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Development of Ifosfamide-Induced Nephrotoxicity: Prospective Follow-Up in 75 Patients

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Purpose. This study was performed to describe prospectively the development and prognosis of severe ifosfamide-induced nephrotoxicity and to define the period of recommended renal follow-up after ifosfamide chemotherapy. ***Patients and Methods.*** Renal function was followed in 75 patients after cessation of chemotherapy starting within the first year off therapy; median follow-up time was 31 months. The glomerular filtration rate was estimated by using the Schwartz formula. Proximal tubular transport capacities were evaluated for amino acids, phosphate, sodium, and glucose. In addition, serum bicarbonate level and alkaline phosphatase were measured. ***Results.*** Five patients developed renal Fanconi syndrome during follow-up, and another seven patients developed a generalized subclinical tubulopathy. The latter condition always preceded Fanconi syndrome. Severe impairment of amino acid and phosphate reabsorption was seen in 28% and 17.3% of patients, respectively. Reductions in amino acid reabsorption preceded impairment of phosphate reabsorption. In patients with early impairment of phosphate reabsorption, renal prognosis was poor, whereas normal or only mildly impaired amino acid handling virtually excluded progressive tubular damage. ***Conclusions.*** Ifosfamide-induced renal tubular damage is a potentially progressive disease. Along with measurement of phosphate reabsorption, additional assessment of tubular amino acid handling is suggested, because it allows early discrimination of poor from favorable renal outcomes. Med. Pediatr. Oncol. 32: 177–182, 1999. © 1999 Wiley-Liss, Inc.

Key words: ifosfamide; nephrotoxicity; cytostatic treatment; renal Fanconi syndrome; renal proximal tubule

Ifosfamide may induce renal Fanconi syndrome; incidence numbers between 1.4% [1] and 5% of treated patients [2,3] have been reported. In the vast majority of these patients, Fanconi syndrome was observed months or even years following cessation of chemotherapy [4]. Only a few patients developed symptoms when they were still on treatment [5]. For most of the affected patients, the proximal tubular damage that leads to the clinical picture of renal Fanconi syndrome did not resolve over the observation period; only a few patients with reversible renal damage have been reported [6]. Consequently, routine monitoring of renal function is recommended following chemotherapy employing ifosfamide. The duration of clinical monitoring, however, has never been specified.

Other than the cumulative ifosfamide dose [3,7], platinum derivatives [3,8] and reduction of kidney mass, i.e. unilateral nephrectomy [3,9,10], have been identified as risk factors. In contrast, methotrexate and gentamicin given between chemotherapy cycles [3] as well as young age [3,7,11] are not risk factors in ifosfamide-induced toxicity.

Pathological amino acid reabsorption is the most frequent tubular dysfunction in ifosfamide-induced renal damage [3,8,11,12]. To date, aminoaciduria is the only identified predictor of increasing ifosfamide-induced renal toxicity when it is determined during ongoing therapy with increasing cumulative doses of ifosfamide [8]. In this latter study, however, the frequency of ifosfamide-induced renal Fanconi syndrome was exceptionally high (7 of 18 patients; 39%), and the hyperaminoaciduria was measured by using a semiquantitative method only; consequently, sensitivity and specificity in predicting the development of renal Fanconi syndrome was not very high. A rise in protein- and enzymuria usually is followed by a rapid return to baseline levels before the next chemotherapy cycle [13,14] and, thus, provides evidence of acute, reversible, subclinical nephrotoxicity in virtually

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every patient treated with ifosfamide. Not even the combination of different glomerular and tubular markers could be related to cumulative toxicity [14]. Only α1- and β2-microglobulinuria appeared to be somewhat cumulative in one study each [15,16], a finding, however, that was not confirmed by others [13,15]. A correlation of these results with long-term renal outcome has not been studied.

The present study was performed to identify renal findings that either exclude progressive renal damage following ifosfamide or indicate the possibility of future deterioration of renal function. For this purpose, renal tubular and glomerular function were monitored prospectively in 75 patients after cessation of chemotherapy to describe the course of renal dysfunction and its possible progression to Fanconi syndrome. Finally, the study was aimed at defining the necessary length of renal follow-up after ifosfamide chemotherapy and to reduce this time for patients with favorable renal findings.

