ABSTRACT. Ifosfamide is widely used in the treatment of pediatric solid tumors. Its main adverse effects are various forms of renal tubular and glomerular damage. Many risk factors have been proposed to play a role in the development and severity of nephrotoxicity in children receiving ifosfamide, among which are 1) patient’s age, 2) cumulative ifosfamide dose, 3) concurrent administration of cis or carboplatinum, 4) unilateral nephrectomy, and 5) method of ifosfamide administration. However, presently there is no consensus regarding the weight of each one of them. Therefore, we critically reviewed the major studies that have evaluated the different risk factors in an attempt to determine the relative importance of each.

Cumulative ifosfamide doses of ≥60 g/m² appears to be the most consistent independent predictor for both the development and the severity of nephrotoxicity, whereas a younger age (<5 years of age) was associated primarily with the more severe and chronic forms of proximal tubulopathy. Comparable incidence and severity forms of proximal tubulopathy among children who had been treated with cis platinum in addition to ifosfamide and those who had not indicated that platinums probably potentiate ifosfamide-induced renal damage rather than act as a major independent risk factor. Finally, although unilateral nephrectomy has been proposed as a significant risk factor in different studies, the relatively small number of nephrectomized children in these cohorts limit the strength of this association.

To reduce the frequency and severity of ifosfamide-induced nephrotoxicity, it appears that cumulative doses of 60 g/m² should be considered carefully, especially in children <5 years of age. Pediatrics 1998;101(6). URL: http://www.pediatrics.org/cgi/content/full/101/6/e8; ifosfamide, nephrotoxicity, proximal tubulopathy, risk factors, cumulative dose, age.

Ifosfamide, a structural analogue of cyclophosphamide, is widely used as a first-line agent in the treatment of a variety of solid tumors in the pediatric age group. Although its early use was limited by severe hemorrhagic cystitis, the introduction of sodium 2-mercaptoethanesulphonate in the 1980s has provided bladder protection, enabling ifosfamide to be used in higher and more frequent dosing.

Preclinical toxicologic studies of ifosfamide failed to detect any significant nephrotoxicity. However, with the extended use of this agent, evidence for nephrotoxicity in children has been accumulated. Although ifosfamide-induced renal toxicity can involve each segment of the nephron, proximal tubulopathy characterized by tubular wasting of glucose, phosphate bicarbonate amino acids, and protein is the most common pattern of toxicity.

As the survival rate of children with cancer improves, both the short- and the long-term toxicity of chemotherapy is receiving greater attention. The importance of long-term ifosfamide-induced renal damage is emphasized further by some reports that have demonstrated persistent renal Fanconi syndrome in up to 5% of ifosfamide-treated patients over a 2-year follow-up period. Many risk factors have been proposed to play a role in the development of nephrotoxicity in children receiving ifosfamide, including patient’s age, cumulative dose of ifosfamide, method of its administration, previous or concurrent administration of platinums or other nephrotoxic agents, radiation, and unilateral nephrectomy.

Presently, the literature is far from consistent regarding the weight of each risk factor. Complicating the issue further, the large interindividual differences in the occurrence and severity of ifosfamide-induced nephrotoxicity in children of similar ages receiving similar doses of the drug may limit the generalization of the predictive value of each risk factor for all ifosfamide-treated patients.

The objectives of this work were to review critically the evidence for each of the different risk factors and to examine the relative importance of each of them in predicting the development and severity of this side effect.

CUMULATIVE IFOSFAMIDE DOSE

As with many other adverse drug reactions, ifosfamide-induced nephrotoxicity was claimed to be dose-dependent. Skinner et al recently studied 23 children who had received ifosfamide for various cancers. None of the children had received cisplatin or undergone nephrectomy, two important founders. In a multiple regression analysis, only the total ifosfamide dose was associated significantly with proximal tubulopathy. Moreover, this study has demonstrated a significant linear correlation between the cumulative dose of ifosfamide and the
different markers of tubulopathy (serum phosphate, serum bicarbonate, and renal tubular threshold for phosphate). This report also indicated that a cumulative ifosfamide dose of 100 g/m² should be avoided in an attempt to reduce the severity and frequency of nephrotoxicity induced by ifosfamide. This recommendation arises from the observation that among the 10 children who had received <100 g/m², only 2 developed moderate toxicity compared with 6 of 10 children who had received ≥100 g/m² who developed moderate to severe tubulopathy. Many other studies have independently supported the observation of dose-dependency of ifosfamide-induced nephrotoxicity. However, most studies have indicated a total dose of 60 g/m² as the cutoff cumulative dose that represents a higher risk for nephrotoxicity.7,8 Clearly, Skinner’s study has a very limited sample size to allow definite delineation of 100 g/m² as a cutoff point.

