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Ifosfamide Tolerance in Osteosarcoma Patients Previously Treated With Cis-Diamminedichloroplatinum-II: Renal, Hematologic, and Neurologic Observations

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We attempted to ascertain renal, hematologic, and neurologic tolerance to ifosfamide (IFX) in pediatric patients previously treated with large single and cumulative doses of cis-Diamminedichloroplatinum-II (CDP) for osteosarcoma (OS). Twenty OS patients were treated with CDP: initially 150 mg/m^2 was administered every 2 weeks for a maximum of seven courses. Later, other agents, including additional CDP, were also administered. Twelve patients were treated with intra-arterial CDP, one with intra-arterial, and later intravenous CDP, and seven with intravenous CDP. Patients who relapsed were treated with IFX. Renal function was monitored by measuring creatinine clearance, serum electrolytes, total protein, albumin and CO_2 content, and urine analysis during IFX therapy. Prior to initiation of IFX, creatinine clearance was above 60 ml/min/m^2 in all except one patient who had developed a hemolytic uremic syndrome (HUS). Cumulative CDP doses ranged from 300 to 22,500 mg/m^2, and cumulative IFX doses 12 to 128 gm/m^2. Myelosuppression was monitored by obtaining routine hemograms midway between each course of treatment. Neurologic tolerance was assessed by reviewing the medical records for any abnormality. The interval between CDP and IFX ranged from 1 to 64 months. All patients experienced a progressive reduction in creatinine clearance with CDP. The reduction in creatinine clearance, measured from baseline after three to four courses varied from 10 to 53.7%, after four to seven courses from 19 to 78%, and after seven courses from 12 to 80.5%. In all patients except five, including the HUS patient, creatinine clearance remained above 60 ml/min/m^2 during IFX therapy. Twelve patients developed hypomagnesemia in the vicinity of 1.4 to 1.6 mg/dl during CDP treatment and required magnesium supplementation. They were asymptomatic and the abnormality did not affect IFX tolerance. Fourteen patients intermittently displayed variable degrees of glycosuria, phosphaturia, and/or proteinuria during IFX therapy. This was considered to be a forma frustre type of Fanconi's syndrome. Approximately 80% of courses of IFX were associated with reversible myelosuppression. No neurologic abnormalities were detected. The abnormalities detected during IFX treatment were not major, did not give rise to symptomatology, and did not require discontinuation of therapy. Renal abnormalities were considered a forma frustre type of Fanconi's syndrome. Provided a creatinine clearance of 60 ml/min/m^2 is accepted as a prerequisite for treatment, and no major preexisting renal disease is present, IFX is well tolerated by most patients previously exposed to very high cumulative doses of CDP.

Key words: osteosarcoma, cis-Diamminedichloroplatinum-II, ifosfamide, renal, tolerance

INTRODUCTION

Cis-Diamminedichloroplatinum-II (CDP) and Ifosfamide (IFX) are chemotherapeutic agents with established activity against many solid tumors, particularly osteosarcoma [1–9]. Both agents may cause common side effects, the most significant of which are nephrotoxicity, hematotoxicity and neurotoxicity. Nephrotoxicity is the most important side effect of CDP [10–19] while myelotoxicity, particularly anemia, is probably related to cumulative dose. Neurotoxicity is more common in adults [19–22]. The side effects of IFX comprise myelosuppression, neurotoxicity, and renal dysfunction [23–35]. Myelosup-

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pression is usually reversible. The latter may also enhance neurotoxicity [28]. In addition, the prior administration of CDP may aggravate tubular nephrotoxicity [29].

In the Pediatric Department of the M.D. Anderson Cancer Center, four CDP based protocols have been utilized as initial treatment for patients with osteosarcoma. The protocols have been designated TIOS I, II, III, IV (*T*reatment and *I*nvestigation of *O*steo*s*arcoma). In TIOS I, II, and III, CDP was administered pre-operatively by the intra-arterial route [1–4] and in TIOS IV by the intravenous route [5]. The intravenous route was also later used post-operatively in TIOS I (vide infra). All protocols utilized Adriamycin. Protocols I, II, and IV utilized high dose methotrexate with leucovorin "rescue" and Protocol III, cyclophosphamide. Patients who relapsed after treatment with the TIOS protocols (pulmonary metastases) were treated with IFX. This sequence of treatment provided an opportunity to review the renal, hematologic, and neurologic tolerance of patients treated initially with CDP and later IFX.

MATERIALS AND METHODS

Among 120 osteosarcoma patients treated on the TIOS protocols, we identified 20 patients between 5–16 years of age (median 14 years) who were treated initially with CDP and later, upon relapse, with IFX. Twelve were treated with intra-arterial CDP, one with intra-arterial followed by intravenous CDP upon the detection of pulmonary metastases which were present in retrospect (TIOS IV), and seven with intravenous CDP. One of the latter seven was treated with the TIOS IV protocol while in the remaining six, the intra-arterial route was considered unsuitable for therapy for the following reasons: young age (2) and tumor site (4); spine (1), jaw (2), and multiple tumors (1) (clavicle, humerus, and lung). The latter patient was also treated with the TIOS IV protocol. The effects of CDP on renal function in these 20 patients was similar to that observed in the previously reported total series [4].

