Pediatr Nephrol (1998) 12:572–575

Pediatric Nephrology

Original article

Long-term nephrotoxicity of cisplatin, ifosfamide, and methotrexate in osteosarcoma

Paulo C. Koch Nogueira[1, 4], **Aoumeur Hadj-Aïssa**[2], **Mathias Schell**[3], **Laurence Dubourg**[1, 2], **Maud Brunat-Mentigny**[3], **and Pierre Cochat**[1]

[1] Unité de Néphrologie Pédiatrique, Hôpital Edouard Herriot and Université Claude Bernard, Lyon, France
[2] Service d'Exploration Fonctionnelle Rénale, Hôpital Edouard Herriot, Lyon, France
[3] Service d'Oncologie Pédiatrique, Centre Léon-Bérard, Lyon, France
[4] Department of Pediatrics, Faculdade de Ciências Médicas de Santos, São Paulo, Brazil

Received September 29, 1997; received in revised form December 12, 1997; accepted February 18, 1998

Abstract. The acute renal effects of chemotherapy are known, but long-term nephrotoxicity has rarely been investigated. The aim of the present study was to assess long-term renal function in children and adolescents who received at-risk chemotherapy, including cisplatin, ifosfamide, and methotrexate, to treat an osteosarcoma. Renal function tests [creatinine clearance, microalbuminuria, and renal excretion of sodium, potassium, chloride, calcium, magnesium (Mg), phosphorus (P), and uric acid] were prospectively performed 5.4±2.2 (±SD) years after chemotherapy (total cumulative dose: methotrexate 41±31 g/m^2, ifosfamide 39±14 g/m^2, cisplatin 674±188 mg/m^2) in 18 children and adolescents. The results were compared with 13 normal volunteers matched for age and sex. Creatinine clearance, which was greater than 80 ml/min per 1.73 m^2 in all patients, correlated with the total dose of ifosfamide (r=0.55, P<0.05) and cisplatin (r=0.48, P<0.05). Microalbuminuria was noted in 4 patients. Hypomagnesemia was present in 4 and hypercalciuria in 3 patients; renal excretion of P, Mg, and uric acid was higher in patients than in controls. Glomerular function was not significantly altered and only mild tubular dysfunction was present. Since renal excretion of P and Mg were increased in patients compared with normal volunteers and hypercalciuria was occasionally seen, divalent ion disorders are the most-likely potential complications.

Key words: Ifosfamide – Cisplatin – Methotrexate – Nephrotoxicity – Osteosarcoma

Introduction

The prognosis of malignancies in children has dramatically improved. As a result interest in chemotherapy-induced nephrotoxicity has grown, since an increasing number of individuals with curable cancer are potentially at risk of long-term renal sequelae. This is especially important when drugs are combined because the toxicity may be additive. The combination of cisplatin, ifosfamide, and methotrexate, which sometimes is employed for the treatment of solid tumors, deserves investigation because toxicity has been assigned to each of the drugs [1]. The nephrotoxicity of cisplatin is considered dose related and includes a variable reduction of glomerular filtration rate (GFR) along with tubular dysfunction; the latter is usually expressed as increased renal magnesium (Mg) excretion and hypomagnesemia [2]. Both glomerular and tubular function may be affected by ifosfamide, and a variety of tubular disorders, such as Fanconi syndrome and hypophosphatemic rickets, has been described [3]. High-dose methotrexate is also considered toxic to renal tubules, and acute renal failure responsible for subsequent accumulation of the drug has been reported [4, 5]. The combination of cisplatin and ifosfamide is particularly hazardous, since evidence suggests that ifosfamide nephrotoxicity is possibly potentiated by cisplatin [6–9].

The majority of studies on nephrotoxicity of cytostatic agents are based on the acute effects of the drugs, and less is known about the long-term consequences of chemotherapy on renal function.There are concerns on the incidence and severity of renal dysfunction. The aim of the present study was to assess long-term renal function in a group of children and adolescents with osteosarcoma who received a combination of cisplatin, ifosfamide, and methotrexate.

