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Renal Function Following Combination Chemotherapy With Ifosfamide and Cisplatin in Patients With Osteogenic Sarcoma

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Background. Ifosfamide and cisplatin are active agents that are currently used in the treatment of osteosarcoma. Nephrotoxicity has been reported following their use in combination and alone. This study evaluates renal function in children and adolescents (median age 16 years) at least 3 months following completion of a chemotherapy regimen which included 54 g/m^2 ifosfamide, 360 mg/m^2 cisplatin, doxorubicin, and high-dose methotrexate. ***Procedure.*** Mean glomerular filtration rate (GFR) was determined by inulin or iothalamate clearance; proximal tubular function was evaluated by measuring fractional excretion of glucose (FEglu), tubular maximum phosphate reabsorption per GFR (TMP/GFR), FE of urate, and 24-hour amino acid excretion. Distal tubular function was evaluated by 24-hour urinary calcium, FE of magnesium, and urinary osmolality after water deprivation. Twenty-four-hour urinary protein excretion was measured. ***Results.*** The mean GFR was 97 ml/min/l.73 m^2. Although 10 of 24 patients had GFRs lower than normal, the lowest value was only 22% below the lower limit of normal and would not account for any clinical compromise. Proximal tubular function evaluation revealed normal FEglu, normal mean TMP/GFR values, and high FE of urate (15.7%). Two of twenty-four patients were shown to have mild generalized aminoaciduria. Distal tubular function evaluation showed normal 24-hour urinary calcium levels (mean 3.4 mg/kg) and FE of magnesium as well as normal urinary osmolality. Twenty-four-hour urinary protein excretion was normal in all patients. ***Conclusions.*** The lack of clinically significant renal abnormalities observed in patients who received combination chemotherapy with ifosfamide and cisplatin for osteosarcoma is encouraging for future osteosarcoma protocol development. Med. Pediatr. Oncol. 32:93–96, 1999. © 1999 Wiley-Liss, Inc.

Key words: nephrotoxicity; ifosfamide; cisplatin; osteosarcoma

INTRODUCTION

Ifosfamide and cisplatin are both active agents in the treatment of osteosarcoma. In the current cooperative group study for osteosarcoma, patients receive multidrug chemotherapy with cisplatin, doxorubicin, high-dose methotrexate, and are randomized to receive ifosfamide. Ifosfamide and cisplatin have both been associated with the development of nephrotoxicity [1–13]. The use of these agents together, either simultaneously or sequentially, has been reported to potentiate the nephrotoxicity of either agent alone. Goren et al. [14] found that the ifosfamide-induced increases of both urinary NAG and urinary total protein were most closely related to the number of prior doses of cisplatin (90–100 mg/m^2 per dose). Cisplatin-related potentiation of ifosfamide nephrotoxicity, in particular proximal tubular function, was reflected by low phosphate reabsorption [15,16]. Severe renal tubular toxicity was found in 7 of 15 patients treated with moderate doses of ifosfamide (30–48 g/m^2). This was attributed to the concomitant use of platinum derivatives, since this cumulative ifosfamide dose is generally not associated with significant tubular toxicity [17]. Other investigators also described potentiation of ifosfamide nephrotoxicity by previous or concomitant use of cisplatin [5,9,12,18].

The goal of this study was to evaluate systematically the proximal, distal, and overall tubular function and glomerular function at least 3 months following completion of therapy in children and adolescents with osteosarcoma who received a combination chemotherapy regimen which included cumulative doses of 54 g/m^2 ifosfamide and 360 mg/m^2 cisplatin.

MATERIALS AND METHODS

Twenty-four patients (16 females, 8 males) were evaluated at least 3 months (range 3–36 months, median

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Wk	0	3	4	5	8	9	10	13	14	15
	A	M	M	A	M	M	A	M	M	Surgery
	I			I			P			
Wk	17	20	21	22	25	26	27			
	A	M	M	A	M	M	A			
	I			I			P			
Wk	30	31	32	35	36	37	40	41	42	
	M	M	I	M	M	I	M	M	P	

Fig. 1. Chemotherapy schema. A = doxorubicin 25 mg/m^2/d × 3 days by 18–24 hour infusion; I = ifosfamide 1.8 g/m^2/d × 5 days with mesna; M = methotrexate 12 g/m^2 over 4 hours with leucovorin; P = cisplatin 120 mg/m^2.

9 months) following completion of a chemotherapy regimen for osteosarcoma which included ifosfamide and cisplatin. At their routine follow-up visit, all patients who had been treated on this chemotherapy regimen were given the opportunity to participate in our study. The sample of 24 patients represents all patients who agreed to participate and comprises 25% of patients enrolled on the chemotherapy protocol. The characteristics of these patients are not significantly different from the entire patient population treated for osteosarcoma in this study.

