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Progressive Glomerular Toxicity of Ifosfamide in Children

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Glomerular toxicity following ifosfamide (IFO) is not as well recognized as renal tubular damage. Following a case of ifosfamide-induced renal failure with histological evidence of glomerular changes, we undertook a retrospective study of all IFO-treated children to assess the extent and severity of its glomerular toxicity and to identify possible predisposing factors. Thirty-seven children with a follow-up of 6 months or more from the end of chemotherapy were studied. They were a median of 10.8 years old (range 3.25–18.5), had received a median of 54 g/m^2 (range 9–135) of IFO, and had a median follow-up of 29 months (range 6–68). The criteria to identify glomerular dysfunction were raised plasma creatinine (P_{cr}) values on two occasions or a low glomerular filtration rate (GFR) measured by Tc-99-DTPA clearance. Detailed assessment was carried out to identify other nephrotoxic influences in these children. Subjects in whom glomerular dysfunction could be causally linked to IFO were compared with the rest of the group for a variety of predisposing factors. Of eight children with glomerular dysfunction, two had other nephrotoxic influences and were excluded from further analysis. In six (17.1%) children, glomerular dysfunction appeared to be causally linked to IFO. Their median GFR was 61.9 ml/min/1.73 m^2 (range 33–85) and P_{cr} was 123 μmol/l (range 85–216). Five of the six had normal glomerular function at the end of therapy and the raised P_{cr} values were first noted 19, 21, 26, 29, and 36 months later. Children with glomerular toxicity had a significantly longer median follow-up (41.5 vs. 19 months; $P = 0.04$) than the rest of the group, suggesting late onset of this problem. They were older at the time of the study and had received nearly twice the dose of IFO, though the differences in age and dose did not reach statistical significance. The earliest signs of renal toxicity were seen in the index case, who had had prior nephrectomy. All affected children had coexistent and preceding tubular toxicity. The inadequacies of tests commonly used to assess glomerular function and the possibility of underestimation of dysfunction are discussed. Glomerular dysfunction following IFO is poorly recognized and evidence from this study of its later onset and progressive nature is a cause for concern. The index case is described with histological findings.

Key words: ifosfamide, children, glomerular, toxicity, renal, oxazophosphorine

INTRODUCTION

Ifosfamide (IFO), an oxazaphosphorine alkylating agent and a close analog of cyclophosphamide, has been in clinical use for more than two decades. Despite evidence of better tumor response and lack of cross resistance with its predecessor, it was not used routinely in children until the early 1980s because of dose-limiting urothelial toxicity. The incidence of hemorrhagic cystitis decreased dramatically after the introduction of mesna as a uroprotector agent. When first introduced, mesna was thought to guard the renal parenchyma as well as urinary bladder [1], though its inability to protect the renal tubule from IFO was reported early. IFO tubulopathy has since been reported extensively in a wide spectrum of presentations, e.g., acute [2] or long term [3]; proximal [4] or distal tubular [5]; subclinical [6]; or full-blown rickets and Fanconi syndrome [7]. On the other hand, reports of glomerular toxicity have been very few, and usually of mild impairment detectable only by highly sensitive biochemical tests. Long-term clinically significant glomerular insufficiency, due to IFO, is not as well recognized. We have previously reported subclinical biochemical abnormalities of glomerular function in patients being followed as part of a prospective study of IFO tubular dysfunction [8]. Our attention was focused on the potential problem of clinical glomerular toxicity when we recently treated a patient who developed abnormal glomerular function during IFO therapy and subsequently progressed to renal

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failure. We undertook a retrospective study to assess the incidence of significant glomerular damage and potential risk factors in children treated with IFO.

CASE REPORT

A 14½-year-old girl with retroperitoneal peripheral neuroectodermal tumor (PNET) suffered from transient glomerular dysfunction during IFO therapy and subsequently developed renal failure 5 months after completing therapy. She had presented initially with a short history of left-sided abdominal pain associated with nausea and vomiting, but without any urinary or bowel symptoms. Abdominal ultrasound, intravenous pyelogram (IVP), and computed tomography (CT) scan revealed a mass in relation to the upper pole of left kidney. Routine hematological and biochemical tests were normal (plasma creatinine [P_{cr}] 65 μmol/l). Radical tumor removal with left nephrectomy was carried out a week later at the referring hospital. There was extensive hemorrhage with clots in the perinephric tissue and replacement of the adrenal gland with tumor. It was not possible to say if the tumor originated within the adrenal gland or invaded it from another retroperitoneal tissue. Resected kidney revealed normal glomerular, tubular, and interstitial architecture, and no tumor involvement. Following referral to St. James' Hospital, full work up showed no evidence of metastatic disease. She was treated on MMT89 Group 'C' protocol consisting of three-weekly courses of IVA (IFO 3 g/m²/day × 3 days, mesna 3 g/m²/day × 3 days, vincristine 1.5 mg/m² × 1 day, and dactinomycin 1.5 mg/m² × 1 day) and received a total of 36 g/m² of IFO.

