of blood urea nitrogen and serum levels of creatinine, phosphorus, uric acid, sodium, and potassium. Urinalysis was performed macroscopically using dipstick and microscopically. Glomerular filtration rate was calculated using the Cockroft-Gault formula for adult patients and the following formula for children: 0.41 × (height/serum creatinine). In patients who demonstrated any abnormalities of the above parameters, additional determinations of 24-hour protein, arterial blood gas, and creatinine clearance were performed, as necessary.

The grade of toxicity was determined according to the National Cancer Institute common toxicity criteria.[8]

RESULTS

Ninety patients (52 males and 38 females) were entered in this study. The age range was 5 to 59 years, and 34 were children and 56 were adults. All of the patients at initial evaluation had normal serum creatinine, urinalysis, and electrolyte levels.

The most important toxicity episodes were as below: after the 1st cycle of ifosfamide therapy, 2 patients (2.2%; 1 male and 1 female) developed rising in serum creatinine, which normalized before treatment cycle without intervention. Nephrotoxic effect of ifosfamide was seen even in much lower doses of drug. The grade of toxicity according to the National Cancer Institute common toxicity criteria was 1.

Proteinuria was detected in 14 (15.5%) of the patients (6.7% of the males and 8.8% of the females), 5 of whom were children and 9 were adults (P = .02; Tables 1 to 3). Glycosuria developed in 7 patients (7.8%), 2 of whom were males and 5 were females. All of them had a positive test in a single cycle (Tables 1 and 3). Both glycosuria and proteinuria were detected in 5 female patients (5.5%), of whom 2 were children (2.2%) and 3 were adults (Tables 1 and 3).

Table 1. Nephropathy in Different Age Groups*

Nephropathy	Age, y			
	5 to 10	11 to 15	≥ 16	*P*
Proteinuria	4 (4.4)	3 (3.3)	7 (7.8)	.39
Glycosuria	4 (4.4)	1 (1.1)	2 (2.2)	.03
Proteinuria and glycosuria	2 (2.2)	1 (1.1)	2 (2.2)	.22

*Values in parentheses are percents.

Table 2. Nephropathy by Sex*

Nephropathy	Sex		*P*
	Male	Female	
Proteinuria	6 (6.7)	8 (8.9)	.01
Glycosuria	2 (2.3)	5 (5.5)	.11
Proteinuria and glycosuria	0	5 (5.5)	.18
Elevated creatinine	1 (1.1)	1 (1.1)	.67

*Values in parentheses are percents.

Table 3. Nephropathy in Adults and Children*

Nephropathy	Patients		*P*
	Children	Adults	
Proteinuria	5 (5.5)	9 (10.0)	.02
Glycosuria	4 (4.4)	3 (3.3)	.31
Proteinuria and glycosuria	2 (2.2)	3 (3.3)	.31
Elevated creatinine	0	2 (2.2)	.16

*Values in parentheses are percents.

Hypophosphatemia was detected in 2 patients (2.2%) with a grading of 1, which was resolved before the next cycle and did not repeat in another cycle. Hematuria was detected in 13 patients (14.4%), but all of them had microscopic hematuria which stopped spontaneously without any specific management. Hematologic toxicity was seen in 21 patients (23.3%), all of which were grade 1 toxicity.

DISCUSSION

The results of the present study showed a low incidence of nephrotoxicity due to ifosfamide therapy. In our previous study, we did not observe any significant toxicity in patients who received ifosfamide, and the most common and only significant toxicity was hematuria.[1] The frequency of ifosfamide nephrotoxicity has been estimated

by various authors as ranging from 1.4% to 60%, and reported with various toxicity levels.[7,9-12]

Stohr and coworkers[3] showed 4.6% tubulopathy, 41% in males and 59% in females. Elevated serum creatinine was reported in another study in 0.33% of the patients, with grade 2 toxicity according to National Cancer Institute's common toxicity criteria.[8] The study of McCune and colleagues[9] revealed an overall nephropathy of 21% (11% in children and 10% in adults). In this study, age did not have any significant relation with toxicity.

Lee and colleagues[13] demonstrated 32.3% tubulopathy, 32.3% proteinuria, 8.1% glycosuria, and 11.3% elevated serum creatinine. In Loebstein and associates'study,[14] these rates were 41.4% for tubulopathy, 40% for proteinuria, 51% for glycosuria, and, 6.3% for elevated creatinine. In this study the major risk factor was an age greater than 5 years old. In the study of Ferrari and colleagues,[15] the most frequent findings were elevated serum creatinine (21%; 5 adults and 4 children), glycosuria (86%; 17 adults and 20 children), proteinuria (67%; 12 adults and 17 children). The overall nephropathy was 45% (19 cases). In this study, the prevalence of toxicity was the same in pediatric and adult patients.

We compared our study with these studies; differences in every population were apparent. In our study, the rise in creatinine was 2.2%, but in the above studies, elevation in creatinine was between 6.3% and 21%.[13-15] Proteinuria was seen in 15.5% of our cohort, while it was more frequent in those studies (32% to 67%).[13-15] The glycosuria was documented 7.8% of our patients, compared to 8% to 86% in those studies.[13-15] The present study also revealed more frequent nephrotoxicity in pediatric patients, but in a study conducted by McCune and colleagues, there was no correlation between ifosfamide nephropathy and age (11% versus 10% in adults and children, respectively).[9]

CONCLUSIONS

Our study showed a low incidence of ifosfamide nephropathy in Iranian patients undergoing chemotherapy for sarcoma. However, specific attention is required in children. Several studies on different populations revealed the wide spectrum of toxicity. These geographic discrepancies were reported in two separate studies by our group.[1,16] This study documented that every population shows different toxicity rates with a single chemotherapeutic agent.

CONFLICT OF INTEREST

None declared.

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