PATIENTS AND METHODS

The study population consisted of 75 consecutive pediatric patients who had completed treatment for various malignancies. In these patients, renal function was followed prospectively, starting in the first year, and it continued for at least one more examination in the second year off therapy. The total data base consists of 347 renal examinations, with a median number of 4 examinations (range, 2–15 examinations) per patient collected over a median follow-up time of 31 months (range, 12–71 months) at intervals of 6–12 months.

The parameters examined included creatinine clearance using the Schwartz formula [17], fractional phosphate reabsorption (TP/CCrea), percent amino acid (%TAA), and glucose (%TGluc) reabsorption as well as fractional sodium excretion (FeNa). These parameters reflect most specifically proximal tubular transport capacities. Methods and reference values have been published elsewhere [3,18]. Reference values for amino acid reabsorption are shown in Figure 1. In addition to these parameters of proximal tubular function, the serum bicarbonate level (to identify renal tubular acidosis) and alkaline phosphatase (to detect metabolic bone disease) were measured by using standard techniques in the hospital laboratory.

The diagnosis of renal Fanconi syndrome was made in the presence of hyperaminoaciduria, phosphaturia (resulting in hypophosphatemia), glucosuria, and renal tubular acidosis: All patients were on phosphate and bicarbonate supplements. Generalized subclinical tubulopathy was defined as the impairment of three or all four parameters of proximal tubular solute transport (amino acids, phosphate, glucose, and sodium) on one and the same occasion in the absence of acidosis or metabolic bone disease. However, these patients received no supplements.

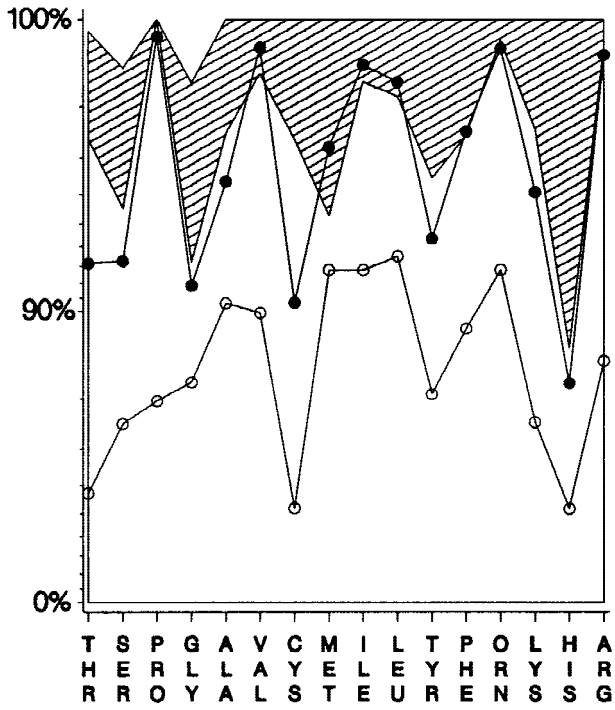

Fig. 1. Percent of amino acid reabsorption. Reference range (shaded area, 16 amino acids; mean ± 2 standard deviations) and median amino acid reabsorption for patients with Fanconi syndrome (FS; median number of amino acids reabsorbed below normal, 16) and generalized, subclinical tubulopathies (GST; median number of amino acids reabsorbed below normal, 10). Open circles, FS (n = 5); solid circles, GST (n = 7).

Reabsorption of 3–7 out of the 16 amino acids analyzed below 2 standard deviations (SD) of normal control values was termed ''mild'' hyperaminoaciduria, and reabsorption of 8–16 amino acids was termed ''generalized'' hyperaminoaciduria (see Fig. 1) to get a simple estimate of the severity of impairment in renal tubular amino acid handling. Measurement of single amino acid transport, as opposed to urinary amino acid excretion, represents most specifically proximal tubular amino acid transport capacity [19].

Statistical analysis was done by using the Statistical Analysis System (version 6.08; SAS Institute, Inc., Cary, NC) with life table procedures and the Friedman test for comparison of follow-up data. The study protocol had been approved by the ethical committee of the local medical school. All patients and/or parents had given consent to the above-mentioned examinations.