Pretreatment requirements for CDP comprised normal values of the hemogram and serum liver function, electrolyte, calcium, and magnesium studies. Normal renal function was established by demonstrating a normal serum creatinine, blood urea nitrogen (BUN), creatinine clearance above 60 ml/min/m^2, and urine analysis. These studies were repeated prior to each course of CDP. The latter was only administered if all values were within normal limits and the creatinine clearance, despite progressive reduction during treatment, remained above 60 ml/min/m^2.

The dose of CDP utilized in all the TIOS protocols was constant: 150 mg/m^2 administered at two weekly intervals for a maximum of seven courses. Subsequently, the same dose was administered intravenously at 3 monthly intervals for approximately 9 months in TIOS I and intra-arterially in TIOS II for approximately 20 months [4]. In TIOS III and TIOS IV, CDP was limited to seven initial intra-arterial and intravenous courses respectively. To our knowledge, the single and cumulative doses of CDP utilized in these protocols are higher than those administered by other investigators.

The administration of CDP (by the intra-arterial or intravenous route) was accomplished with prehydration utilizing 5% dextrose in 0.5% saline 24 hours prior to the CDP infusion. The prehydration infusion was administered at a rate to deliver a fluid intake of 3 L/m^2/24 hours. Prior to the administration of CDP, the fluid intake was augmented to administer 2 liters of 5% dextrose in 0.5% saline over 8 hours. This was followed by 500 ml of the same infusion (reduced to 250 ml in children under 6 years of age) in the ninth hour. Immediately prior to the intravenous CDP infusion, 50 ml of 20% mannitol (reduced to 25 ml in children under 6 years) was administered intravenously over 15 minutes. CDP was then administered. The 150 mg/m^2 dose was diluted in 300 ml of normal saline (reduced to 200 ml in children under 6 years) for administration over 2 hours. After completion of the infusion, the intravenous infusion was altered to administer 1,000 ml of 5% dextrose in 0.5% saline plus 200 ml of 20% mannitol for delivery over 8 hours. In the ninth hour, it was replaced by 1 liter of 5% dextrose in 0.5% saline with 10 ml of 10% calcium gluconate, 10 ml of 50% magnesium sulfate, and 20 mEq of potassium chloride and infused at 3 1/m^2/24 hours. This was administered as a maintenance infusion for 2 days after treatment. Pretreatment studies were also repeated daily during the post therapy (hydration) phase.

The dose of IFX was similar to that generally utilized in pediatric patients. Initially, in a pilot study 2 gm/m^2/day was investigated in four patients; subsequently, 1.8 gm/m^2 for 5 days was adopted as the standard treatment for all patients. It was administered as a "pulse" over 1 hour together with MESNA (2-mercaptoethane sulfonate) 360 mg/m^2 as a uroprotectant. That was followed by a maintenance infusion of 5% dextrose in 0.5% normal saline at 3 L/m^2/24 hours. Additional MESNA (360 m/m^2) over 3 hours was then administered. Thereafter, 3 hours later, three more identical MESNA doses over 15 minutes were administered, each dose being 3 hours apart.

Pretreatment requirements for IFX comprised a hemogram with a minimum white blood count of 2,000/mm^3 and a total phagocyte count of 1,000 or above (neutrophils, bands, and monocytes), hemoglobin above 8 gms% and a platelet count above 75,000/mm^3. All patients were required to have an absence of renal disease and satisfactory renal function as manifested by normal electrolytes, BUN, creatinine, urine analysis, and a 12-

or 24-hour creatinine clearance above 60 ml/min/m^2. Initial normal renal function was also established by a normal serum CO_2 content, and the absence of hypophosphatemia (as determined by serum phosphate), proteinuria, glycosuria, and hematuria (as determined by dipstix analysis).

IFX was administered at 3 to 4 weekly intervals, depending upon the hemogram (most courses were administered at 3 weekly intervals). Hemograms were obtained in the intervals between each course to determine the degree of myelosuppression. The first hemogram was obtained 10 days from initiation of treatment and was repeated at 2–3 day intervals until an elevation in the different components was observed. This permitted an opportunity to determine the nadir of myelosuppression. All patients were in a satisfactory state of health prior to *initiation* of CDP and IFX. Tolerance to IFX and the impact of prior treatment with CDP were determined by recording cumulative dose of CDP and IFX and renal status prior to and after treatment with each drug. Hematologic function during IFX therapy was determined by noting the value of the hemoglobin, white blood count, and platelet count prior to and during treatments. Neurologic function was assessed clinically by reviewing the records for any abnormality. No patient received furosemide or a nephrotoxic antibiotic during IFX therapy.

The creatinine clearance (glomerular function) was adopted as the major parameter of renal function for CDP: values were examined after three to four courses, after four to seven courses and after seven or more courses. These time frames had been utilized in previous studies to determine the efficacy of treatment and were arbitrarily selected to attain a consistent comparison [3,4]. Similarly, creatinine clearance prior to, and after completion of IFX therapy, was also examined. Other parameters to determine renal function during IFX therapy comprised estimations of the serum phosphate, sodium, protein, albumin, magnesium, and carbon dioxide content and a search for proteinuria, glycosuria, and hematuria.

