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Clinical report

Prospective evaluation of high-dose ifosfamide-related nephrotoxicity in young adult patients with recurrent osteosarcoma previously treated with cisplatin, methotrexate and standard-dose ifosfamide

S Ferrari, C Zolezzi,[1] M Cesari, MC Fasano,[1] G Lamanna[2] and G Bacci
Department of Chemotherapy and [1]Laboratory Medicine, Istituto Ortopedico Rizzoli, Bologna, Italy.
[2]Department of Nephrology and Dialysis of the University, Bologna, Italy.

A prospective evaluation of high-dose ifosfamide (IFO)-related nephrotoxicity in adults and young adults previously treated with cisplatin, methotrexate (MTX) and standard-dose IFO was performed. Eighteen patients (median age 22) with recurrent osteosarcoma were studied: 11 were pretreated with MTX, cisplatin and standard-dose IFO, and seven with MTX and cisplatin. The treatment was comprised of four cycles of high-dose IFO (15 g/m^2 over 5 days CI) and mesna at equivalent dose with granulocyte colony stimulating factor support. Renal function was assessed before treatment, after each IFO cycle and after chemotherapy completion. Acute nephrotubular damage was always observed after each IFO cycle with significant changes of renal tubular enzymes *N*-acetyl-β-D-glucosaminidase, alanine aminipeptidase, urinary excretion and reduction of tubular reabsorption of phosphate. The appearance of glycosuria was related to the cumulative dose received. Transient and reversible renal tubular acidosis was observed in three patients. WHO grade I renal toxicity was observed in two patients. After chemotherapy completion, persistent mild glomerular and nephrotubular impairment was observed in one patient who had also received aminoglycoside antibiotics due to febrile neutropenia. Persistent and mild glycosuria was documented in another patient. No significant changes compared to baseline values were observed in the remaining patients. We conclude that a chemotherapy regimen with high-dose IFO in young adults pretreated with MTX, cisplatin and standard-dose IFO is feasible with a mild, usually reversible, nephrotoxicity. [© 1999 Lippincott Williams & Wilkins.]

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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: chemior@sextant.it

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Introduction

Ifosfamide (IFO) is an oxazaphosphorine alkylating agent active against sarcomas. At standard-dose (up to 10 g/m^2) IFO is widely used in first-line multidrug chemotherapy regimens for osteosarcoma,[1-3] Ewing's sarcoma[4-7] and soft tissue sarcomas.[8,9]

Renal toxicity represents the main form of non-hematologic toxicity caused by standard-dose IFO, whose incidence and gravity is related to the cumulative dose received,[10-12] to the age of patients (particularly high in childhood)[10-16] and to prior treatment with cisplatin.[11,12,17-19] A prospective evaluation of standard-dose IFO-related nephrotoxicity has been conducted in patients who received standard-dose IFO (9 g/m^2) in a multidrug regimen for high-risk sarcoma.[20] In that study evidence of acute reversible subclinical nephrotoxicity was observed for all patients.

The present trend in the treatment of recurrent sarcoma is towards use of high-dose IFO[21-25] rather than standard-dose (< 10 g/m^2/cycle). However, while the toxicity of standard-dose IFO and particularly its nephrotoxicity are well known, the profile of nephrotoxicity of high-dose IFO is not well defined yet.

In 1993 a single-agent chemotherapy protocol based on the use of high-dose IFO at a dose of 15 g/m^2 with mesna and granulocyte colony stimulating factor (G-CSF) support as second-line treatment for recurrent osteosarcoma was activated at the Rizzoli Institute. Clinical, and subclinical nephrotoxicity was prospectively evaluated and reported in this article.

Patients and method

Patients with recurrent osteosarcoma of the extremity with white blood cell count $\geqslant 3000/\mu l$, platelet count $\geqslant 100\,000/\mu l$, serum creatinine concentration $\leqslant 1.4$ mg/dl, creatinine clearance $\geqslant 60$ ml/min, SGOT $\leqslant 40$ U/l and bilirubin $\leqslant 1.5$ mg/dl were eligible for the study.