Abnormal renal function was noticed after the first course of chemotherapy when P_{cr} rose to 94 μmol/l (normal range 45–80). She developed hypophosphatemia (0.63 mmol/l) and hypokalemia (2.8 mmol/l). Two further courses of IVA were well tolerated. After the fourth course, she developed hypomagnesemia (0.72 mmol/l), metabolic acidosis (serum HCO_3 17.3 mmol/l), and glycosuria and P_{cr} rose to 150 μmol/l. Just before the fifth cycle, the glomerular filtration rate (GFR measured by Tc-99m DTPA clearance) was 54 ml/min/1.73 m². In view of nephrotoxicity, IFO was replaced by cyclophosphamide for the remaining two courses. There was an improvement in P_{cr} to 100 μmol/l, though Fanconi syndrome persisted. For the first 5 months after completion of chemotherapy, there was a general improvement in her well-being and weight, but there was a slow and gradual increase in P_{cr}.

Follow-up was complicated by two episodes of intestinal obstruction due to adhesions 5 and 8 months after the completion of chemotherapy needing laparotomy to divide adhesions. The adhesions did not involve the renal tracts. During the first episode, her P_{cr} rose to 416 μmol/l and blood urea to 21.9 mmol/l. She also had hypokalemia (2.0 mmol/l) and metabolic acidosis (serum HCO_3 16.2 mmol/l). On recovery from these episodes, P_{cr} stabilized between 200–300 μmol/l and the GFR (Tc-99m DTPA clearance) was 33 ml/min/1.73 m². Serum levels of aminoglycosides and vancomycin throughout her current and previous therapy were never in the toxic range and she did not receive any other nephrotoxic drug. Currently, 34 months after the end of chemotherapy, she continues to have glomerular and tubular impairment and needs phosphate, potassium, and bicarbonate supplementation. She has developed anemia of renal failure and has a very low serum erythropoeitin level (less than 5 μmol/l measured by radioimmunoassay). Blood pressure was recorded at regular intervals and was always found to be within the normal range. Her current P_{cr} is 216 μmol/l and the GFR is 34 ml/min/1.73 m².

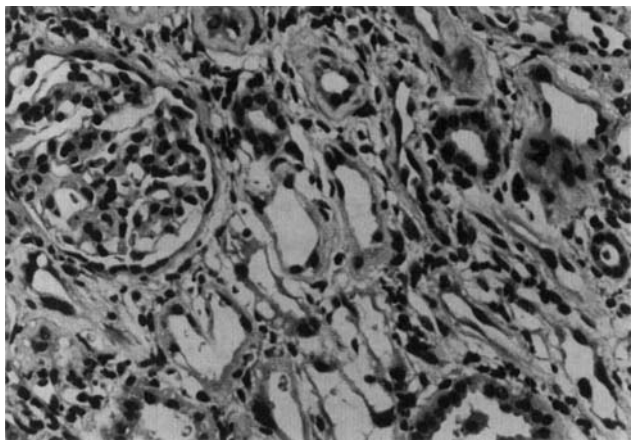

Fig. 1. The tubules in the center of the field show loss of epithelium, hyperchromasia, and irregular lumina. The tubules above center show thickened basement membrane. The glomerulus on the left shows mild mesangial expansion and mild capillary collapse. Paraffin section H+E. ×500.

Open renal biopsy was performed at the time of the laparotomy to relieve intestinal obstruction. The specimen contained 17 glomeruli, one fourth of which showed early capsular thickening and mild mesangial matrix expansion and some appeared sclerosed. The immunopathology preparations on frozen and paraffin sections showed only insignificant amounts of IgM in glomerular capillary walls. Electron microscopy of one representative glomerulus showed mild ischemic collapse of the capillary tuft and early periglomerular fibrosis. The prominent abnormality of the biopsy consisted of a severe degree of tubular damage and interstitial fibrosis (Fig. 1). The tubular epithelium showed increased eosinophilia, gross vacuolation, and complete loss of epithelium leading to unidentifiable tubular profiles with thickened basement membrane. In some tubules, cytoplasmic vacuolation is associated with nuclear enlargement and hyperchromasia. A few multinucleated cells were present. The interstitium

showed moderate fibrosis and light mixed cellular inflammatory infiltrate. The blood vessels appeared essentially normal.