Treatment with the TIOS and IFX protocols was administered under informed consent and each protocol was approved by the Institutional Review Board.

RESULTS

Cis-Diamminedichloroplatinum-II

One hundred and thirty-three courses of CDP were administered. The total cumulative CDP dose varied from 417 mg to 3,127 mg and 300 to 22,500 mg/m^2. All patients experienced a reduction in creatinine clearance. The abnormality was directly proportional to the cumulative dose of CDP and could clearly be demonstrated by arbitrarily examining the results after three to four courses, after four to seven courses, and after seven or more courses. The baseline creatinine clearance and the magnitude of the reduction are depicted in Table I and the median values and range in Table II and Figures 1 and 2. The reduction in the baseline pretreatment creatinine clearances after three to four courses varied from 10 to 53.7% and after four to seven courses from 19 to 78%. (Four courses were previously found to be the minimum number required to produce a satisfactory therapeutic effect [3]). Only five patients received seven or more courses with a reduction in the baseline from 12 to 80.5%. Twelve patients experienced reductions in serum magnesium despite supplemental magnesium therapy. These reductions persisted during IFX therapy. There were no complications attributable to hypomagnesemia and all patients except one, by their own volition during IFX therapy, discontinued oral magnesium supplementation; there was no change in the serum magnesium levels and no clinical side effects.

Ifosfamide

The interval between termination of CDP and initiation of IFX varied from 1 to 64 months (mean 16.73, median 6). A total of 136 courses (mean 6.8, median 4) was administered. Over 80% of the courses were delivered at 3 weekly intervals; in the others, because of occasional episodes of myelosuppression, a delay up to 1 week was permitted to accommodate pre-therapy requirements. The cumulative IFX dose ranged from 21.12 to 180 gm and 12 to 128 gm/m^2. At initiation of IFX therapy, the creatinine clearance was above 60 ml/min/m^2 in all patients except one who previously had experienced an attack of the hemolytic-uremic syndrome (HUS). Upon recovery, his creatinine clearance was 50.13 ml/min/m^2 (patient #1). Because of progressive enlargement of pulmonary metastases and with informed consent, it was considered appropriate to attempt treatment with IFX.

The above patient developed a progressive elevation in the serum creatinine, potassium, and BUN with increasing evidence of renal dysfunction finally manifesting as oliguria. The creatinine clearance was reduced from 50.13 to 18 ml/min/m^2. However, there was no evidence of the de Toni Fanconi Debrè syndrome (Fanconi's syndrome).

From a clinical perspective all patients tolerated treatment extremely well. However, a reduction in creatinine clearance below 60 ml/min/m^2 was encountered in four other patients (Table I). One of the four patients developed renal failure 10 days after the second course of IFX (patient #20). Details of the event unfortunately were sparse: her condition and renal status after the first two treatments with IFX were satisfactory; however, she apparently developed oliguria 2 weeks after the second course and was treated by a family practitioner in Mexico. The oliguria resolved and upon return to M.D.

TABLE I. Renal Function and Cumulative Dose in Patients Treated With cis-Diamminedichloroplatinum (CDP) and Ifosfamide (IFX)

Patient	Cr Cl[a] before CDP (ml/min/m^2)	Cr Cl afer CDP (ml/min/m^2)	% Reduction Cr Cl	Total cumulative dose CDP		CDP-IFX interval (months)	Cr Cl before IFX (ml/min/m^2)	Cr Cl after IFX (ml/min/m^2	% Reduction Cr Cl	Total cumulative dose IFX	
				mg	gm/m^2					gm	gm/m^2
1	170	72	78	1,350	750	3	50.13	18	64	74	40
2	93	50	53.7	1,425	750	19	81.62	52.8	35	121.6	60
3	161	87.3	71	640	1,050	2	161	144	11	24.4	40
4	104	61	42	3,127	22,500	48	91.76	69.9	24	27.8	20
5	155	131	15	1,490	1,050	3	82.28	65.34	21	102.24	72
6	119	67.8	48	1,522	1,050	42	71.4	61.0	15	178.35	128
7	149	82	45	2,739	16,500	64	94.7	51.3	46	99.6	60
8	128	99.45	32	2,200	1,050	6	90.6	90	0.01	147	70
9	147	96.2	35	1,000	750	23	169	167	1.2	39.9	30
10	169	137.5	19	1,648	1,050	1	128.7	108	26	62.8	40
11	230	126	45	417	300	3	151	189	—	21.12	15
12	175	85	52	1,440	900	2	106	79.92	25	48	30
13	101	89.6	12	1,155	1,500	10	96	68.2	29	77	100
14	129	67	48	825	750	3	108	75.36	30.2	110	100
15	123	72	42	1,890	1,050	37	70.5	77.5	—	180	100
16	331	115	65	1,530	1,050	39	133	128	3.8	119	70
17	148	70	53	2,364	1,200	7	82	77	7	51.22	26
18	119	112	6	1,440	1,050	15½	75	86.25	25	16.56	12
19	147	62	58	1,963	1,050	3	69.4	46.2	33	71.06	38
20	140	49	65	1,638	1,050	4	62	1	98	28.08	18

[a]Creatinine clearance.