IFO and mesna were administered by continuous infusion each at a dose of 3 g/m^2/day over 5 days. IFO and mesna were infused i.v. in 3 l/m^2/day of basal solution. One litre of basal solution consisted of 5% glucose plus 40 mEq $NaHCO_3$ (sodium bicarbonate) and 20 mEq KCl. Patients were pretreated with mesna 0.5 g/m^2 in 0.5 l of basal solution. After completion of IFO/mesna infusion, patients received a 12 h infusion of mesna 1.5 g/m^2 dissolved in 1.5 l/m^2 of basal solution. Additional alkalinization with 1 mEq/kg sodium bicarbonate was delivered when serum bicarbonate level was below 20 mEq/l.

Starting 48 h after completion of IFO infusion, patients were given G-CSF 5 μg/kg s.c. daily until granulocyte count $\geqslant 10\,000/\mu l$. The subsequent IFO cycle was given in the presence of a granulocyte count $\geqslant 1500/\mu l$ determined 48 h after the last injection of G-CSF. The treatment plan consisted of four cycles for a cumulative IFO dose of 60 g/m^2.

Pretreatment evaluation included complete blood cell count and platelet count, transaminases and bilirubin, alkaline phosphatase, and the following tests for the assessment of renal function: serum and urine creatinine, serum and urine electrolytes (sodium, potassium, magnesium, calcium and phosphate), urine analysis, serum osmolality, glycosuria, plasma bicarbonate, urinary excretion of *N*-acetyl-β-D-glucosaminidase (NAG) and alanine aminipeptidase (AAP), creatinine clearance, and renal threshold for phosphate. NAG and AAP are renal tubular enzymes used as sensitive markers for the early detection of acute tubular damage.[26] NAG and AAP activity were assayed on a sample of a 24 h collection of urine by a spectrophotometric assay with commercial kits (FAR, Verona, Italy) and expressed as U/24 h diuresis. Creatinine clearance was determined on a sample of a 24 h collection of urine and expressed in ml/min/1.73 m^2. 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: $Tmp/GFR = P_p - ([U_p \times P_{cr}]/U_{cr})$ where U_p is the urine phosphate concentration, P_p is the plasma phosphate concentration and U_p is the urine creatinine concentration.[27] On day 1, 3 and 5 of each treatment cycle, complete blood cell count and platelet count, transaminases, serum creatinine, urine analysis, and plasma bicarbonate were checked. On day 6 of each cycle, the renal function was investigated by measuring serum and urine creatinine, serum and urine electrolytes, serum osmolarity, glycosuria, NAG and AAP urinary excretion, creatinine clearance, and renal threshold for phosphate. The same tests were repeated at 2 month intervals after chemotherapy completion.

The Statview 4.5 statistical package (Abacus Concepts, Berkeley, CA) was used for the statistical analysis. The χ^2 and *t*-test were performed when appropriate. Repeated measures analysis of variance was used to compare the values of parameters of renal function measured at the baseline, day 6 of each IFO cycle and 2 months after chemotherapy completion. 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 a circle.

Results

Patient characteristics

Eighteen patients (12 male and six female) with recurrent osteosarcoma of the extremity entered the study. The median age was 22 (range 14-31). All patients had previously received chemotherapy with high-dose methotrexate (MTX; cumulative dose 40-60 g/m^2), cisplatin (cumulative dose 600 mg/m^2) and doxorubicin (cumulative dose 390-480 mg/m^2). For 11 patients the first-line treatment included also standard-dose IFO (cumulative dose 30-36 g/m^2). The median interval between first-line treatment completion and start of treatment with high-dose IFO was 18 months (range 4-62). None of the patients had any history of renal failure.

Compliance with protocol

All patients but one received the planned four cycles of high-dose IFO; the last IFO cycle was omitted in a patient who experienced CNS toxicity during the third cycle. Seventy-one cycles were assessable for toxicity. In five patients, six chemotherapy cycles had to be discontinued, four because of a fall of neutrophil count and two because of CNS toxicity during IFO infusion. Of the 71 cycles delivered, 65 (91%) were at full dose, and six at a dose ranging between 9 and 12 g/m^2.

The median interval between cycles, calculated from day 1 to day 1 of the subsequent cycle was of 17 days (range 13-26).

Acute nephrotoxicity

The glomerular function expressed as creatinine clearance (Figure 1) showed a significant reduction compared to baseline, but no differences were seen between the baseline values and the samples collected 2 months after chemotherapy completion.

