Prospective evaluation of renal function in pediatric and adult patients treated with high-dose ifosfamide, cisplatin and high-dose methotrexate

Stefano Ferrari[a], Franca Pieretti[b], Elisabetta Verri[b], Loredana Tolentinis[b], Marilena Cesari[a], Michela Versari[a], Carola Zolezzi[b], Gaetano Lamanna[c] and Gaetano Bacci[a]

We investigated the renal function of pediatric and adult patients who had been submitted to chemotherapy with high-dose methotrexate (MTX), cisplatin and high-dose ifosfamide (IFO). We observed 43 osteosarcoma patients aged 4–34 years (median 16 years). The median received cumulative doses of MTX, cisplatin and IFO were 60.1 g/m^2, 598 mg/m^2 and 73.5 g/m^2. Renal function was assessed by measurement of creatinine clearance, renal threshold for phosphate (Tmp/GFR), urinary α_1-microglobulin (A1M):creatinine ratio, urinary albumin:creatinine ratio, 24-h glycosuria and proteinuria. The median interval between chemotherapy completion and first renal function assessment was 2 months (range 2–4 months); assessments were then performed at a median interval of 16 months (range 9–49 months). A significant decrease of TmP/GFR was observed only in the pediatric group (under 18 years): the percentage of patients with TmP/GFR < 1 mmol/l increased from 21% (six of 28) at the end of treatment to 46% (13 of 28) at the late assessment. Glycosuria in 10 (67%) of 15 adults and 21 (75%) of pediatric patients was detected with an increased incidence compared to the early post-chemotherapy assessment (13% adults and 29% children). A significant increase of the albumin:creatinine ratio and A1M:creatinine ratio was observed only in adults. Overall, 21 patients had a reduced glomerular function at the latest evaluation, associated with glycosuria in 15 patients (71%), proteinuria in 14 (67%) and TmP/GFR < 1 mmol/l in 11 (52%). We conclude that strict monitoring of renal function should be recommended in pediatric and adult patients after chemotherapy with high-dose MTX, cisplatin and high-dose IFO. *Anti-Cancer Drugs* 16:733–738 © 2005 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2005, **16**:733–738

Keywords: cisplatin, high-dose ifosfamide, high-dose methotrexate, nephrotoxicity, osteosarcoma

[a]Chemotherapy Section and, [b]Laboratory of Medicine, Istituto Ortopedico Rizzoli, Bologna, Italy and [c]Department of Nephrology and Dialysis, University of Bologna, Bologna, Italy.

Correspondence to S. Ferrari, Sezione di Chemioterapia, Istituto Ortopedico Rizzoli, Via Pupilli 1, 40136 Bologna, Italy.
Tel: +39 51 6366 829; fax: +39 51 6366 277;
e-mail: Stefano.ferrari@ior.it

Received 28 December 2004 **Accepted** 29 April 2005

Introduction

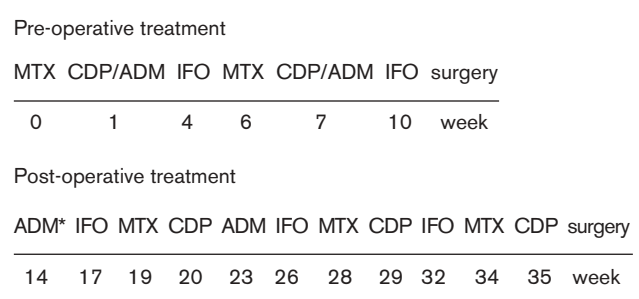
Renal impairment has been reported [1–7] in long-term cancer survivors after chemotherapy treatment based on ifosfamide (IFO) and cisplatin with or without methotrexate (MTX). These studies involved pediatric patients treated according to different protocols with different cumulative doses of the drugs with different results [2,4,5]. All studies included patients treated with standard-dose (9 g/m^2/cycle or below) IFO. In more recent years, IFO at a high dose (14–15 g/m^2/cycle) has been used [8] and its pattern of renal toxicity has been recently reported [9]. There is a lack of information about renal function in adult patients after treatments based on MTX, cisplatin and IFO, as well as about chemotherapy-induced renal impairment being a progressive phenomenon requiring long-term monitoring of the renal function in adults and pediatric patients. Moreover, there are no data about renal function after treatments including high-dose IFO added to cisplatin and MTX. The aim of this monoinstitutional study was to report the results of a prospective analysis of the renal function of pediatric and adult patients after chemotherapy with high-dose MTX, cisplatin and high-dose IFO.