TABLE II. Median and Range Values Following Treatment With cis-Diamminedichloroplatinum-II (CDP) and Ifosfamide (IFX)

Variable	Range		
	Low	High	Median
CDP			
Baseline creatinine clearance	93	310	147
% Decrease in creatinine clearance			
after 3–4 courses	10	53.7	42
after 4–7 courses	19	78	42
after 7 or more courses	12	80.5	42
Cumulative dose (mg/m^2)	300	22,500	1,050
Number of courses	2	15	7
Interval			
Months between CDP and IFX	1	64	6
IFX			
% Decrease in creatinine clearance	0.01	98	25
Cumulative dose (gm/m^2)	12	10.0	38
Number of courses	2	18	4
Difference in total serum protein before and after IFX (gm/dl)	−1.30	+2.70	0.6
Difference in serum albumin before and after IFX (gm/dl)	−1.0	+2.20	0.5
Difference in serum CO_2 before and after IFX	−7.0	+8.0	2.0

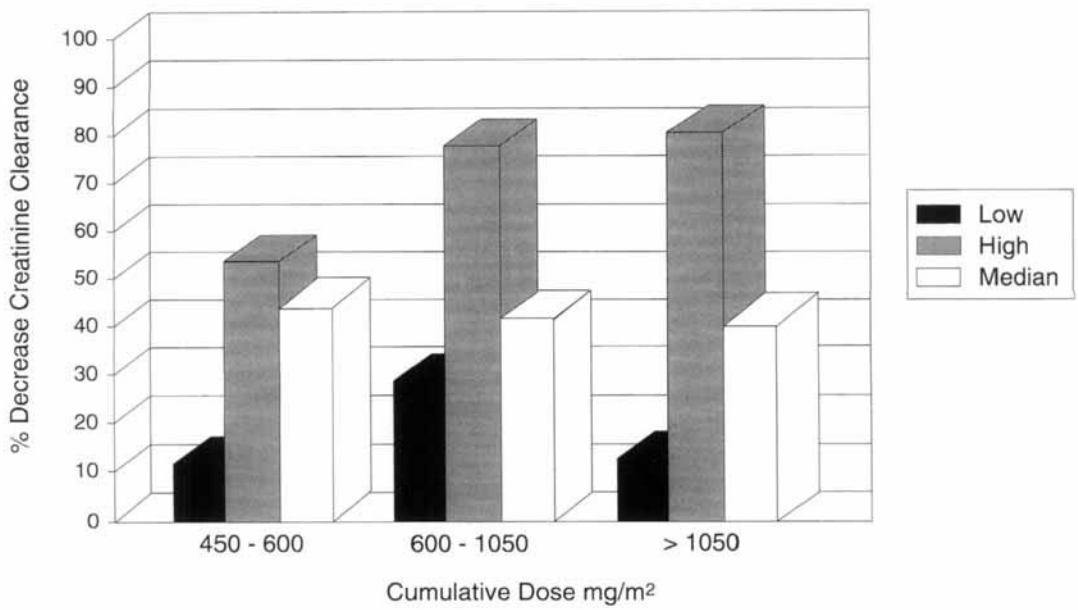

Fig. 1. Decrease in creatinine clearance with cis-Diamminedichloroplatinum-II. Percentage decrease in creatinine clearance after three to four courses (450–600 mg/m^2), after four to seven courses (600–1,050 mg/m^2), and seven or more courses (>1,050 mg/m^2) of CDP. Key indicates low, high, and medium values.

Anderson Cancer Center approximately 2 weeks later, a serum creatinine of 14 and a BUN of 36 were noted. The cause was undetermined; the only details which could be ascertained with certainty was the development of nausea and vomiting followed by oliguria (? acute tubular necrosis) several days after discharge. An infection was suspected and she was treated with a variety of medications which, in addition to the infection, could have been contributory. She is currently (2 years later) in chronic renal failure, requires daily peritoneal dialysis, and is awaiting a renal transplant.

The three other patients developed a modest reduction in the creatinine clearance from 69.4 to 46.2 cc/min/m^2, 81.62 to 52.8 cc/min/m^2, and 94.7 to 51.3 cc/min/m^2, respectively. The reduction in creatinine clearance was not associated with any side effects or an abnormality in the serum sodium or potassium. The effects of the cumulative doses of IFX on creatinine clearance are illustrated in Tables I and II and Figures 3 and 4.