Acute renal tubular damage was shown by determining the excretion of urinary enzymes NAG (Figure 2) and AAP (Figure 3). After an acute, remarkable increased elimination after each IFO cycle both NAG and AAP returned to baseline 2 months after chemotherapy completion. No significant changes in serum levels of potassium and magnesium were recorded, whereas the serum level of calcium showed a significant reduction during treatment, returning to baseline after chemotherapy completion (data not shown).

The tubular phosphate reabsorption (Figure 4) was significantly affected by IFO, but the samples collected 2 months after chemotherapy did not show a tubular phosphate reabsorption significantly reduced compared to baseline.

The incidence of glycosuria appeared to be related to the cumulative dose of IFO. Glycosuria was not detected in the pretreatment samples; after the first cycle of IFO one patient had glycosuria, two patients after the second, five after the third and seven of the 18 patients evaluated showed glycosuria after a cumulative dose of IFO of 60 g/m^2. A persistent mild glycosuria was detected in four patients (22%) 2 months after chemotherapy completion.

WHO grade I renal toxicity developed in two patients (11%) in five cycles (7%). Serum creatinine levels returned to baseline before the subsequent cycle of chemotherapy; however, after the last chemotherapy cycle, one of them had persistent WHO grade I renal toxicity. This last patient was treated with aminoglycoside antibiotics for febrile neutropenia.

Plasma bicarbonates fell below 20 mEq/l (range 15-19) in three patients after five cycles. Renal tubular acidosis was usually detected on day 5, only in one case was a low level of plasma bicarbonates observed on day 3. An i.v. supplement of bicarbonates resolved the metabolic acidosis in all patients. No cases of renal tubular acidosis required discontinuation of IFO infusion.

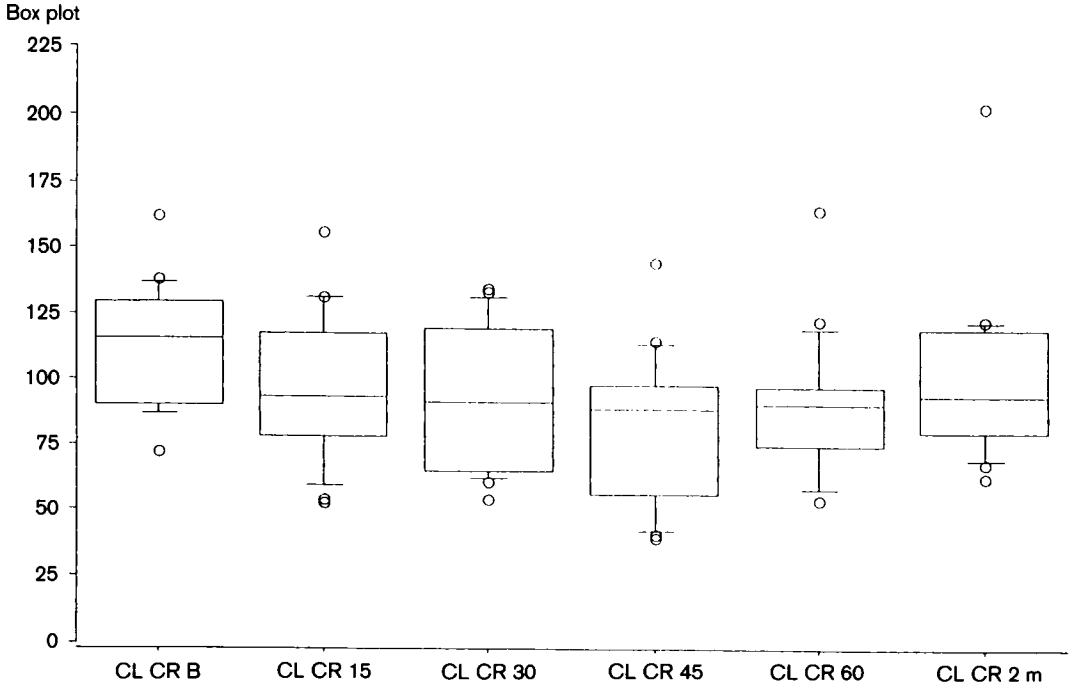

Figure 1. Changes in clearance of creatinine (CL CR). Baseline values (CL CR B) were compared with values measured after infusion of the first cycle of IFO (CL CR 15), second cycle (CL CR 30), third cycle (CL CR 45), fourth cycle (CL CR 60) and 2 months after chemotherapy completion (CL CR 2 m). Fisher's PLSD; significance level: 5%: CL CR B versus CL CR 15, $p=0.075$; CL CR B versus CL CR 30, $p=0.042$; CL CR B versus CL CR 45, $p=0.0009$; CL CR B versus CL CR 60, $p=0.013$; CL CR B versus CL CR 2 m, $p=0.16$.