RESULTS

Patients' diagnoses are listed in Table I. Median age at completion of chemotherapy was 12.1 years, ranging from 1.1 year to 24.1 years; 15 patients were younger

TABLE I. Distribution of Primary Diagnosis

Diagnosis	Number
Sarcoma (osteosarcoma, Ewing, soft-tissue)	49
Recurrent (lymphoma/leukemia)	13
Neuroblastoma	6
Brain tumor	5
Miscellaneous malignancies	2

than 5 years of age. All patients had been treated according to appropriate polychemotherapy regimens of the German Society of Pediatric Hematology and Oncology, all of them including ifosfamide and mesna. Cumulative doses and concomitant therapy relevant to renal function are listed in Table II.

Overall results in renal function are shown in Table III. With respect to individual parameters of proximal tubular transport, a reduction of amino acid and phosphate reabsorption was seen in highest frequencies (68.0% and 44.6%). Impairment of glucose or sodium transport was observed less frequently (23.6% and 12.0%) and was found predominantly in patients with either Fanconi syndrome or generalized subclinical tubulopathy.

During prospective follow-up, five patients developed renal Fanconi syndrome, and another seven patients developed a generalized subclinical tubulopathy, as defined above; their specifics of treatment are given in Table IV. Generalized hyperaminoaciduria was observed in overall 21 patients; it was a feature of all patients with Fanconi syndrome and of all but one patient with generalized subclinical tubulopathy. Severe impairment of phosphate reabsorption, which was seen 13 times, was found in all five patients with Fanconi syndrome. In these two subgroups of patients, median cumulative ifosfamide doses were not different from one another (55 g/m^2 vs. 52 g/m^2) but were significantly higher compared with the overall group (27 g/m^2; $P < 0.05$; Chi-square-test).

Figure 1 compares amino acid reabsorption of normal controls to patients with Fanconi syndrome and generalized subclinical tubulopathy. These two latter subgroups had impairment of renal tubular amino acid handling, but this impairment was more profound in patients with a Fanconi syndrome.

The course of the development of both Fanconi syndrome and generalized subclinical tubulopathy is shown in Figure 2. Fanconi syndrome occurred up to 3 years off therapy, generalized subclinical tubulopathies developed within the first 2 years off therapy only. The latter condition always preceded Fanconi syndrome.

Reductions in amino acid reabsorption preceded impairment of phosphate reabsorption. Cumulative probabilities for severe reductions in amino acid and phosphate reabsorption were 18% vs. 8%, respectively, at the end of the first year and 28% vs. 14%, respectively, at the end of the second year (Fig. 3).

TABLE II. Medical, Surgical, and Radiotherapeutic Treatment

	Cumulative dose		
Agent/treatment[a]	Median	Range	Number
Ifosfamide (g/m^2)	30.0	2–95	75
Mesna (g/m^2)	55.1	5–185	75
Cisplatin (mg/m^2)	402.0	97–600	35
Methotrexate (g/m^2)	88.4	3–168	35
Gentamicin (mg/kg)	32.5	4–217	46
Unilateral nephrectomy			3
Abdominal radiotherapy			3

[a]Only medication and treatment modalities relevant to renal function are listed.

TABLE III. Patients' Renal Function*

Renal function	Number	Percent
Renal Fanconi syndrome	5/75	6.7
Generalized subclinical tubulopathy	7/75	9.3
Severe impairment of phosphate reabsorption	13/75	17.3
Generalized hyperaminoaciduria	21/75	28.0

*For definition of clinical conditions, see text. Listed are the frequencies of combined renal dysfunction (FS/GST) and of impairment in single tubular transport capacities.

TABLE IV. Specifics of Treatment in Patients With Fanconi Syndrome and Generalized Subclinical Tubulopathy

Diagnosis	$\sum$ Ifo (g/m^2) median (range)[a]	Cisplatin	Abd RT	N$^-$
FS (n = 5)	54 (18–95)	3/5	1/5	2/5
GST (n = 7)	51 (24–83)	4/7	1/7	1/7

[a]FS, renal Fanconi syndrome; GST, generalized subclinical tubulopathy; Abd RT, radiation to at least one kidney; N$^-$, unilateral nephrectomy. For definitions of clinical conditions, see text.