PATIENTS AND METHODS

A retrospective analysis of case records at the Yorkshire Regional Paediatric Oncology Unit identified a total of 59 IFO-treated children with at least 6 months post-chemotherapy follow-up. The first patient received IFO in July 1986. Mesna had been used in every patient. Twenty-six patients have died. Biochemical records of 22 of the dead patients were not stored in the computer and they were excluded from the study. Thirty-seven patients who were suitable for inclusion had their two highest P_{cr} values recorded. Patients found to have raised P_{cr} values for age and sex [9] were identified and their GFR was measured by Tc-99m DTPA clearance in all but one case. Glomerular function was classified as per the criteria of Skinner et al. [10]: Normal $\geq$90 ml/min/1.73 m^2; grade 1 impairment, 60–89; grade 2, 40–59; grade 3, 20–39; and grade 4, $\leq$19 ml/min/1.73 m^2. Children with an abnormal GFR underwent tests for fractional excretion of sodium, calcium, magnesium, phosphate, bicarbonate, as the measures of tubular function.

The total dose of IFO was calculated in all children. The use of all potentially nephrotoxic anticancer agents including cisplatin, carboplatin, and melphalan was recorded. The use of nephrotoxic antibiotics (e.g., amphotericin, vancomycin, aminoglycosides, and acyclovir) was recorded and noted either if their serum levels were found to be supratherapeutic, or if their use was associated with rising P_{cr} values. A record was made of abnormal renal function or renal tract involvement at diagnosis, nephrectomy, and abdominal radiotherapy. Most of these children were followed up according to our current practice of measuring P_{cr} values at the end of therapy, after 6 months, and then yearly in routine cases and more frequently if any renal abnormalities are present. Body mass index [11] (BMI-weight in kilograms/height in meters^2) was calculated for each patient's actual as well as expected 50th centile values and was used as a guide to nutritional status. Statistical analysis was performed using the non-parametric Mann-Whitney test and the chi-square test on Minitab Series 9 statistical software.

RESULTS

Of the 37 children included in this study, 16 were boys. Their median age at the start of IFO therapy was 8.1 years (range 0.75–14.58 years) and at the time of this study was 10.8 years (range 3.25–18.5 years). They received a median 54 g/m^2 (range 9–135) of IFO, 15 patients as fractionated (1 or 3-hour infusions daily $\times$ 2 or 3 days) and 22 as continuous infusions ($\times$ 2 or 3 days). Median duration of follow-up from the end of therapy was 29 months (range 6–68). Underlying diagnoses were rhabdomyosarcoma (14), Ewing's sarcoma (10), PNET (5), osteosarcoma (2), soft tissue sarcoma (2), malignant Langerhan's cell tumor (1), malignant fibrous histiocytoma (1), Wilm's tumor (1), and neuroblastoma (1).

Eight children (five boys, three girls) were identified as having glomerular dysfunction with raised P_{cr} and low GFR values. Detailed information about them and evidence for causal association to IFO are given in Table I. Two patients, a boy with renal tract involvement and raised P_{cr} values at presentation and a girl who received both cisplatin (total dose 420 mg/m^2) and carboplatin (total dose 2.2 g/m^2) in addition to IFO, were excluded from further analysis. Six of 35 (17.1%) children were found to have evidence of glomerular dysfunction due to IFO. Details of their renal investigations are given in Table II. Three patients had grade 1, one had grade 2, and two had grade 3 glomerular impairment. Five of these had normal P_{cr} values at the end of therapy and raised P_{cr} values were first noted 19, 21, 26, 29, and 36 months later. Hypertension was not seen in any patient. The six affected children were compared with the rest (29) of the group and the findings are given in Table III. Duration of follow-up was significantly longer in the affected group (41.5 vs. 19 months; $P = 0.04$). Affected children were older at the start of IFO treatment (median 8.37 vs. 6.08 years; $P = 0.44$) as well as at the time of this study (13.7 vs. 9.5 years) and received a higher cumulative dose of IFO (93.7 vs. 54 g/m^2), though the differences did not reach statistical significance. No statistical difference was seen between the two groups for the following variables: IFO infusion schedules; frequency of platinum use; nephrectomy; nephrotoxic antibiotic use; abdominal radiotherapy; and preexisting renal disease. All the children with glomerular impairment had coexistent tubulopathy evidenced by increased fractional excretion of one or more of the following electrolytes, i.e., sodium, calcium, phosphate, and magnesium. BMI in the whole group was significantly lower than the expected 50th centile ($P = .0002$), suggesting undernutrition in the study population compared with normal children.

DISCUSSION

Glomerular toxicity due to IFO is not as well recognized as the tubular toxicity. A recent review of the published literature [10] identified only seven cases of moderate glomerular toxicity (GFR 20–39 ml/min/1.73 m^2) and none with severe renal failure (GFR <20 ml/min/1.73 m^2). This is in contrast to the tubular toxicity of IFO which is well known and widely reported [2–7,10,12–17].