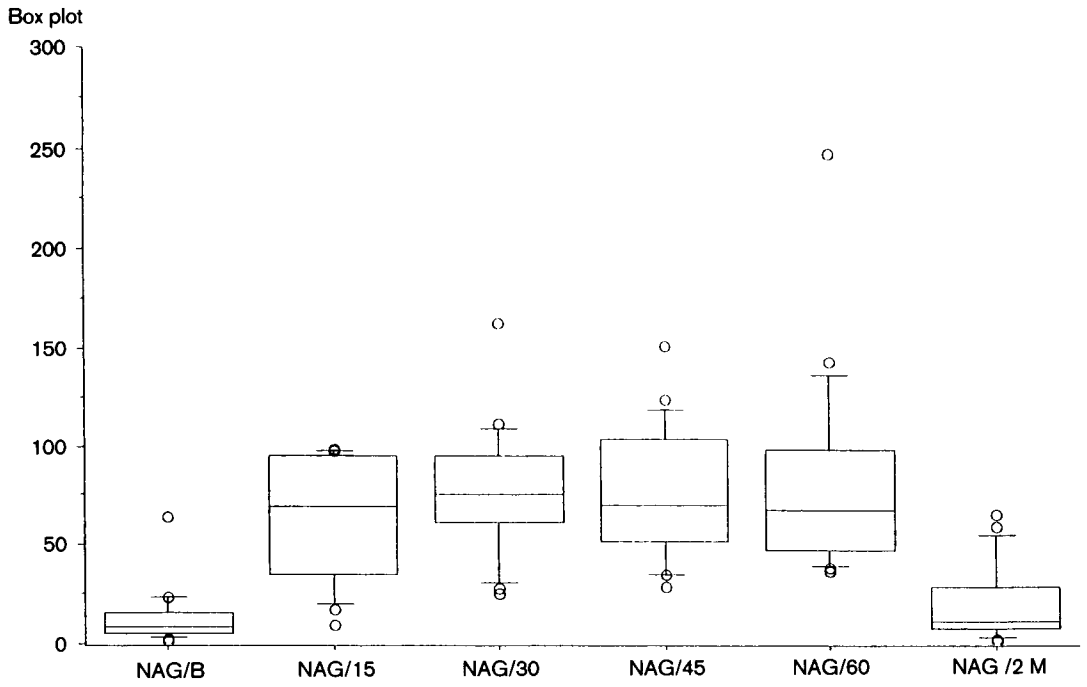

Figure 2. Changes in NAG excretion. Baseline values (NAG/B) were compared with values measured after infusion of the first cycle of IFO (NAG/15), second cycle (NAG/30), third cycle (NAG/45), fourth cycle (NAG/60) and 2 months after chemotherapy completion (NAG/2 M). Fisher's PLSD; significance level: 5%: NAG/B versus NAG/15, $p<0.0001$; NAG/B versus NAG/30, $p<0.0001$; NAG/B versus NAG/45, $p<0.0001$; NAG/B versus NAG/60, $p<0.0001$; NAG/B versus NAG/2 M, $p=0.54$.