Severe impairment of phosphate reabsorption at the first renal examination was rare (4.4% of all renal examinations), but, if it was present, it had 100% specificity and positive predictive value for the development of Fanconi syndrome; the same applied for the development of Fanconi syndrome and generalized subclinical tubulopathy (Table V). A phosphate reabsorption of less than 1.0 μmol/ml was still rare (10.1%): its positive predictive value for the development of either Fanconi syndrome or generalized subclinical tubulopathy was 71.4%. Early impairment of phosphate reabsorption, therefore, was highly predictive for the development of Fanconi syndrome or generalized subclinical tubulopathy.

Normal amino acid reabsorption or only mild hyperaminoaciduria, however, had a negative predictive value of 98.3% for the occurrence of Fanconi syndrome alone and 93% for the occurrence of the combination of generalized subclinical tubulopathies with renal Fanconi syndrome. Lowering of the cut-off point to less than 6 amino acids even resulted in a 100% negative predictive value for the occurrence of Fanconi syndrome and a 98 %

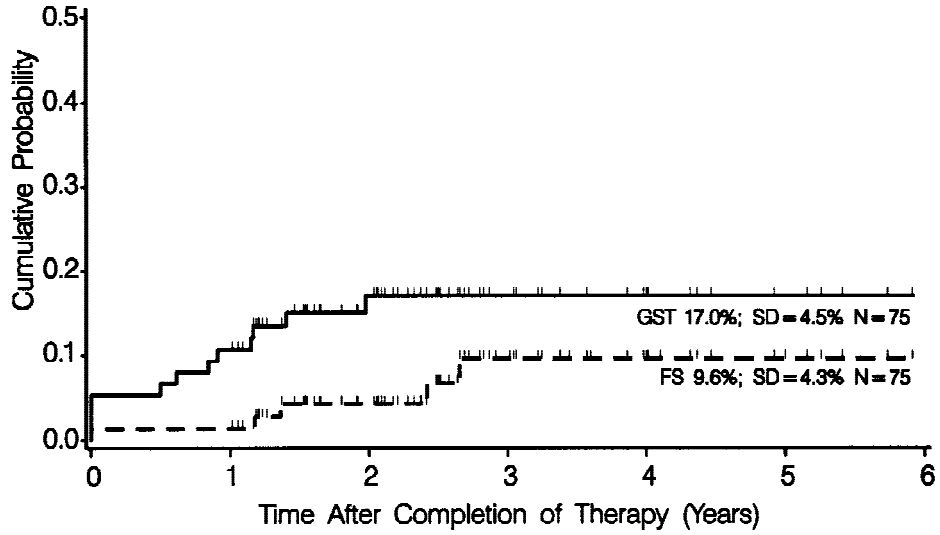

Fig. 2. Cumulative probability of renal FS and GS. For definition of clinical conditions, see text.