Patients and method

Forty-three patients (29 males and 14 females) with osteosarcoma of the extremities who completed scheduled neoadjuvant chemotherapy (Fig. 1) and underwent at least two renal function assessments after that entered the study. The median age was 16 years (range 4–34 years); 15 (35%) patients were aged 18 years or older (adult group). The median received cumulative doses of MTX, cisplatin and IFO were 60.1 g/m^2, 598 mg/m^2 and 73.5 g/m^2, respectively. The median interval between the first renal function assessment (early post-chemotherapy renal function assessment) and chemotherapy completion was 2 months (range 2–4 months); the subsequent renal function assessment (late post-chemotherapy renal function assessment) was performed at a median

0959-4973

Fig. 1



Chemotherapy scheme. MTX = methotrexate 12 g/m^2, CDP = cisplatin 120 mg/m^2, ADM = doxorubicin 75 mg/m^2, IFO = ifosfamide/MESNA 15 g/m^2, ADM* = doxorubicin 90 mg/m^2.

interval of 16 months (range 9–49 months) after chemotherapy completion.

Chemotherapy

Normal bone marrow, hepatic and renal function were required to receive the planned chemotherapy. Chemotherapy consisted of MTX, doxorubicin, cisplatin and IFO. All drugs were given i.v. MTX (12 g/m^2) was administered in a 4 h infusion with leucovorin (folinic acid) rescue (8 mg/m^2) every sixth hour, beginning 24 h after the MTX infusion by 11 doses. In the first 48 h after starting MTX infusion, hydration (2000 ml/m^2) was given. Adequate alkalinization was required to keep the urinary pH at 7 or higher starting from the time of the MTX infusion up to a serum MTX < 0.2 μmol/l. Cisplatin was delivered over a 48 h continuous infusion at the dose of 120 mg/m^2. IFO, in combination with an equimolar dose of MESNA, was delivered as a continuous infusion at the dose of 3 g/m^2/day for 5 consecutive days.

Renal function assessment

Using a 24 h collection of urine and a corresponding fasting blood sample, the following parameters were analyzed: serum and urine creatinine, serum and urine electrolytes (sodium, potassium, calcium and phosphate), urinary excretion of albumin, α_1-microglobulin (A1M), glucose and protein. The evaluation of the renal function was performed by measurement of creatinine clearance, renal threshold for phosphate (Tmp/GFR), urinary A1M:creatinine ratio, urinary albumin:creatinine ratio, 24-h glycosuria and proteinuria.

Creatinine clearance was determined on a sample of a 24 h collection of urine and expressed in ml/min/1.73 m^2 with 90 ml/min as the lower limit of normal [1]. Renal threshold for phosphate (Tmp/GFR) was expressed in mmol/l and determined on a sample of a 24 h collection of urine according to the formula: $\text{Tmp/GFR} = P_p - ([U_p \times P_{cr}]/U_{cr})$, where P = plasma concentration, p = phosphate, U = urine concentration, cr = creatinine [10]. The lower limit of normal was set at below 1 mmol/l in children [1]. Urinary A1M:creatinine ratio was expressed as mg/mmol and urinary albumin:creatinine ratio was expressed as mg/mmol. A1M and albumin were assayed on a sample of a 24 h collection of urine by an immunoturbidimetric assay with commercial kits (Tina-quant; Roche/Hitachi, Mannheim, Germany) and expressed as mg/l. Glycosuria and proteinuria were reported as mg/day. The detection of any amount of glucose in the 24 h collection of urine identified patients with glycosuria; the detection of urine protein loss above 150 mg/day identified patients with proteinuria.

Statistics

Statview 4.5 statistical package (Abacus Concepts, Berkeley, California, USA) was used for the statistical analysis. The χ^2-test and non-parametric tests (Wilcoxon and Mann–Witney U-test) were performed when appropriate. Results are displayed as box plots. Each box plot is composed of five horizontal lines that display the 10th, 25th, 50th, 75th and 90th percentiles of a variable. All values for the variable above the 90th percentile and below the 10th percentile are plotted separately as circles. Simple regression analysis was used to correlate continuous variables.