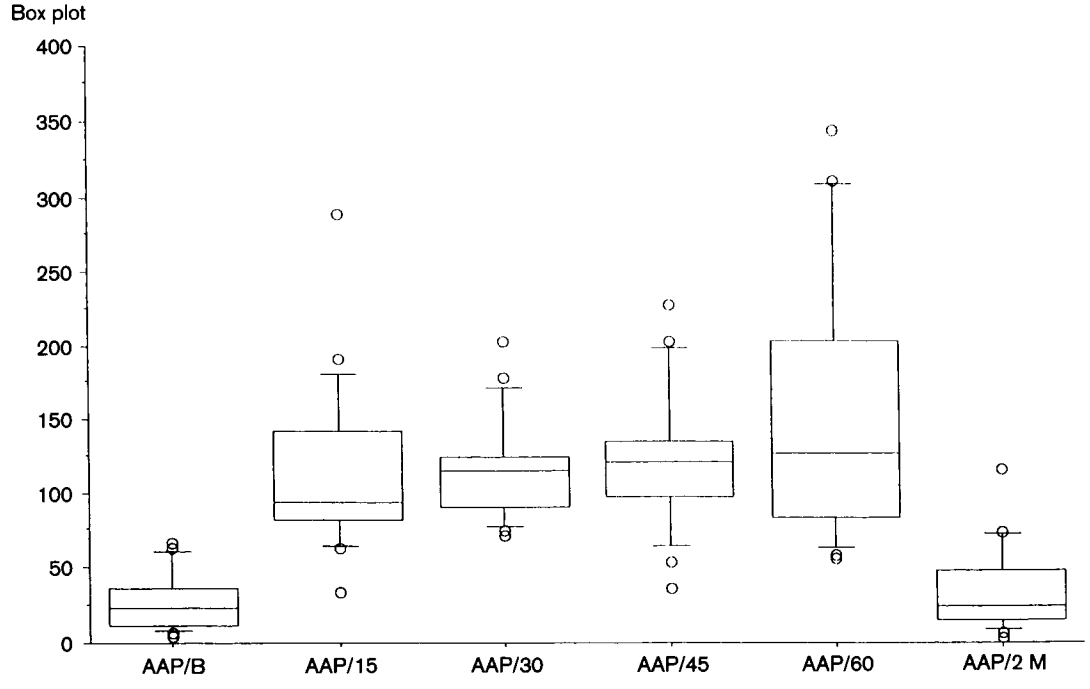

Figure 3. Changes in AAP excretion. Baseline values (AAP/B) were compared with values measured after infusion of the first cycle of IFO (AAP/15), second cycle (AAP/30), third cycle (AAP/45), fourth cycle (AAP/60) and 2 months after chemotherapy completion (AAP/2 M). Fisher's PLSD; significance level: 5%: AAP/B versus AAP/15, $p<0.0001$; AAP/B versus AAP/30, $p<0.0001$; AAP/B versus AAP/45, $p<0.0001$; AAP/B versus AAP/60, $p<0.0001$; AAP/B versus AAP/2 M, $p=0.66$.

Microscopic hematuria (>50 red blood cells/high power field) was documented in two patients after the second and third IFO cycle, respectively. In the subsequent cycles, the same doses of IFO and mesna were given without evidence of microscopic hematuria.

At the baseline evaluation, renal function was in the normal range for all the parameters investigated, apart from tubular reabsorption of phosphate, which was <0.8 mmol/l in two patients—one preatreated with ifosfamide, the other without.

Comparing the values measured 2 months after chemotherapy completion, no significant differences were found between patients pretreated with or without IFO, apart from a comparison of tubular reabsorption of phosphate, which was close to statistical significance (pre-treatment with IFO: mean 0.809 mmol/l SD 0.211; pre-treatment without IFO: mean 0.1.03 mmol/l SD 0.221; p=0.066). Glycosuria was found in three of the 11 patients (27%) who had previously received standard-dose IFO and only one of seven patients (14%) who were not pretreated with IFO (p=0.948).

Chronic nephrotoxicity

The patient who had persistent WHO grade I renal toxicity after the last chemotherapy cycle is presently alive with no evidence of disease. Four years after chemotherapy completion the serum creatinine is 2.4 mg/dl, with a creatinine clearance of 39 ml/min. The assessment of tubular function shows persistent mild glycosuria (0.95 g/24 h) and proteinuria (1.1 g/24 h) with relatively low tubular phosphate reabsorption (0.8 mmol/l). The serum levels of potassium, calcium and magnesium are in the normal range without oral supplementation of those electrolytes.

Three of the four patients with glycosuria were followed up to 12, 15 and 17 months, respectively, after chemotherapy completion and only one showed persistent mild glycosuria as a unique sign of renal tubular impairment.