Ifosfamide is metabolized to 4-hydroxyifosfamide, chloroacetaldehyde, and acrolein, all reactive metabolites that have been demonstrated to induce oxidative stress by depleting lymphocytes glutathione.19 Although renal tubular cells contain relatively high concentrations of glutathione, these may be subject to a degree of depletion, especially during high individual and cumulative doses of ifosfamide.

AGE

Data on age-dependent differences in ifosfamide-induced nephrotoxicity have emerged from different studies; we analyzed rates of nephrotoxicity among 102 children who received the drug between 1984 and 1989 in Toronto, Canada, and who had sufficient tests performed.10 The 25 children exhibiting nephrotoxicity were younger (78.1 ± 64.1 months) than those without nephrotoxicity (104 ± 67 months) (P < .05). The two groups did not differ in their numbers of ifosfamide cycles or its cumulative dose, or dose of sodium 2-mercaptopethanesulphonate per cycle. However, the children exhibiting nephrotoxicity had been more likely exposed to cisplatin (40% vs 18%) (P < .05) and had significantly larger decreases in their height percentile, suggesting that more severe renal changes may result in stunted growth.

These data were confirmed independently by Skinner and colleagues,11 who have shown that in children treated with ifosfamide, those <5 years of age had significantly lower plasma phosphate concentrations (0.69 ± 0.17 mmol/L) than those ≥5 years of age (1.17 ± 0.9 mmol/L) (P = .03). The researchers noted that younger children generally should have higher plasma phosphate concentrations, further emphasizing the differences. In this study, children exposed to ifosfamide were not treated with cisplatin, thus correcting for the potential confounder in our larger study.

A total of 74 children with malignant mesenchymal tumors who have all received the same ifosfamide chemotherapy protocol were studied 1 year after the completion of treatment.12 None of the children had received cisplatin chemotherapy; and all of them were in complete remission correcting for these two important risk factors. Severe toxicity resulting in Fanconi syndrome was correlated with both younger age (<30 months) and higher cumulative dose of ifosfamide (60 g/m²). Lower rates and mild forms (mild generalized aminoaciduria only) of tubulopathy were noted after a relatively high total dose of ifosfamide (72 g/m²) in an older cohort of patients (age range, 7–20 years) to further support younger age as an important risk factor especially for the severe forms of tubulopathy.13

Compared with tubulopathy, ifosfamide-induced glomerular toxicity commonly affects older children, probably reflecting the late onset of this problem.14 That ifosfamide tends to be more nephrotoxic in the young is in contrast to the pathology seen with aminoglycosides and cisplatin and suggests a very different mechanism of renal damage. A previous report,15 together with preliminary data from our laboratory (C. Woodland, S. Ito, J. Klein, personal communication), suggests renal capacity to metabolize ifosfamide as the mechanism of renal damage. Whether age-dependent differences in renal drug metabolism or active metabolites detoxification play a role in ifosfamide renal toxicity is currently under investigation.

CONCURRENT AND/OR PREVIOUS PLATINUMS THERAPY

Among all nephrotoxic agents, cisplatinum and carboplatinum had received the greatest attention as potential risk factors for ifosfamide-induced renal toxicity. Rossi and coworkers studied 120 children and adolescents 3 or more months after completion of chemotherapy including treatment with ifosfamide.9 Using the different nephrotoxic agents (cisplatin, methotrexate, gentamycin) as independent variables in a stepwise regression model proved a highly significant influence, with a calculated odds ratio of 6.4 of concomitant cisplatin therapy on ifosfamide nephrotoxicity. Interestingly, neither gentamycin nor methotrexate had any influence on the incidence or severity of ifosfamide-induced tubulopathy. Goren et al evaluated the influence of previous therapies with three tubular nephrotoxins (cisplatin, high-dose methotrexate, and aminoglycosides), lower abdominal irradiation, and unilateral nephrectomy on ifosfamide-related tubulopathy in 36 patients with solid tumors.16 A multiple linear regression analysis showed the number of previous cisplatin doses (90 to 100 mg/m² per dose) to be the factor related most closely to the total urinary protein excretion. This analysis indicated that patients who had received at least three doses of cisplatin had significantly higher levels of urinary protein excretion, compared with those who had received three or fewer doses. Because all of the other agents were distributed evenly between the two groups, it is probably the cisplatin that potentiates ifosfamide toxicity. However, it is noteworthy that urinary protein excretion is a nonspecific indicator of renal damage in general rather than a specific indicator of either ifosfamide or proximal tubular damage. Moreover, there are no data to relate the magnitude of urinary protein excretion to the severity of nephrotoxicity induced by ifosfamide. Our study further...
supports concurrent platinum treatment as a significant risk factor by showing that among the 25 children with ifosfamide-induced tubulopathy, 40% had received previous cisplatin therapy, compared with 18% in those with normal renal function ($P < .05$).