Results

Early post-chemotherapy renal function assessment

The creatinine clearance values ranged between 43 and 160 ml/min (median value 82 ml/min), with 24 (56%) patients with lower levels than 90 ml/min. The percentage of patients with a low level of creatinine clearance was not significantly different between the pediatric (61%) and the adult (47%) group.

The renal threshold for phosphate (Tmp/GFR) ranged between 0.41 and 1.69 mmol/l. Lower levels were found in adult patients (Table 1). A renal threshold for phosphate (Tmp/GFR) below 1 mmol/l was detected in six (21%) patients in the pediatric group.

Normal serum levels of calcium and potassium were detected in all patients.

Glycosuria ranging from 10 to 700 mg/day was detected in 10 (23%) patients [two adults (13%) and eight (29%) pediatric patients; $p = 0.5$]. In three patients (two children and one adult) it exceeded 300 mg/day.

Proteinuria exceeding 150 mg/day was detected in 21 (49%) patients: 16 (57%) children and five (33%) adults ($p = 0.3$). In three patients (two children and one adult) it exceeded 500 mg/day (maximum value 696 mg/day).

Table 1 Renal function at the early assessment after chemotherapy according to age (adult and pediatric patients)

	Age ≥ 18 years	Age <18 years	*p*
Creatinine clearance [ml/min (mean ± SD)]	104 ± 56	89 ± 29	0.7[a]
TmP/GFR [mmol/l (mean ± SD)]	0.89 ± 0.28	1.14 ± 0.24	0.004[a]
Patients (percentage) with glycosuria	2/15 (13%)	8/28 (29%)	0.5[b]
Patients (percentage) with glycosuria >300 mg/day	1/15 (7%)	2/28 (7%)	0.8[b]
Patients (percentage) with proteinuria	5/15 (33%)	16/28 (57%)	0.3[b]
Patients (percentage) with proteinuria >500 mg/day	1/15 (13%)	2/28 (7%)	0.6[b]
Urinary albumin:creatinine [mg/mmol (mean ± SD)]	1.5 ± 0.9	2.4 ± 3.3	0.7[a]
Urinary A1M:creatinine [mg/mmol (mean ± SD)]	3.8 ± 2.6	4.5 ± 6	0.5[a]

[a]Mann–Whitney *U*-test.
[b]χ^2-test.

The urinary albumin:urinary creatinine ratio ranged between 0.4 and 13.5 (median value 1.1), the A1M: urinary creatinine ratio ranged between 0.6 and 27.1 (median value 2.3). No differences were found between the pediatric and adult groups (Table 1).

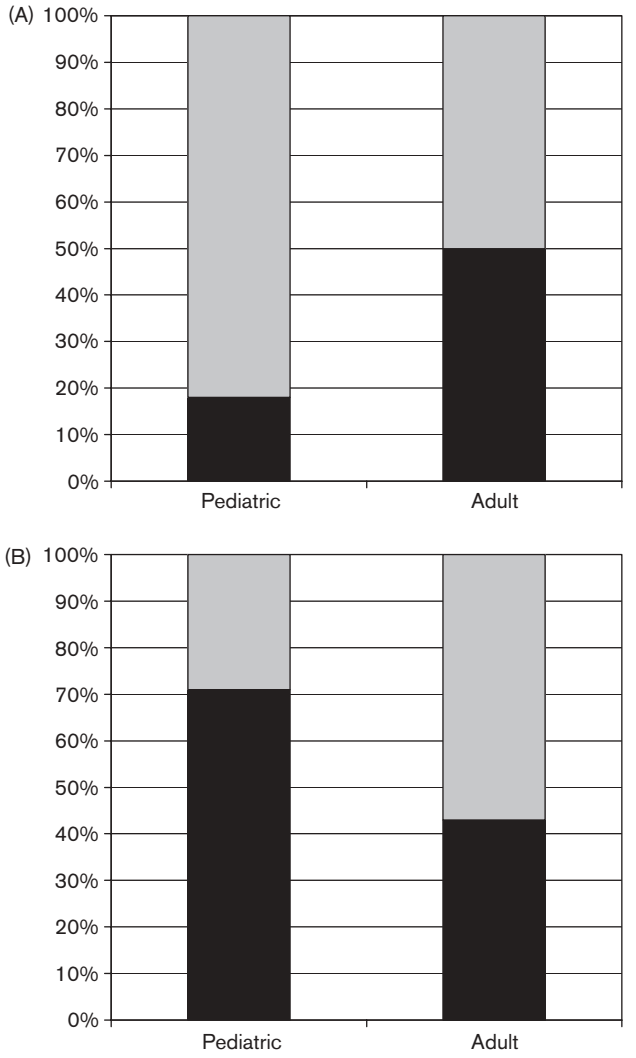
Late post-chemotherapy renal function assessment