Fourteen patients intermittently developed variable degrees of renal tubular abnormalities manifesting as phosphaturia (inferred from serum hypophosphatemia), pro-

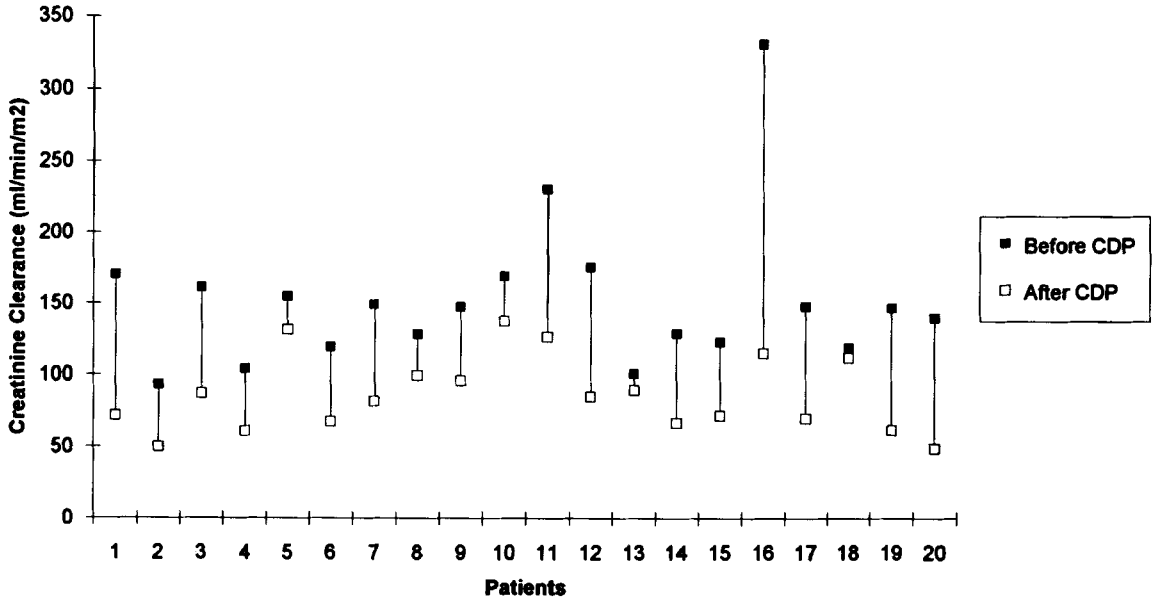

Fig. 2. Decrease in creatinine clearance in patients treated with cis-Diamminedichloroplatinum-II (CDP). Dark squares above show baseline creatinine clearance of individual patients and open squares below indicate values after completion of treatment.

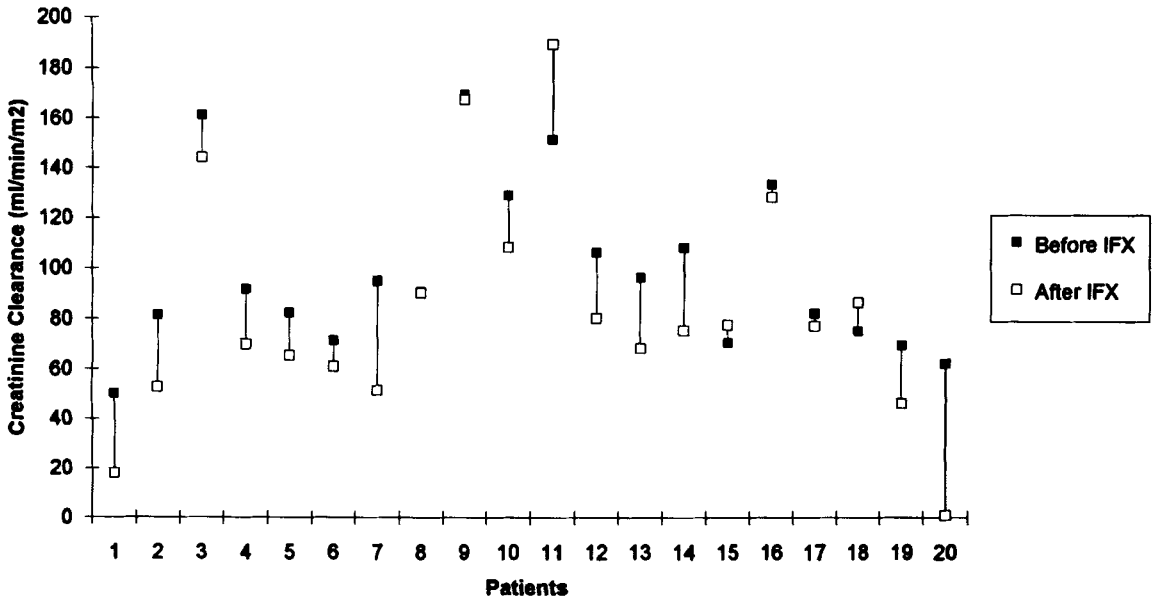

Fig. 3. Decrease in creatinine clearance in patients treated with ifosfamide (IFX). Dark squares show pretreatment creatinine clearance of individual patients and open squares indicate values after completion of treatment.

teinuria, and/or glycosuria (Table III). Reductions in excess of 2 mg% from the serum carbon dioxide level as determined prior to IFX therapy were noted in six patients. An isolated patient also developed mild to trace hematuria. The findings were considered to be a forma fruste manifestation of Fanconi's syndrome. The abnormalities developed during the fifth to the seventh courses of IFX therapy. They were not constant; they waxed and waned and did not appear to be a contraindication to the continued administration of IFX. The findings were particularly evident in two patients in whom large doses of CDP and IFX had been administered.