Patients and methods

Eighteen patients (13 girls) with biopsy-proven osteosarcoma at a mean age of 15.2±2.3 years (range 10.0–19.7 years) received combined chemotherapy as part of their treatment, which consisted of an induction with weekly repeated pulses of high-dose methotrexate [8 g/m^2 body surface area (BSA) before puberty and 12 g/m^2 BSA after puberty], followed by local treatment (surgery or radiotherapy), followed by repeated sessions (every 3 weeks) of

Correspondence to: P. Cochat, Unité de Néprologie Pédiatrique, Hôpital Edouard Herriot, F-69437 Lyon Cedex 03, France

chemotherapy consisting of ifosfamide (3 g/m^2 BSA on days 1 and 2), vindesine (4 mg/m^2 BSA on day 1), and cisplatin (100 mg/m^2 BSA on day 3). The total duration of treatment was 28.7±5.6 weeks (range 20.1–40.3 weeks) and involved a mean of 4.6±3.2 cycles of methotrexate (range 0–9) and 6.6±1.4 cycles of cisplatin, ifosfamide, and vindesine (range 4–9). Since vindesine has a low nephrotoxic potential, this drug was not evaluated as a possible cause of renal dysfunction in the present series.

Alkalinization and folic acid (15 mg/m^2 every 6 h) were combined with methotrexate infusions, while mesna (3.6 mg/m^2 BSA) was given together with ifosfamide. Hyperhydration (3 l/m^2 BSA) was used during triple chemotherapy.

All individuals had a normal serum creatinine at the start of treatment; subsequently 11 of 18 patients had at least one episode of a greater than 20% rise in creatinine, but at the end of chemotherapy serum creatinine was statistically comparable to the values observed at the beginning (61±13 µmol/l and 66±11 µmol/l, respectively). Only 1 of the patients had a reversible episode of acute renal failure associated with methotrexate infusion, which has been reported elsewhere [5].

Kidney function was assessed after a follow-up of 5.4±2.2 years (range=1.2–10.3 years) after the last cycle of chemotherapy. Biochemical determinations included serum creatinine urea, sodium (Na), chloride (Cl), potassium (K), calcium (Ca), phosphorus (P), Mg, osmolality, and uric acid. The same parameters, as well as microalbuminuria, were determined in 24-h urine samples. Creatinine clearance was then calculated. Renal excretion of Na, Cl, K, Ca, P, Mg, and uric acid were expressed as the ratio of each substance to urine creatinine to avoid problems with urine collection. For P and Mg, renal excretion was also expressed as the phosphate threshold (TmP/GFR) and the fractional reabsorption of Mg, respectively.

The methods employed for biochemical determinations were: Na and K, flame photometry; Cl, colorimetric titration; Ca, fluorimetric method with EGTA; Mg, atomic absorption spectrophotometry; osmolality, Fiske osmometer; uric acid, enzymatic method; microalbumin, immunonephelometry. Urea, P, and creatinine were determined with colorimetric methods.

With the exception of microalbuminuria, the same renal function tests were performed in a group of 13 normal volunteers matched for age and sex (Table 1). The chi-squared test, Wilcoxon matched pairs test, Mann-Whitney U test, and Pearson's correlation were used for statistical analysis. Results are expressed as mean plus or minus standard deviation and statistical significance was assessed at 5% level in two-tailed tests.

Results

All patients had a creatinine clearance higher than 80 ml/min per 1.73 m^2. A significant negative correlation was observed between creatinine clearance and the cumulative dose of both ifosfamide (r=0.55, P<0.05) and cisplatin (r=0.48, P<0.05), but not with methotrexate (Fig. 1). Elevated microalbuminuria (urine albumin >30 mg/24 h) was noted in 4 patients, without significant correlation with any of the three drugs. No significant correlation was seen between microalbuminuria and GFR.

Hypercalciuria (urine Ca/creatinine >0.49 mmol/mmol) was present in 3 patients (range=0.56– 0.86); hypomagnesemia (serum Mg<0.75 mmol/l) (range=0.51–0.72) was present in 4 patients. Compared with normal volunteers, patients had a significantly higher renal excretion of Mg. The TmP/GFR was not significantly different between the two groups but, the urine P/creatinine ratio was higher in patients. Moreover, serum uric was lower in patients (Table 1).