Among the patients with normal creatinine clearance at the end of chemotherapy, 13 (68%) also showed normal values at the late assessment, whereas low levels were detected in six (32%). An improvement of the creatinine clearance value up to a value above 90 ml/min was found in nine (37.5%) patients with low creatinine clearance levels at the end of chemotherapy. In 18% of pediatric patients with normal values at the end of treatment the creatinine clearance decreased to levels lower than 90 ml/min; the same occurred in four (50%) adult patients. An improvement of the glomerular function was detected in five (29%) pediatric and four (57%) adult patients (Fig. 2). Overall, 21 patients presented with a reduced glomerular function at the late evaluation and this was associated with glycosuria in 15 (71%), proteinuria above 150 mg/day in 14 (67%) and TmP/GFR values below 1 mmol/l in 11 (52%) patients.

TmP/GFR values significantly decreased over the follow-up period in the pediatric group (Fig. 3). The percentage of patients with TmP/GFR values below 1 mmol/l increased from 21% (six of 28) at the end of treatment to 46% (13 of 28) at the late assessment. Nine of 22 (41%) pediatric patients with normal TmP/GFR values at the end of treatment showed later levels lower than 1 mmol/l. On the other hand, a recovery of tubular reabsorption of phosphate was documented in two (33%) of the six patients with low TmP/GFR at the end of treatment.

In 10 (67%) of 15 adults and 21 (75%) of 28 pediatric patients glycosuria ranging from 40 to 5800 mg/day was detected with an increased incidence compared to the early assessment (Fig. 4). Frank glycosuria (above 300 mg/day) was detected in three (7%) patients at the first and in 11 (26%) in the subsequent assessments. In more detail, three (14%) of the 21 pediatric patients and eight of the 10 adults with glycosuria showed levels higher than 300 mg/day.

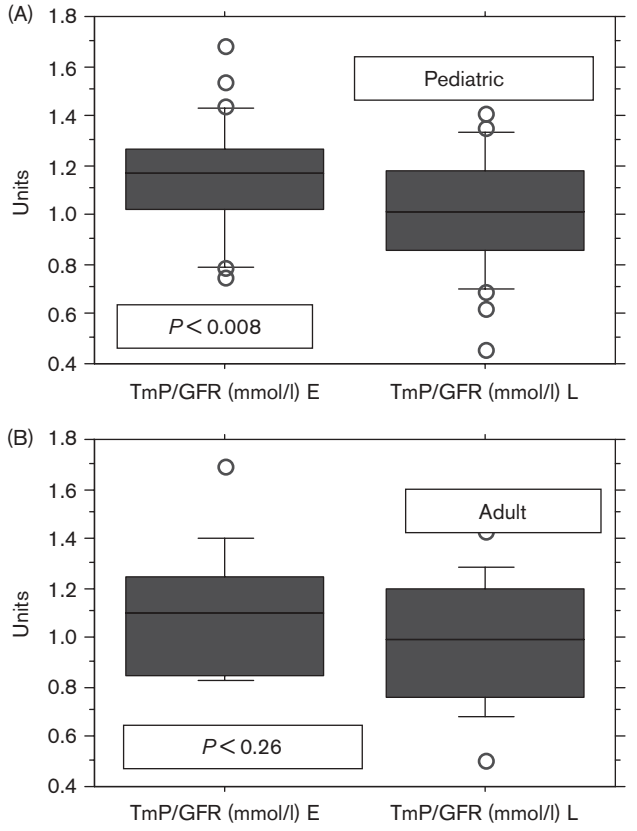
Fig. 2



(A) Creatinine clearance at the late renal function assessment in patients with normal values at the early assessment. (B) Creatinine clearance at the late renal function assessment in patients with low values at the early assessment. Shaded bars = normal; sold bars = low.