Over 80% of the patients developed myelosuppression (Table IV). For all patients, the median nadir of the white blood count ranged from 0 to 1,200, platelet count 12 to 17,000, and hemoglobin 78 to 11.2 mgs%. Nine patients

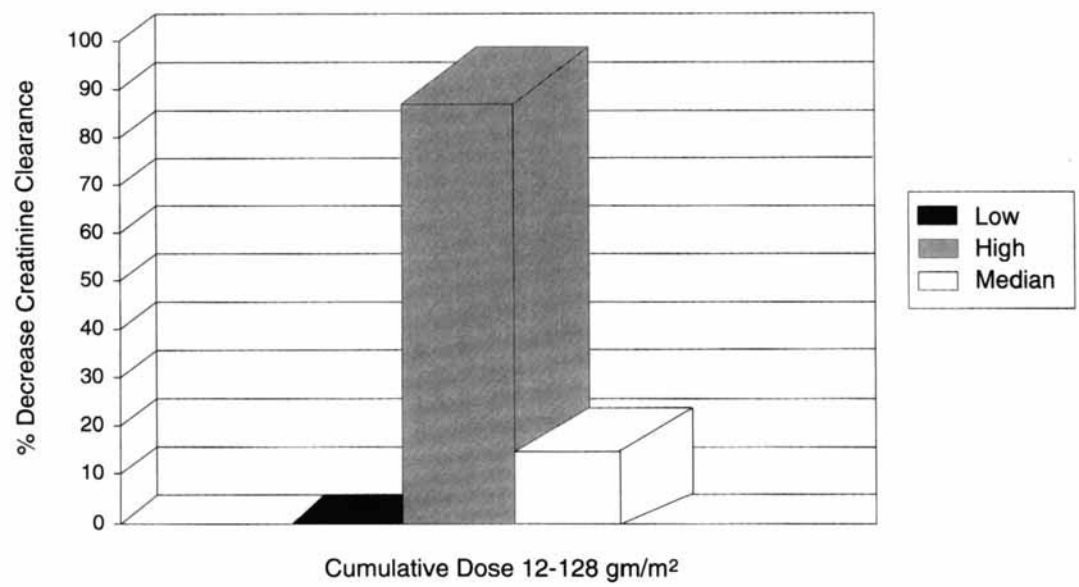

Fig. 4. Decrease in creatinine clearance with ifosfamide. Low, high, and medium values of the percentage decrease in creatinine clearance with a cumulative dose of 12 to 128 gm/m^2 are depicted in the figure.

required hospitalization and were treated with antibiotics for a suspected infection. However, fever and neutropenia generally resolved after 5–7 days and an organism was rarely identified. There were no neurologic disturbances or complications.

DISCUSSION

The results of this study confirm previous reports that large doses of CDP cause progressive deterioration in renal function [10–19]. After discontinuation of therapy, and an elapse of an undetermined interval, some recovery in renal function (at times reversal to normal) may occur. This has been reported previously [17,36]. Alternatively, in some patients deterioration was encountered. Occasionally, there were also significant changes in the mean creatinine clearance to the pre-IFX clearance levels. In some instances, the interval for improvement or deterioration was very short. For example patient #3 went from a creatinine clearance of 87.3 to 161 in less than 2 months and patient #5 went from 131 to 82.28 in less than 3 months. We are unable to account for these variations.

Despite the abnormalities in renal function, the integrity of the renal system (as monitored by creatine clearance) was sufficiently intact to permit the administration of IFX. Thus, in the dose and schedule utilized in our patients, 15 of 20 tolerated treatment without compromise in glomerular function as documented by a persistent creatinine clearance above 60 ml/min/m^2. In three patients, the creatinine clearance actually improved, while in three others there was a modest reduction of 43.4, 28.8, 23.2 ml/min/m^2, respectively. There were no obvious renal, hematologic, or neurologic characteristics which distinguished these patients from others. In contrast, two additional patients did not tolerate IFX satisfactorily: one who previously had developed HUS and another in whom the cause for renal failure after the second course of IFX was undetermined.

Fanconi's syndrome is a generalized disorder of the proximal renal tubule. It may be an uncommon serious complication of IFX and is characterized by excessive renal excretion of glucose, amino acids, phosphate, bicarbonate, uric acid, sodium, potassium, magnesium, and low molecular weight proteins [33–35]. In a fairly large series, Pratt et al. described 3 of 218 children who developed Fanconi's renal syndrome following IFX therapy; all were in a subgroup of 86 children who also received CDP or carboplatin [34]. The abnormalities exhibited in their patients comprised glycosuria, hypophosphatemia, proteinuria, hypokalemia, hypocalcemia, and hypomagnesemia. A similar syndrome was noted in 14 of our patients treated with cumulative IFX doses varying from 21 to 180 gm/m^2. In four, the cumulative IFX dose varied from 21 to 48 gm/m^2, while in the remaining 10 it varied from 51 to 180 gm/m^2. The latter is consistent with the report that the greatest risk for developing Fanconi's syndrome occurs when the cumulative dose exceeds 50 gm/m^2 [34]. However, despite the high IFX doses, a full blown Fanconi's syndrome was not encountered. The abnormalities were considered minor; they were not constant and we elected to continue treatment. There was no deterioration of renal function and in some cases the abnormalities disappeared. We would consider this inconsistent constellation of findings a forma frustre type of Fanconi's syndrome.