All the patients who had baseline tubular phosphate reabsorption in a normal range and low tubular phosphate reabsorption during treatment, reached values ⩾1 mmol/l after a minimum of 4 months after chemotherapy completion. The two patients with baseline low tubular phosphate reabsorption did not

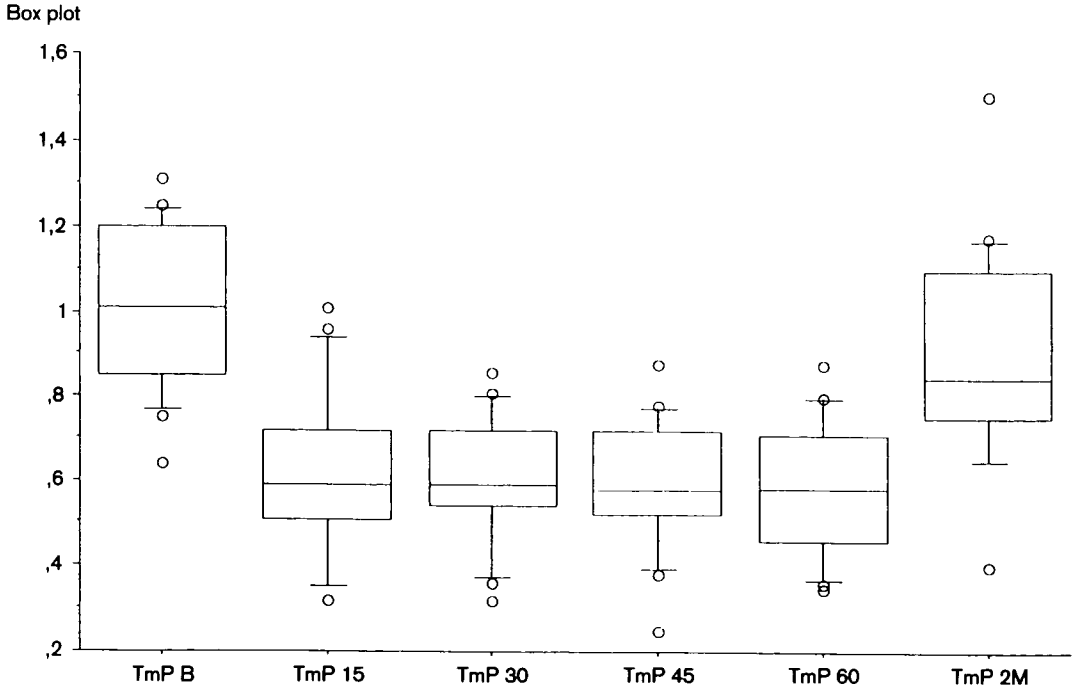

Figure 4. Changes in TmP. Baseline values (TmP B) were compared with values measured after infusion of the first cycle of IFO (TmP 15), second cycle (TmP 30), third cycle (TmP 45), fourth cycle (TmP 60) and two months after chemotherapy completion (TmP 2M). Fisher's PLSD; significance level: 5%: TmP B versus TmP 15, p<0.0001; TmP B versus TmP 30, p<0.0001; TmP B versus TmP 45, p<0.0001; TmP B versus TmP 60, p<0.0001; TmP B versus TmP 2M, p=0.081.

present any further reduction in the tests performed in the following months.

Discussion

One of the major concerns regarding the use of IFO is the nephrotoxicity, expecially in patients previously treated with cisplatin.[11,12,17-19] Our study population consisted of patients heavily pretreated with high-dose MTX (8-12 g/m^2/course, cumulative dose 40-60 g/m^2) cisplatin (120 mg/m^2/course, cumulative dose 600 mg/m^2) and, in 60% of them, standard-dose IFO (cumulative dose 30-36 g/m^2).

The use of standard-dose IFO in the prior treatment was not a risk factor for nephrotoxicity since no significant differences were found between patients pretreated with or without IFO. Only the comparison of tubular reabsorption of phosphate was close to statistical significance and it was found lower in those patients who had been previously treated with standard-dose IFO. It is interesting to note that those patients were given a cumulative dose of ifosfamide of 90-96 g/m^2 with a median interval between standard- and high-dose IFO of 17 months with a range of 4-44 months.