Table 1. Comparisons between patients and normal volunteers[a]

Parameter	Patients (n=18)	Volunteers (n=13)	P
Age (years)	20.6±2.8	24.3±5.5	NS
Male/female	5/13	8/5	NS
Weight (kg)	59.8±11.6	67.3±8.5	NS
Height (cm)	165.6±10.4	174.2±7.8	<0.05
Serum creatinine (µmol/l)	78±16	86±12	NS
Serum urea (mmol/l)	5.2±1.3	5.1±1.5	NS
Serum Na (mmol/l)	140±2	140±1	NS
Serum K (mmol/l)	3.7±0.4	3.8±0.3	NS
Serum Ca (mmol/l)	2.36±0.08	2.34±0.08	NS
Serum P (mmol/l)	1.3±0.1	1.2±0.1	NS
Serum Mg (mmol/l)	0.79±0.10	0.85±0.05	NS
Serum uric acid (µmol/l)	240±67	337±46	<0.05
Serum osmolality (mosmol/kg)	285±3	283±5	NS
Urine osmolality (mosmol/kg)	716±212	579±290	NS
Cr clearance (ml/min per 1.73 m^2)	112±22	103±30	NS
Urine Ca/Cr ratio (mmol/mmol)	0.33±0.18	0.26±0.08	NS
Urine P/Cr ratio (mmol/mmol)	2.2±0.4	1.8±0.5	<0.05
Urine Mg/Cr ratio (mmol/mmol)	0.31±0.09	0.24±0.10	<0.05
Urine uric acid/Cr (mmol/mmol)	0.28±0.07	0.24±0.06	NS
TmP/GFR (mmol/l)	1.09±0.15	1.01±0.11	NS
Fractional reabsorption Mg (%)	95.6±1.7	96.8±1.2	<0.05

Na, sodium; K, potassium; Ca, calcium; P, phosphorus; Mg, magnesium; Cr, creatinine; NS, not significant; TmP/GFR, phosphate threshold

[a] Values expressed as mean±SD except for male/female ratio

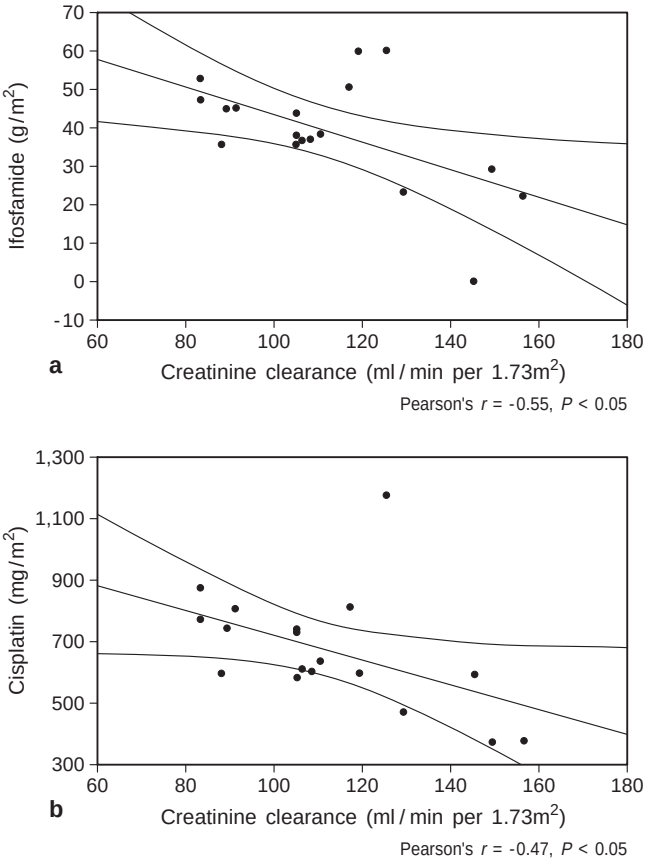

Fig. 1. Linear correlation between creatinine clearance and total dose of ifosfamide (**a**) and cisplatin (**b**)

Discussion

Protocols involving combination of different cytostatic drugs are one of the reasons for the improvement in the outcome of children with cancer; nevertheless toxicity to various organs is likely. The kidney is a particularly exposed target of drug metabolism and clearance; consequently a significant group of children are theoretically at risk of renal dysfunction due to cytostatic agents.