CDP causes cumulative renal damage leading to im-

TABLE III. Renal Tubular Abnormalities Detected During Ifosfamide (IFX) Therapy*

Patient	Cumulative dose (gm/m^2)	Number of courses	Decrease in serum phosphorus	Decrease in serum sodium	Proteinuria	Glycosuria	Hematuria	Total serum protein (gm/dl)		Serum albumin (gm/dl)		Serum CO_2 (mg %)	
								Before IFX	After IFX	Before IFX	After IFX	Before IFX	After IFX
1	74	4	+	+	+			6.8	5.8	3.8	3.3	26	29
2	121.6	6	+		Trace	Trace	Trace	7.1	5.6	5.0	3.1	28	24
3	24.4	4	+					5.7	3.2	6.0	3.8	28	24
4	27.8	2		+				7.6	6.2	4.8	3.8	24	22
5	102.24	12			Trace			7.8	7.2	4.1	3.6	19	23
6	178.35	15	+	+	++	Trace		5.8	6.3	3.7	3.1	23	15
7	99.6	6	+	+	Trace			7.1	8.4	3.2	4.2	24	24
8	147	7	+					7.4	7.4	4.1	3.8	28	24
9	39.9	3						7.1	4.4	3.6	2.2	29	28
10	62.8	4						5.2	6.4	3.3	3.9	24	25
11	21.12	3	+	+				6.5	6.5	3.6	3.4	30	28
12	48	3	+	+				5.5	5.4	3.6	3.4	30	28
13	77	10	+	+				6.5	4.9	3.5	3.0	25	22
14	110	10						7.4	6.0	4.1	3.21	28	25
15	180	18	+					6.1	5.5	2.9	3.2	31	29
16	119	7						7.1	7.2	4.4	4.3	27	27
17	51.22	4	+	+	Trace			6.9	6.7	3.7	3.8	21	28
18	16.58	2						7.6	6.7	4.4	3.4	27	29
19	71.06	5		+	+	Small		7.6	6.6	4.0	3.7	28	26
20	28.08	2						6.5	6.2	3.8	3.2	26	24

*Twelve patients developed serum magnesium levels in the vicinity of 1.4–1.6 mg/dl (see text).

TABLE IV. Hematologic Function in Patients Treated With Ifosfamide (IFX)

Patient	No. of courses	No. of courses associated with myelosuppression	Hemoglobin (gm/dl)		Leucocyte count (per mm^3)		Phagocyte[a] count (per mm^3)		Platelet count (per mm^3) × 1,000	
			Mean nadir	Day of nadir	Average nadir	Day of nadir	Average nadir	Day of nadir	Average nadir	Day of nadir
1	4	3	9.1	12.3	0.106	12.3	0.016	12.3	19.3	12.3
2	6	4	9.17	10.75	0.525	10.5	0.085	10.5	63.5	10.5
3	4	1	7.8	11	0.3	11	0.03	11	30	11
4	2	2	11.2	15	0.75	14	0.206	11.5	37.5	15
5	12	2	6.8	17	0.85	17	0.245	17	242	20
6	15	3	9.13	12.6	0.5	12.6	0.28	12.6	75	10
7	6	1	10.3	15	0.9	15	0.54	15	272	15
8	7	0	10.46	12	2.3	12	1.2	12	272	12
9	3	3	8.2	9.3	0.56	9.3	0.19	9.3	107	10
10	4	3	11.6	13.5	1.0	13.5	0.26	13.5	228	7
11	3	1	7.8	7	0.4	7	0.3	7	234	7
12	3	0	7.9	11	0.6	11	0.36	11	142	11
13	10	0	8.9	9	0.9	9	0.65	9	425	9
14	10	3	10.5	12.5	0.68	12.5	0.4	12.5	227	12.5
15	18	3	10.8	11.6	0.9	11.6	0.39	11.6	234	11.6
16	6	0	11.2	10	3.8	10	2.6	10	186	10
17	4	4	8.3	10	0.125	9.5	0.018	9.5	33	8.7
18	2	1	8.2	14	0.4	14	0.2	14	76	14
19	5	0	10.1	12	3.6	10	1.4	10	332	10
20	2	1	8.2	14	0.4	14	0.2	14	191	14

[a]Phagocyte = neutrophil, band, and monocyte.