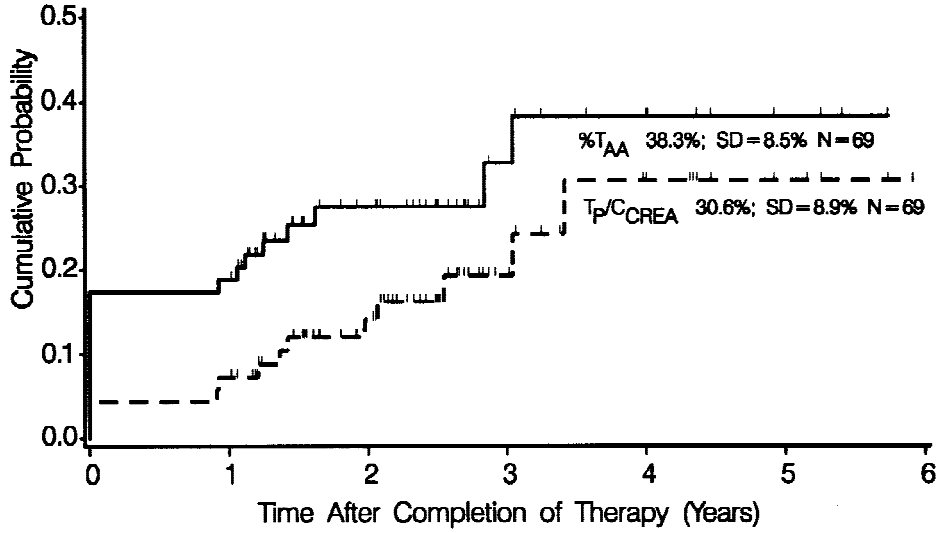

Fig. 3. Cumulative probability of severe reduction in amino acid and phosphate reabsorption. %TAA, percent amino acid reabsorption (''generalized'' hyperaminoaciduria); TP/CCrea, fractional phosphate reabsorption (<0.84 μmol/ml).

TABLE V. Frequency, Sensitivity, Specificity, and Positive and Negative Predictive Values of Single Tubular Dysfunctions for the Development of Renal Fanconi Syndrome or Generalized Subclinical Tubulopathy*

Parameter	Frequency (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
TP/CCrea (<0.84 μmol/ml)	4.4	25.0	100.0	100.0	86.4
%TAA (<8 AA)	82.6	66.7	93.0	66.7	93.0
%TAA (<6 AA)	71.0	91.7	84.2	55.0	98.0

*All calculations are based on the first renal examination of a given patient. PPV, positive predictive value; NPV, negative predictive value. TP/CCrea, fractional phosphate reabsorption; %TAA, percent aminoacid reabsorption. The cut off gives the number of amino acids reabsorbed less than 2 S.D. below normal controls.

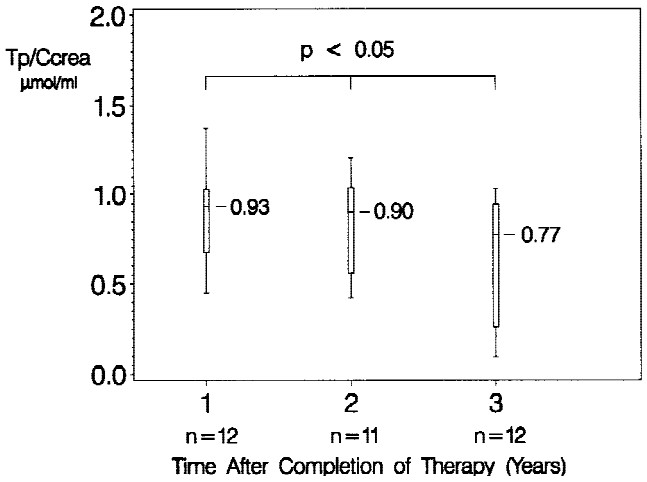

Fig. 4. Time course of fractional phosphate reabsorption in patients with renal FS (n = 5) and GST (n = 7). TP/CCrea, fractional phosphate reabsorption (median, minimal and maximum values as well as 25 and 75 percentiles). Groups were compared by using the Friedman test.

negative predictive value for the occurrence of Fanconi syndrome or generalized subclinical tubulopathies. This criterion was fulfilled by 71% of all patients.

In patients with Fanconi syndrome and generalized hyperaminoaciduria follow-up data did not show any improvement of renal dysfunction over the observation time. Median creatinine clearance rates (92 ml/minute/1.73 m^2 initially, 63 ml/minute/1.73 m^2 at last follow-up) showed a moderate reduction over time, and all patients continued to have a generalized hyperaminoaciduria. Median phosphate reabsorption in these patients, however, decreased significantly from 0.93 µmol/ml to 0.77 µmol/ml (Fig. 4).

DISCUSSION

Ifosfamide-induced nephrotoxicity is a potentially progressive disease. All patients who went on to develop Fanconi syndrome showed some progressive subclinical tubulopathy in advance. The time interval between cessation of therapy and diagnosis of Fanconi syndrome extended up to 3 years. Generalized subclinical tubulopathies, however, developed within the first 2 years off therapy. This observation is supported by numerous publications in which the majority of patients with ifosfamide-induced renal Fanconi syndrome were diagnosed with this condition within the first 2 years off therapy [4,11]. Although, to the best of our knowledge, terminal renal failure in the context of ifosfamide-induced renal Fanconi syndrome has not yet been observed, creatinine clearance rates as low as 40 ml/minute × 1.73 m^2 seen in two of our five patients with Fanconi syndrome indicate the risk of further progression to terminal renal failure [20]. Terminal renal failure, in fact, has been observed in Fanconi syndrome of other origins [19]. On the other hand, it is apparent from this study that patients without a generalized subclinical tubulopathy within the first 2 years off therapy will not progress to Fanconi syndrome later on. So far, tubular amino acid handling represents the most frequently impaired [3,12, present study] and the most sensitive parameter of permanent renal damage following ifosfamide.