A schema of the chemotherapy regimen is shown in Figure 1. The patients ranged in age from 6 to 23 years (median 16 years). No patients received amphotericin B therapy or radiation therapy. All had normal renal function at the onset of treatment as determined by prechemotherapy serum creatinine levels and urinalysis. All patients or guardians gave written informed consent prior to evaluation. The evaluation protocol was approved by the Institutional Review Board.

Ifosfamide was administered as a 1-hour infusion of 1.8 g/m^2 daily for 5 days. Mesna was given at a dose of 360 mg/m^2 with ifosfamide, as a 3-hour infusion immediately following ifosfamide, and then as a bolus over 15 minutes every 3 hours for six additional doses. Cisplatin 120 mg/m^2 was given as a 4-hour infusion with normal saline and mannitol diuresis. Methotrexate was given over 4 hours at a dose of 12 g/m^2 (maximum 20 g) with hydration, alkalinization, and leucovorin rescue.

The mean cumulative dose of ifosfamide was 53 g/m^2 (range 36–54 g/m^2). Twenty-two patients received a cumulative dose of 54 g/m^2 of ifosfamide; one patient received a cumulative dose of 45 g/m^2 ifosfamide; and one patient received a cumulative dose of 36 g/m^2 ifosfamide. The mean cumulative dose of cisplatin was 322 mg/m^2 (range 120–360 mg/m^2). Eighteen patients received 360 mg/m^2 cisplatin, five received 240 mg/m^2 cisplatin, and one received 120 mg/m^2. Some of the planned chemotherapy was omitted due to cisplatin-induced hearing loss or because of ifosfamide-induced myelosuppression or infection.

Glomerular function was assessed by standard inulin clearance [19] in 17 patients and by iothalamate infusion in 7 patients [20]. Renal blood flow was determined in 17 patients by p-aminohippuric acid (PAH) clearance. Proximal tubular function was evaluated by the measurement of serum and urine concentrations of glucose, uric acid, and phosphate. Fractional excretions of glucose (FEglu), phosphate (as tubular maximum phosphate reabsorption per glomerular filtration rate [TMP/GFR]), and uric acid were calculated. FE of magnesium was calculated and the serum bicarbonate level was measured with investigation of renal bicarbonate handling only in patients who were acidotic. The 24-hour excretion of calcium, amino acids, and protein was measured in all patients. Urinary osmolality following overnight water deprivation was determined so as to evaluate the concentrating ability of the nephron. Routine urinalysis was performed, as was a general physical examination, with measurement of blood pressure.

RESULTS

Glomerular Function

Glomerular function analysis is detailed in Figure 2. The mean GFR was normal at 97 ml/min/1.73 m^2. Ten of the twenty-four patients had GFRs lower than normal; however, the lowest value was only 22% below the lower limit of normal. Seventeen patients had determination of renal plasma flow and filtration fraction; these were also normal with mean values of 450 ml/min/1.73 m^2 and 20%, respectively.

Proximal Tubular Function

The FE of glucose was normal in all patients, with a mean value of 0.10%. Seven of the twenty-four patients had urinary glucose measured by a method with a limit of sensitivity of 20 mg/dl and all were <20 mg/dl. The mean FE of urate was high at 15.7% with only six patients having normal values. The mean TMP/GFR was normal at 3.6 mg/dl. Figure 3 depicts the TMP/GFR values and FE of urate on a scattergram. Two patients had mild generalized aminoaciduria (with greater than twice the

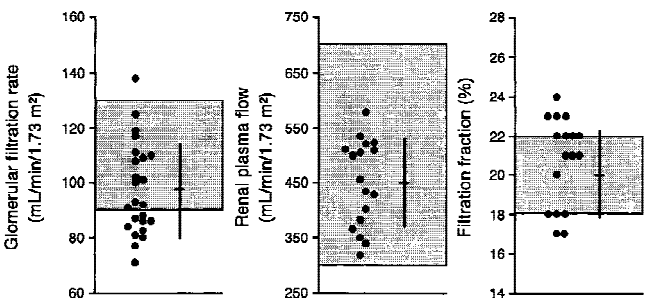

Fig. 2. Glomerular function parameters. Closed circles represent actual patient values. Shaded areas indicate the normal range. Lines represent mean values ± 1 standard deviation.

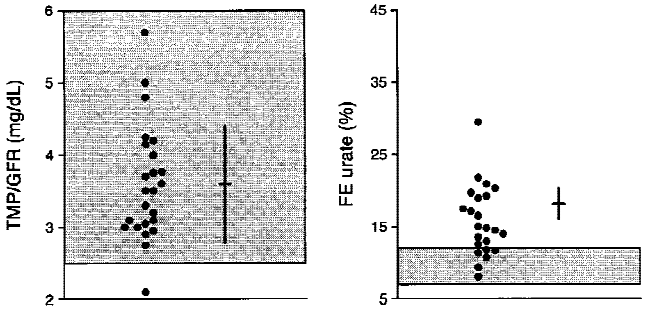

Fig. 3. Proximal tubular function parameters. Closed circles represent actual patient values. Shaded areas indicate the normal range. Lines represent mean values ±1 standard deviation.

normal excretion of more than half of the amino acids per 24 hours).