The majority of studies published to date have evaluated acute kidney damage or renal function after a relatively short follow-up; information is scarce on long-term renal function. Suarez et al. [10] found that 22% of 74 children who received six to ten cycles of ifosfamide, vincristine, and dactinomycin had renal abnormalities 1 year after chemotherapy; of these, 4 (5% of the total population) had major toxicity resulting in Fanconi syndrome. Bianchetti et al. [11] found mild tubular dysfunction (hypocalciuria, renal Mg deficiency, and metabolic alkalosis), in 9 of 12 patients 4–43 months after receiving cisplatin for solid tumors, and Arndt et al. [12] found little reduction in GFR (maximal decrease observed=18% below normal), and mild tubular dysfunction (high fractional excretion of urate and mild generalized aminoaciduria) in 6 of 18 patients 3 months after a cumulative dose of 72 g/m^2 of ifosfamide. More recently, Skinner et al. [13] found that six of ten patients who received more than 100 mg/m^2 of ifosfamide developed moderate nephrotoxicity 1–28 months after treatment; the lower GFR observed was 61 ml/min per 1.73 m^2 and tubular alterations included six children with hypophosphatemic rickets and/or renal tubular acidosis and 1 child with nephrogenic diabetes insipidus. Our data are different in many ways from the above, since the follow-up is longer and the population presented here was exposed to a combination of three known nephrotoxic agents. Our results essentially suggest a preservation of GFR and a persistence of mild tubular damage in these patients (mainly involving divalent ion and uric acid excretion), which is not very different from previous studies.

Although we did not observe any significant reduction in GFR, elevated microalbuminuria was present in 4 individuals. Furthermore, a significant negative correlation was found between GFR and the cumulative doses of ifosfamide and cisplatin, but not with methotrexate, which suggests that the influence of ifosfamide and cisplatin on GFR is long lasting. We have no data on the renal growth of the patients and we can not rule out that microalbuminuria was caused by hyperfiltration of inadequately growth kidneys. One of the patients with increased urine albumin also had a high creatinine clearance (145 ml/min per 1.73 m^2), while the other 3 had GFR in the normal range. One could argue that assessment of GFR by creatinine clearance instead of inulin clearance, as in the present study, might underestimate the true extent of mild glomerular damage after chemotherapy [14, 15]; however, the GFR of the patients was identical to that of normal volunteers.

The hypercalciuria observed in 3 patients is most probably secondary to ifosfamide, since a moderate reduction in calciuria has been observed after cisplatin [11]. Moreover, hypercalciuria was also noted by Arndt et al. [12] in 6 of 18 patients who received high-dose ifosfamide.

Despite assessment of the fact that tubular function was incomplete because glucosuria, enzymuria, and aminoaciduria were not measured, the present data suggest that Mg, and probably Ca and P, reabsorption were decreased. This suggests a diffuse rather than localized tubular damage, since P is predominantly reabsorbed in the proximial tubule, Ca is reabsorbed proximally and distally, whilst most Mg reabsorption takes place distally. Increased renal excretion of uric acid is another indicator of tubule dysfunction in the present series, since we observed reduced uricemia with a high urine acid uric/creatinine ratio, although the later did not reach statistical significance. Again this is in agreement with the data from Arndt et al. [12] who found that 16 of 18 patients had a high excreted fraction of uric acid after ifosfamide treatment.

Another important issue is whether acute nephrotoxicity provoked by chemotherapy is progressive. Heney et al. [16] suggested that renal damage after ifosfamide was progressive because glomerular proteinuria was present in only 2 of 11 patients early after chemotherapy and in 5 of 7 individuals who were studied again 7 months later. However, Brock et al. [17] showed that all but 2 of 24 children who had a GFR <80 ml/min per

1.73 m^2 at the end of chemotherapy including cisplatin, demonstrated a variable degree of recovery. Brillet et al. [18] described mild but significant reduction in both GFR and renal blood flow in 35 patients who received a cumulative dose of 603±37 mg/m^2 of cisplatin; after 12–24 months, 12 patients were re-evaluated and renal function was stable. Our data do not permit a definitive judgement on this issue because renal function was evaluated only once, but considering the long period of follow-up and the persistence of tubule abnormalities, it is possible that tubule damage is definitive.

In conclusion, long-term nephrotoxicity after chemotherapy with cisplatin, ifosfamide, and methotrexate seems to be mild, involving mainly tubular function. Despite the absence of clinical consequences in the present study, the renal risk should not be ignored, since tubule damage is long lasting. Divalent ion disturbances, such as hypomagnesemia or hypophosphatemic rickets, are the most-likely clinical consequences and should be monitored long-term after chemotherapy.