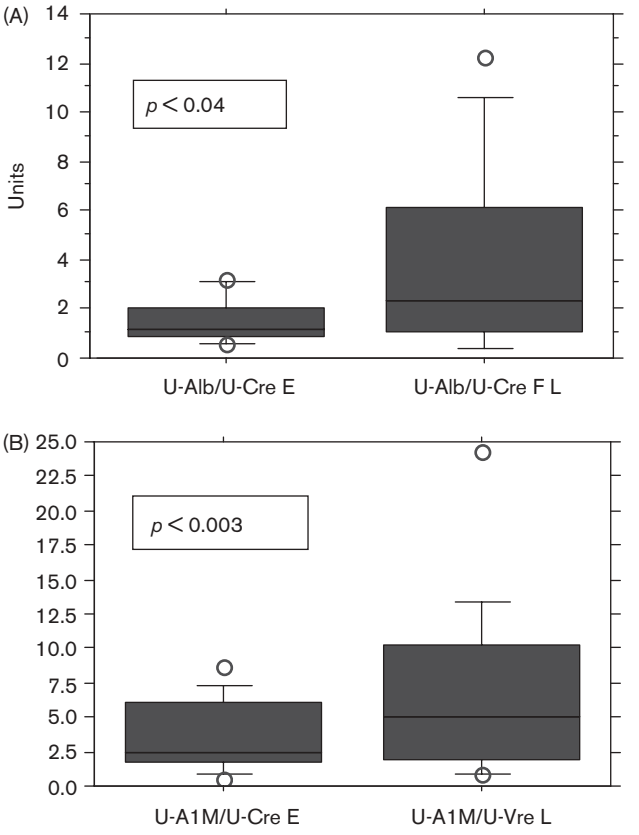
A significant increase of urinary albumin:urinary creatinine and A1M:urinary creatinine ratios was found in adult patients (Fig. 5).

Fig. 3



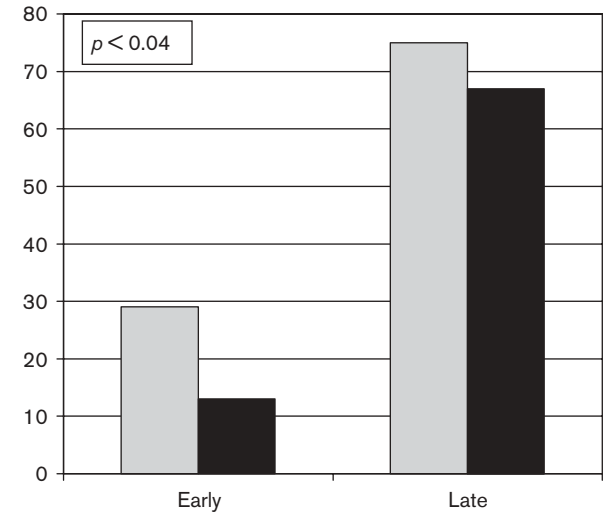
TmP/GFR at the early (E) and late (L) renal function assessment in adult and pediatric patients.

Fig. 5



Urinary albumin and A1M at the early (E) and late (L) renal function assessment in adult patients.

Fig. 4



Percentage of pediatric (shaded bars) and adult patients (solid bars) with glycosuria at the early and late renal function assessment.

A possible relationship among excretion of albumin and A1M and creatinine clearance, TmP/GFR and glycosuria was looked for. In pediatric patients, a statistically significant relationship was found between A1M and glycosuria ($r = 0.52$, $p = 0.004$) and TmP/GFR ($r = 0.39$, $p = 0.04$) at the early assessment. No statistically significant relationship was found at the late renal function assessment. In adults, a relationship close to significance was found only at the late assessment between A1M and creatinine clearance ($r = 0.48$, $p = 0.61$) and TmP/GFR ($r = 0.48$, $p = 0.061$) and albumin and creatinine clearance ($r = 0.49$, $p = 0.06$). In our study group, no cases of Fanconi's syndrome were detected during the study period.

Discussion

In this prospective evaluation of renal function in pediatric and adult patients who underwent chemotherapy treatment with high-dose MTX, cisplatin and high-dose IFO, glomerular and tubular impairment was observed. About half of patients showed a reduction of GFR and proteinuria, and about one-quarter glycosuria

and (in pediatric patients) reduction of tubular resorption of phosphate.