Distal Tubular Function

The mean 24-hour urinary calcium excretion was 3.4 mg/kg and the mean FE of magnesium was 4.4% (Fig. 4). Mean urinary osmolality after overnight water deprivation was 757 mOsm/kg. Four patients with urinary osmolality <600 mOsm/kg had not maintained water deprivation overnight.

Other Findings

The 24-hour urinary protein excretion was normal in all patients (one patient did not have a determination). Serum bicarbonate and calcium levels were normal in all patients. There was no correlation between the abnormal parameters noted among the patients (i.e., those patients with the lowest GFRs were not necessarily the same group who had elevated amino acid or calcium excretion). All patients had normal blood pressures and urinalyses.

DISCUSSION

In this group of patients with osteosarcoma treated with both cisplatin and ifosfamide, there were clinically insignificant abnormalities suggestive of mild tubular and glomerular dysfunction. Elevation of the FE of urate was the most constant finding in all the patients. However, urate handling is very complex. It is difficult to localize renal damage to any particular part of the nephron on the basis of urate handling abnormalities. The mild aminoaciduria seen in two patients would suggest a mild proximal tubular leak. However, this aminoaciduria is not clinically significant and the normal glucose and phosphate handling suggests that the proximal dysfunction is minimal, and this aminoaciduria is not clinically significant. The somewhat low GFRs are the most notable clinical laboratory abnormality detected. However, the lowest GFR observed would not result in a decrease of any routinely used drugs. In contrast to findings of investigators quoted earlier, we did not detect any abnormalities in renal phosphate handling.

Hacke et al. [5] investigated the nephrotoxicity of CDDP with or without ifosfamide in a randomized trial of patients with disseminated testicular cancer. They showed a normal GFR in both groups following therapy. A 200-fold increase in the β2 microglobulin excretion was noted in the ifosfamide group, whereas a 10-fold increase was noted with the non-ifosfamide regimen. Although magnesium and phosphate handling was not analyzed, they concluded that combination regimens including both ifosfamide and CDDP can be used without major risk of acute or chronic renal insufficiency. Canpolat et al. [21] evaluated ifosfamide tolerance in 20 patients with relapsed osteosarcoma who had previously been treated with large single and cumulative doses of cisplatin. Although 14 of 20 patients intermittently had variable amounts of glycosuria, phosphaturia, and/or proteinuria during ifosfamide therapy, they were not major, did not result in symptoms, and did not require discontinuation of therapy. Their conclusion was that, provided a creatinine clearance of 60 ml/min/m^2 is accepted as a prerequisite for treatment, ifosfamide can be given safely to most patients treated previously with CDDP.

CONCLUSIONS

We have previously reported a detailed analysis of renal function in patients following a cumulative dose of 72 g/m^2 ifosfamide without CDDP [22]. The renal function in that group of patients was similar to the group described here with a planned cumulative dose of 54 g/m^2 ifosfamide and 360 mg/m^2 CDDP. This suggests that giving three cycles of CDDP together with a slightly reduced cumulative dose of ifosfamide is safe for patients with osteosarcoma. The difference between our results and those of others may be related to the older median age of our patients, lower cumulative doses of ifosfamide and CDDP, the longer interval between ifosfamide courses, and the fact that ifosfamide and CDDP

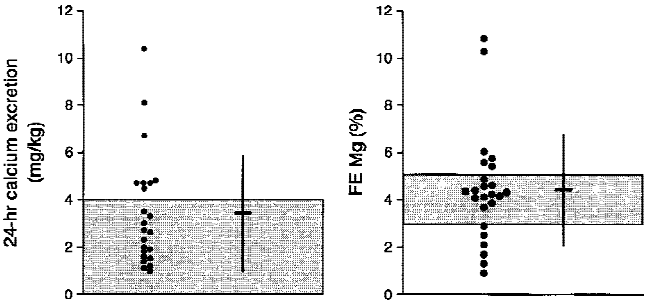

Fig. 4. Distal tubular parameters. Closed circles represent actual patient values. Shaded areas indicate the normal range. Lines represent mean values ±1 standard deviation.

were not given simultaneously. It is encouraging, however, that in this effective treatment regimen for osteosarcoma, there is no evidence of significant nephrotoxicity following completion of therapy, although the patients will require long-term follow-up to detect very late effects on renal function.

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