In our patients, the use of high-dose ifosfamide did not significantly affect the glomerular function. Only 7% of the cycles were followed by mild glomerular impairment, expressed as a rise in serum creatinine. Although creatinine clearance showed a significant reduction compared to baseline, no significant differences were seen between the baseline values and the samples collected 2 months after chemotherapy completion. Only one patient (5%), alive without evidence of disease 4 years after high-dose IFO treatment completion, has a persistent, mild impairment of glomerular function. At a dose level of 14 g/m^2, Patel *et al.*[23] reported transient grade 1-2 renal toxicity in 9% of the cycles evaluated and two cases of severe renal toxicity which occurred in two patients who were given six cycles of high-dose IFO for a cumulative ifosfamide dose of 84 g/m^2. Severe renal toxicity requiring dialysis was reported by Rosen *et al.*[24] in one of 13 patients treated with 14-18 g/m^2 of IFO, whereas six of 13 had reversible elevations in their creatinine levels. At a dose level of 14-16 g/m^2, Elias *et al.*[28] reported serum creatinine levels >2 mg/dl in three (20%) of the 15 patients treated. Furthermore, Elias *et al.*[28] reported that renal insufficiency always occurred in combination with renal tubular acidosis. The same experience was reported by Le Cesne *et al.*[22] in a population with advanced soft tissue sarcomas treated with 12 g/m^2 of ifosfamide. In the latter studies, renal tubular acidosis (RTA) frequently occurred: 40% of cycles at a dose of 12 g/m^2, 73% of cycles at a dose of 14-16 g/m^2.[28] In our experience, mild renal tubular acidosis was observed only in 7% of the cycles and it was not associated with significant glomerular impairment. As previously reported by Patel,[23] the present report confirms that the hydration and the supplementation of bicarbonate are key factors in preventing glomerular function impairment or renal tubular acidosis in patients treated with high-dose IFO.

In our prospective study, the use of high-dose IFO was associated with a subclinical tubular nephrotoxicity in all the patients treated. In fact we observed an increased urinary excretion of renal tubular enzymes AAP and NAG, a reduced tubular reabsorption of phosphate with ipophosphatemia, and glycosuria. This pattern of tubular nephrotoxicity is similar to that described[20] in 23 patients treated with standard-dose IFO (9 g/m^2). In that study, β_2-microglobulin, a low molecular weight protein, was used as a marker of renal tubular damage. Its behavior was similar to that of AAP and NAG in our patients treated with high-dose IFO with an acute increment demonstrated after a relatively low cumulative dose of IFO. Similarly, the tubular reabsorption of phosphate was significantly reduced after a relatively low cumulative dose of IFO and an increment of the cumulative dose of IFO was not associated with a further and progressive reduction. In both studies glycosuria was related to the cumulative dose of IFO; however, whereas in the study with standard-dose IFO glycosuria was observed in those patients who received greater than 75 g/m^2 IFO, in our study glycosuria was found in 27% of patients after 45 g/m^2 and in 39% of patients after 60 g/m^2.

The acute subclinical renal tubular toxicity due to high-dose IFO is usually reversible, as demonstrated in our patients. Chronic nephrotoxicity with a Fanconi-like syndrome developed in only one patient. It is interesting to note that this patient had been pretreated not only with cisplatin and MTX but also with standard-dose IFO for a cumulative dose of IFO of 90 g/m^2. Furthermore he had been treated with aminoglycosides for febrile neutropenia.

Globally, the nephrotoxicity observed was mild, especially considering that all patients were pretreated with cisplatin and that 11 of 18 patients had received a cumulative dose of IFO of 90-96 g/m^2. Besides the hydration and the supplementation of bicarbonate, a possible explanation of this relatively low nephrotoxicity could be the continuous infusion of the drug; another study reported[29] a minor nephrotoxicity in patients treated with continuous infusion compared to short infusion. Patel *et al.*[23] reported an incidence of

grade 1-2 renal toxicity in 9% of the cycles in which IFO was delivered as a continuous infusion and in 32% of the cycles in which the drug was given by bolus. Another important factor was the age of our population (young adults) since it is well known that age is an important risk factor for nephrotoxicity,[10-16] and it has been suggested to avoid cumulative dose of IFO greater than 50[12] or 60 g/m^2[2,11] in children.[11,12]

In conclusion, a second-line chemotherapy regimen with high-dose IFO in young adults pretreated with MTX, cisplatin and standard-dose IFO is feasible with a mild and usually reversible nephrotoxicity when the drug is delivered as a continuous infusion, with a high hydration and supplement of bicarbonate. The use of nephrotoxic drugs such as aminoglycosides must be avoided during treatment with high-dose IFO.

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