Acknowledgements. Dr. Koch Nogueira has received a postdoctoral grant (no. 95/4832-0) from Fundação de Amparo à Pesquisa do Estado de São Paulo.

References

1. Schärer K (1986) Nephrotoxicity action of immunosuppressive and cytostatic agents. Helv Paediatr Acta 41:103–104
2. Daugaard G, Abildgaard U (1989) Cisplatin nephrotoxicity. Cancer Chemother Pharmacol 25:1–9
3. Stevens MCG, Brandis M (1993) Incidence and etiology of ifosfamide nephrotoxicity. Med Pediatr Oncol 21:640–644
4. Condit PT, Chanes RE, Joel W (1969) Renal toxicity of methotrexate. Cancer 23:126–131
5. Dalla-Vale F, Cochat P, Bouffet E, Frappaz D, Bigot P, Vial M, Glastre C, Floret D (1994) Intoxication aiguë au methotrexate: intérêt de l'hémodialyse couplée à l'hémoperfusion sur charbon activé. Ann Pédiatr (Paris) 41:60–63
6. Goren MP; Wright RK, Pratt CB, Horowitz ME, Dodge RK, Viar MJ, Kovnar EH (1987) Potentiation of ifosfamide neurotoxicity, hematotoxicity, and tubular nephrotoxicity by prior *cis*-diamminedichloroplatinum (II) therapy. Cancer Res 47:1457–1460
7. Shore R, Greenberg M, Geary D, Koren G (1992) Iphosphamide-induced nephrotoxicity in children. Pediatr Nephrol 6:162–165
8. Pratt CB, Meyer WH, Jenkins JJ, Avery L, McKay CP, Wyatt RJ, Hancock ML (1991) Ifosfamide, Fanconi's syndrome and rickets. J Clin Oncol 9:1495–1499
9. Rossi R, Danzebrink S, Hillebrand D, Linnenbürger K, Ullrich K, Jürgens H (1994) Ifosfamide-induced subclinical nephrotoxicity and its potentiation by cisplatinum. Med Pediatr Oncol 22:27–32
10. Suarez A, McDowell H, Niaudet P, Comoy E, Flamant F (1991) Long-term follow-up of ifosfamide renal toxicity in children treated for malignant mesenchymal tumors: an international society of pediatric oncology report. J Clin Oncol 9:2177–2182
11. Bianchetti MG, Kanaka C, Ridolfi-Lüthy A, Hirt A, Wagner HP, Oetliker OH (1991) Persisting renotubular sequelae after cisplatin in children and adolescents. Am J Nephrol 11: 127–130
12. Arndt A, Morgenstern B, Wilson D, Liedtke R, Miser J (1994) Renal function in children and adolescents following 72 g/m^2 of ifosfamide. Cancer Chemother Pharmacol 34:431–433
13. Skinner R, Pearson ADJ, English MW, Price L, Wyllie RA, Coulthard MG, Craft AW (1996) Risk factors for ifosfamide nephrotoxicity in children. Lancet 348:578–580
14. Skinner R, Pearson ADJ, Coulthard MG, Skillen AW, Hodson AW, Goldfinch ME, Gibb I, Craft AW (1991) Assessment of chemotherapy-associated nephrotoxicity in children with cancer. Cancer Chemother Pharmacol 28:91–92
15. Jones DP, Chesney RW (1995) Renal toxicity of cancer chemotherapeutic agents in children: ifosfamide and cisplatin. Curr Opin Pediatr 7:208–213
16. Heney D, Wheeldon J, Rushworth P, Chapman C, Lewis IJ, Bailey CC (1991) Progressive renal toxicity due to ifosfamide. Arch Dis Child 66:966–970
17. Brock PR, Koliouskas DE, Barratt TM, Yeomans E, Pritchard J (1991) Partial reversibility of cisplatin nephrotoxicity in children. J Pediatr 118:531–534
18. Brillet G, Deray G, Jacquiaud C, Mignot L, Brunker D, Meillet D, Raymond F, Jacobs C (1994) Long-term renal effect of cisplatin in man. Am J Nephrol 14:81–84