Importantly, ifosfamide-induced tubulopathy was detected in the same range of incidences (16% to 30%) and severity in studies that controlled for platinum therapy.5,11 This fact indicates that concurrent and/or previous cis/carboplatin administration probably is not a major single predictive risk factor.

### UNILATERAL NEPHRECTOMY

Among a cohort of 120 children studied by Rossi and colleagues,6 10 had undergone unilateral nephrectomy. Subanalysis of these patients revealed that 3 of them developed the full Fanconi syndrome and another 3 generalized tubulopathy, whereas only 4 remained with normal renal functions. Comparison of the nephrectomized versus the nonnephrectomized patients showed a relative risk of 11.4 to develop renal Fanconi syndrome among the former. Despite the small sample size, these data raise concerns that nephrectomy might be an important risk factor for ifosfamide tubulopathy.

### METHOD OF ADMINISTRATION

There are no convincing data from clinical studies that the method of intravenous ifosfamide administration (bolus vs short infusion vs continuous infusion) affects the risk of nephrotoxicity. Although continuous infusion of ifosfamide over 5 days (an extreme dose fractionation) had been reported to increase the maximal tolerated dose,12 a recent study reported a lower response rate after 2 g/m²/day of ifosfamide administered as a continuous infusion for 4 days, compared with that seen after the same total dose administered as a daily 4-hour infusion on 4 consecutive days in adults with soft tissue sarcomas.13 Moreover, there are several reports of severe forms of tubulopathy with either forms of administration.14–21

### SUMMARY

Taken together, the data appear to indicate that the most consistent predictive risk factor for renal toxicity is the cumulative dose of ifosfamide. This factor is proved to be related to both the incidence and the severity of proximal tubulopathy in almost all of the studies that have analyzed the different risk factors. It is unclear whether there is a safe threshold above which the risk of developing renal toxicity increases significantly. Although many studies indicate a cumulative dose of 60 g/m² as the cutoff point, a recent publication suggested a less conservative cumulative dose of 100 g/m² as the dose that should not be exceeded. It is important, however, to realize that avoidance of cumulative doses of either 60 g/m² or 100 g/m² will probably lead to reduced frequency and severity of nephrotoxicity rather prevent it altogether. This is primarily attributable to the large interindividual variability in ifosfamide-induced nephrotoxicity, which can be explained in part by the interindividual differences in the extent and rate of ifosfamide metabolism.

Both concurrent cisplatinum administration and a single functioning kidney probably potentiate renal damage induced by ifosfamide. However, studies that controlled for cisplatinum administration and the small number of nephrectomized patients who were analyzed exclude these factors as major independent predictive determinants.

As opposed to many other agents, ifosfamide appears to be related to younger age in induced renal toxicity, and especially to more severe forms of proximal tubulopathy. Presently, almost nothing is known about the renal handling of ifosfamide and its metabolites. Any attempt to explain age-dependent changes must await detailed characterization of the renal handling of the drug and its metabolites. Subsequently, it may be possible to try to develop approaches to protect the developing kidney while allowing the benefits of this important agent.

### ACKNOWLEDGMENT

This work was supported by a grant from The Medical Research Council of Canada.

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Ifosfamide-induced Nephrotoxicity in Children: Critical Review of Predictive Risk Factors
Ronen Loebstein and Gideon Koren

*Pediatrics* 1998;101:e8
DOI: 10.1542/peds.101.6.e8

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Ifosfamide-induced Nephrotoxicity in Children: Critical Review of Predictive Risk Factors
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_Pediatrics_ 1998;101;e8
DOI: 10.1542/peds.101.6.e8

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