In addition, impairment of tubular amino acid handling precedes disturbances in phosphate reabsorption as well as glucosuria, pathological sodium excretion, renal tubular acidosis, and reductions in creatinine clearance (data not shown). This early impairment of amino acid reabsorption allows one to discriminate between patients who are at risk for progressive tubular damage following ifosfamide from those who are not at risk: Normal tubular amino acid handling or only mild impairment of amino acid reabsorption, defined as pathological reabsorption of less than 6 amino acids, was seen in 71% of our patients; none of these patients developed Fanconi syndrome over the observation period, and only one patient developed a generalized subclinical tubulopathy later on. The negative predictive value for the combination of these two conditions (Fanconi syndrome plus generalized subclinical tubulopathy) was 98%. On the other hand, early and severe impairment of phosphate reabsorption (TP/CCrea < 0.84 µmol/ml; i.e. mean ± 3 SD) is highly specific and has a 100 % positive predictive value for the development of either Fanconi syndrome or generalized subclinical tubulopathy. This condition, however, is rare. Consequently, early impairment of phosphate reabsorption following ifosfamide carries a poor renal prognosis, whereas normal or only mildly disturbed amino acid reabsorption within the first year off therapy virtually excludes progression to Fanconi syndrome or generalized subclinical tubulopathy. Accordingly, a great number of patients following ifosfamide therapy may be excluded from continued renal survey.

The progressive course of ifosfamide-induced nephrotoxicity and its potential progression to Fanconi syndrome is not seen in other manifestations of toxin-induced Fanconi syndrome. Renal Fanconi syndrome following heavy metals or outdated tetracyclines will resolve or improve following discontinuation of toxin exposure [19]. Those forms of Fanconi syndrome induced by metabolic diseases like cystinosis are progressive; here, the toxic products accumulate in the renal tubular cells. The only variant of progressive tubular damage leading to Fanconi syndrome is probably the Luder-Sheldon syndrome [21,22], a very rarely reported disease. Its possible relation to mitochondrial defects, however, has never been clarified.

The pathophysiology of ifosfamide-induced nephrotoxicity has not been clarified. It may be related to tox-

icity of the metabolite chloracetaldehyde [23], to glutathione depletion of the renal proximal tubular cells by the ifosfamide/mesna combination [24], to direct toxic action of ifosfamide itself, or to metabolism of ifosfamide in the proximal tubular cell. Ultimately, ifosfamide may interfere with proximal tubular energy supply [25]. However, none of these possible pathways has been proven to be responsible for the nephrotoxicity seen in man.

In summary, ifosfamide-induced renal tubular damage is potentially progressive. Ifosfamide-induced renal Fanconi syndrome may evolve over the first 3 years off therapy, and subclinical forms of tubulopathy precede the final manifestation of Fanconi syndrome. Early impairment of phosphate reabsorption is a rare but highly specific indicator for severe tubular damage following ifosfamide. Normal tubular amino acid handling or only mild impairment of amino acid reabsorption within the first year off therapy excludes progressive tubular damage.

In renal survey following ifosfamide chemotherapy, measurement of serum bicarbonate and renal phosphate handling is mandatory, because these parameters will indicate the need for any supplementary therapy. Due to the findings of the present study, additional monitoring of tubular amino acid reabsorption is suggested, because it may allow discrimination between poor and favorable renal prognosis and thereby reduce the number of patients with continued renal monitoring. In patients with normal or only mild impairment of renal tubular amino acid handling at the end of the first year off therapy, renal survey possibly can be stopped. Patients with severe renal dysfunction following ifosfamide should be followed for a period of 3 years. For those who develop renal Fanconi syndrome, continued renal survey is mandatory to guide the supplementation therapy and to detect possible progression to terminal renal failure.

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