The pattern of renal toxicity did not differ significantly between children and adults, and the lower level of the renal tubular threshold for phosphate reported in adults is due to the age-related difference in phosphorous metabolism [11].

The renal function did not show univocal behavior over time in our study population. Progressive proximal tubular damage was documented both in adults and children: glycosuria was detected in an increased percentage of patients without differences between adult and pediatric patients. A reduction of Tmp/GFR was observed in pediatric, but not in adult patients, and an increased urinary excretion of low-molecular-weight proteins was observed only in adult patients. On the other hand, recovery of tubular reabsorption of phosphate was documented in two of the six patients with low TmP/GFR at the end of treatment.

Disparate behavior of glomerular function was observed, with a complete recovery in some patients, whereas others, mainly adults, showed a progressive impairment.

Our data of renal function after chemotherapy completion are worse than those reported in a population of 24 children and adolescents with osteosarcoma treated with the same drugs we used [5], and this is probably related to the higher cumulative dose of cisplatin and IFO received by our patients. The use of cisplatin can increase the risk of renal toxicity in patients treated with IFO [2,3] and the nephrotoxicity due to IFO is related to its cumulative dose [1,6]. Furthermore, our patients received IFO at a high dose per cycle, which is responsible for acute tubular toxicity [9].

Most of papers on this issue report experiences on pediatric patients. In this age group, some studies [3,6] failed to find the age to be a risk factor of renal toxicity in patients treated with IFO with or without concomitant combination of MTX and cisplatin, whereas a greater proximal tubular toxicity was documented in patients less than 3 years of age [12,13]. In the present study, the age does not seem to be a risk factor for acute renal toxicity. The age of our study population ranged between 4 and 34 years, and in patients with a normal baseline renal function the same pattern of renal toxicity was observed, in pediatric patients and adults up to the age of 34 years, after chemotherapy with MTX, cisplatin and IFO.

In a previous paper on 37 children who received a median cumulative dose of IFO of 54 g/m^2 [14], a progressive glomerular function impairment with coexistent tubular toxicity was reported. Our data support these findings since in the majority of our patients a reduced glomerular function was associated to some features of proximal tubular toxicity.

Progressive tubular toxicity was documented in the present study. Glycosuria was the proximal tubular damage feature most frequently observed, with a similar incidence in pediatric and adult patients. Several reports documented the high incidence of glycosuria in patients following treatment with IFO [1–5] and in a recent report of the UKCCSG Late Effect group a high fractional excretion of glucose was detected in 88% of the evaluable patients studied [6]. In the present study we observed how the glycosuria is a progressive phenomenon, with the percentage of patients with glycosuria increasing from 23% at the first evaluation after chemotherapy completion to 72% during the follow-up period, with no differences between pediatric and adult patients. The progressive impairment of the tubular resorption of phosphate was a specific phenomenon of the pediatric group. In a recent prospective study [15] on a large group of pediatric patients the predictive significance of a severe impairment of phosphate resorption for the development of Fanconi's syndrome or generalized subclinical tubulopathy was reported. In our study group, no cases of Fanconi's syndrome were detected during the study period and only a mild impairment of the tubular resorption of phosphate was documented.

The measurement of urinary excretion of A1M and albumin gave different results, with a relationship with glycosuria and TmP/GFR in the early renal function assessment in pediatric patients. However, in spite of the demonstrated progression of tubular damage, this relation was not found at the late renal function assessment. These observations are in agreement with the demonstrated importance of A1M as a marker of acute tubular damage [16], but some doubts can be addressed to the possible role in monitoring the tubular function, at least in this subset of patients. In adults, increased urinary excretion of A1M and albumin was observed. The observed progressive tubular damage and the reported relation between renal function and albumin excretion [17,18] observed in other settings could suggest future investigations on the possible role of albuminuria in monitoring the renal function after chemotherapy based on nephrotoxic drugs.

In the present study, a similar pattern of nephrotoxicity was observed in pediatric and adult patients after chemotherapy with high-dose MTX, cisplatin and high-dose IFO, and the strict monitoring of the renal function which is recommended for pediatric patients is also suggested for adult patients.

References

1 Skinner R, Sharkey IA, Pearson ADJ, Craft AW. Ifosfamide, Mesna and nephrotoxicity in children. *J Clin Oncol* 1993; **11**:173–190.