TABLE V. Review of Ifosfamide Studies

Investigator	CDP	CDP dose (mg/m^2)	Cumulative CDP dose (mg)	Interval between CDP-IFX (month)	IFX dose (gm/m^2)	Cumulative IFX dose (gm)	Glomerular toxicity no./total patients	Tubular toxicity no./total patients
Canpolat (present study)	+	150	417–3,127	1–64	6–9	16.56–180	6/20	14/20 (formes frustres Fanconi's syndrome)
Pratt et al. [24]	+	Not stated	Not stated	Not stated	6.399–9.216	70,389–8,294	Not stated	3/10
	−	Not stated	Not stated	Not stated	6.399–9.216	95.98–147.5	Not stated	2/10
Davies et al. [23]	−		—	—	6–9	36–54	13/20	19/20 (Hematuria) 4/20 (Glycosuria) 22/20 (Proteinuria)
	+	Not stated	581	Not stated	3		2/20	Not stated
Patterson and Khojasteh [31] (Adults)	−	—	—	—	—	6.25–18.75	1/4	1/4 Fanconi's syndrome 1/4 Partial defect 3/4 Decrease in HCO_3 1/4 Glucosuria
Skinner et al. [30]	−	—	—	—	Not stated	55.5–124.4	6/11	11/11
Hacke et al. [18] (adults)	+	75–225	2,475–7,425		5–17.5	165–577.5	0/8	8/8
	+	180–225	3,780–4,725	Concomitant			0/6	6/6
Marti et al. [6]	−	—	—	—	6–9	6–72	0/18	2/18 (Slight microhematuria and proteinuria)
Wheeler et al. [41] (adults)	+	Not stated	Not stated	Not stated	5–10	10–88	3/30	0/30
Skinner et al. [42]	+	75–200	496.4–609.1	—	—	—	0/28	28/28
				3	104.7–105.3	1–18	11/18	
Caron et al. [43]	+	Not stated	180–720 CDP 600–3,200	Combination	Not stated	12–48	Not stated	12/15 (5/12 "Grade 1" dysfunction 7/12 Fanconi's syndrome)
Pratt et al. [34]	+	Not stated	1–>600	Not stated	Not stated	<10–99.9	Not stated	3/218

paired glomerular filtration [14]. This renal insufficiency has been implicated in the prolonged excretion of cyclophosphamide and its metabolites [37,38]. A similar abnormality could be invoked in IFX induced renal toxicity. Further, in the study reported by Goren et al., the prior administration of three or more doses of CDP at 90 to 100 mg/m^2/dose appeared to be sufficient to potentiate IFX toxicity [29]. However, they also demonstrated that not all patients treated with CDP developed renal impairment. Our findings are consonant with this observation. Despite large prior doses of CDP, far in excess of those reported by other investigators, our patients only developed a forma frustre type of Fanconi's syndrome. Further, despite a low serum magnesium level in several of our patients, complications attributable to hypomagnesemia were not observed. All patients except one discontinued oral magnesium supplementation.

We also reviewed the incidence of Fanconi's syndrome and other renal abnormalities in the published literature (Table V). Particular attention was devoted to the prior administration of CDP in view of the large individual and cumulative doses administered to our patients. The incidence of renal abnormalities in our patients compares favorably with that reported by other investigators. In many series, a higher incidence of abnormalities was encountered in patients treated with smaller doses of CDP and IFX [4,18,23,24,30,31,36, 41–43].

The incidence of IFX-induced neurotoxicity in pediatric patients has been reported to vary from 5 to 22% [29,44–46]. However, no neurologic complications were encountered in our series. This contrasts with the observation that neurotoxicity in IFX treated patients may be aggravated by the prior administration of CDP [28]. The myelosuppression associated with most courses was similar to that reported by other investigators [23,29]. Complete recovery was generally observed 3–4 weeks after treatment.

Prior treatment with CDP has been shown to potentiate IFX neurotoxicity, hematotoxicity, and tubular nephrotoxicity [28,29]. Essentially, this was not observed in any of our patients: the large prior cumulative doses of CDP did not appear to compromise the administration of IFX. Tolerance was only poor in one patient with a preexisting HUS. The latter could possibly have been induced by the prior administration of CDP as has been reported previously [39,40]. Further, that IFX may aggravate pre-existing renal disease and precipitate terminal renal failure has also been reported [23]. These experiences suggest that IFX exposure to a kidney which had not fully recovered contributes to, or exacerbates, renal failure induced by other causes. This may also have been responsible for the oliguria in the second patient, although the exact cause could not be determined.

Although this was a retrospective analysis, and there was significant variability in the cumulative CDP dosage, route of administration, and elapsed time between CDP and IFX administration, the data are clinically useful in evaluating the risks of administering ifosfamide following CDP. The results are also noteworthy because both single and cumulative CDP dosages used were relatively large. Unfortunately the numbers are too small to permit meaningful statistical analysis.

In conclusion, our data reveal that patients treated with prior high cumulative doses of CDP tolerated IFX reasonably well. There was minimal effect on glomerular function (creatinine clearance). Except for the intermittent forma frustre type of Fanconi's syndrome, no substantive deterioration in renal function was observed. This finding is only valid if a creatinine clearance above 60 ml/min/m^2 is utilized as a prerequisite for satisfactory renal function, and no major preexisting renal disease is present.

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