2 Rossi R, Danzebrink S, Hillebrand D, Linnenburger K, Ullrich K, Jurgens H. Ifosfamide-induced subclinical nephrotoxicity and its potentiation by cisplatinum. *Med Pediatr Oncol* 1994; **22**:27–32.

3 Rossi R, Godde A, Kleinebrand A, Riepenhausen M, Boos J, Ritter J, *et al.* Unilateral nephrectomt and cisplatin as risk factors of ifosfamide-induced nephrotoxicity: analysis of 120 patients. *J Clin Oncol* 1994; **12**:159–165.

4 Canpolat C, Pearson P, Robertson R, Jaffe N. Ifosfamide tolerance in osteosarcoma patients previously treated with *cis*-diamminedichloroplatinum-II: renal, hematologic and neurologic observations. *Med Pediatr Oncol* 1996; **26**:36–47.

5 Arndt C, Morgenstern B, Hawkins D, Wilson D, Liedtke R, Miser J. Renal function following combination chemotherapy with ifosfamide and cisplatin in patients with osteogenic sarcoma. *Med Pediatr Oncol* 1999; **32**:93–96.

6 Skinner R, Cotterill SJ, Stevens MCG. Risk factors for nephrotoxicity after ifosfamide treatment in children: a UKCCSG Late Effects Group study. *Br J Cancer* 2000; **82**:1636–1645.

7 Skinner R. Chronic ifosfamide nephrotoxicity in children. *Med Pediatr Oncol* 2003; **41**:190–197.

8 Patel SR, Vadhan-raj S, Papadopulos N, Plager C, Burgess MA, Hays C, *et al.* High-dose ifosfamide in bone and soft tissue sarcomas: results of phase II and pilot studies-dose response and schedule dependence. *J Clin Oncol* 1997; **15**:2378–2384.

9 Ferrari S, Zolezzi C, Cesari M, Fasano MC, Lamanna G, Bacci G. Prospective evaluation of high-dose ifosfamide-related nephrotoxicity in young adult patients with recurrent osteosarcoma previously treated with cisplatin, methotrexate and standard-dose ifosfamide. *Anticancer Drugs* 1999; **10**:25–31.

10 Brodehl J, Krause A, Hoyer PF. Assessment of maximal tubular phosphate reabsorption: comparison of direct measurement with the nomogram of Bijvolet. *Pediatr Nephrol* 1988; **2**:183–189.

11 Holick MF, Krane SM. Introduction to bone and mineral metabolism. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL (editors): *Harrison's Principles of Internal Medicine*, 15th edn. *N*ew York: McGraw-Hill; 1999, pp. 2192–22196.

12 Shore R, Greenberg M, Geary D, Koren G. Ifosphamide-induced nephrotoxicity in children. *Pediatr Nephrol* 1992; **6**:162–165.

13 Raney B, Ensign LG, Foreman J, Khan F, Newton W, Ortega J, *et al.* Renal toxicity of ifosfamide in pilot regimens of intergroup rhabdomyosarcoma study for patients with gross residual disease. *Am J Pediatr Hematol Oncol* 1994; **16**:286–295.

14 Prasad VK, Lewis IJ, Aparicio SR, Heney D, Hale JP, Bailey CC, *et al.* Progressive glomerular toxicity of ifosfamide in children. *Med Pediatr Onco*l 1996; **27**:149–155.

15 Rossi R, Pleyer J, Schafers P, Kuhn N, Kleta R, Deufel T, *et al.* Development of ifosfamide-induced nephrotoxicity: prospective follow-up in 75 patients. *Med Pediatr Oncol* 1999; **32**:177–182.

16 Penders J, Delanghe JR. Alpha 1-microglobulin: clinical laboratory aspects and applications. *Clin Chim Acta* 2004; **346**:107–118.

17 Kern W, Braess J, Kaufmann CC, Wilde S, Schleyer E, Hiddemann W. Microalbuminuria during cisplatin therapy: relation with pharmacokinetics and implications for nephroprotection. *Anticancer Res* 2000; **20**: 3679–2688.

18 Bakris GL. Microalbuminuria: what is it? Why is it important? What should be done about it? *J Clin Hypertens* 2001; **3**:99–102.