We identified eight patients with raised P_{cr} and low GFR values, two of whom were excluded because their glomerular insufficiency may have been caused by factors

TABLE I. Detailed Information About Patients With Glomerular Impairment

Patient no.	Diagnosis	Age (years) Sex	Chemotherapy[a]	IFO (g/m^2)	Follow-up months	GFR (ml/min/ 1.73 m^2)	Renal tract involvement	Abdominal radiation	Tubulopathy
1[b]	PNET	16.3 F	I,V,A,D,Cy	36	17	33	No	No	Yes
2	Ewing's	10.8 M	I,V,A,D	120	44	55.8	No	No	Yes
3	Rhabdomyosarcoma	14.7 M	I,V,A,D,Cy	78	68	39	No	Yes[c]	Yes
4	Ewing's	12.7 F	I,V,A	90	40	85	No	No	Yes
5	Ewing's	17.5 M	I,V,A,D	121	35	68[d]	No	No	Yes
6	Rhabdomyosarcoma	6.9 M	I,V,A,D,Cy	97.5	43	85	Yes[e]	No	Yes
7	Rhabdomyosarcoma	17.6 M	I,V,A,D,Cy	9	53	47.5	Yes[f]	No	Yes
8[b]	Neuroblastoma	14.2 F	I,P,J,E,V	18	57	68,98[g]	No	No	Yes

[a]V, vincristine; A, actinomycin D; D, doxorubicin; P, cisplatin; J, carboplatin; E, etoposide; I, ifosfamide; Cy, cyclophosphamide.
[b]Patient 1 had nephrectomy and patient 8 had received platinum therapy; none of these cases had toxic antibiotic level.
[c]Radiotherapy (30 Gy) to the liver; the upper pole of right kidney is included in the field.
[d]GFR measured by Schwartz's formula [35]; 99-Tc-DTPA clearance in all other patients.
[e]Rhabdomyosarcoma of urinary bladder; though normal GFR (123 ml/min/1.73 m^2) before IFO treatment.
[f]Bilateral hydronephrosis and renal failure at presentation.
[g]GFR 68 ml/min/1.73 m^2 1 year after and 98 ml/min/1.73 m^2 4 years after completion of treatment.

TABLE II. Renal Function in Children Who Received IFO (and no Other Nephrotoxic Drugs) and Developed Glomerular Impairment (n = 6).

Parameter	Value	Reference values
1. GFR Median (range) ml/min/1.73 m^2	61.47 (33–85)	≥90 ml[a]
2. P_{cr} Median (range) (μmol/l)	123 (85–216)	Variable[b]
3. Fractional excretion % Mean (SD)		
Sodium	1.47 (0.11–2.68)	0.67 ± 0.37
Calcium	4.91 (4.33–5.81)	<2.0[c]
Phosphate	23.91 (10.47–34.89)	<20.0[b]
Magnesium	4.76 (4.38–11.61)	~3.0[b]

[a]Skinner et al. [10]
[b]Schwartz et al. [33]
[c]Sutton and Dirks [37].

other than IFO (Table I—patient 7 had renal tract involvement with malignancy; patient 8 received platinum). The remaining six patients had normal glomerular function before IFO treatment. Serum levels of aminoglycosides and vancomycin were not toxic in any patient and none had received cisplatin, carboplatin, melphalan, intravenous amphotericin, acyclovir, or any other nephrotoxic drug. One (patient 3) had received radiotherapy (30 Gy) to the liver and the upper pole of the right kidney. His GFR was normal 3 years after radiotherapy when he was treated with IFO for relapse. IFO was the most likely cause of glomerular impairment in five of six children and was at least partly responsible in the child who received radiotherapy. In the index case, IFO can be further implicated as the pretherapy nephrectomy specimen had a normal histology, and the abnormalities developed later.

Glomerular histology of IFO toxicity is previously unreported in children, though hyalinization of some glomeruli was seen in an adult [18]. Severe tubular atrophy and interstitial nephritis following IFO therapy have been reported in an infant [19].

Before IFO was introduced clinically, laboratory and animal studies had not shown its nephrotoxic potential [20], though significant glomerular toxicity was reported in an adult soon after its clinical use [21]. Subsequent data from phase II studies in children generally used P_{cr} values as a measure of glomerular function and revealed either none [22,23] or infrequent and transitory [24] dysfunction. The first report of persistent and significant glomerular impairment in children in 1988 [25] was followed by two others [5,14] over the next few years. An incidence of glomerular impairment in 17.1% following IFO is higher than previous reports of 0–9.9% [4,13, 26–28]. Inclusion of every IFO-treated patient since the computerization of biochemical data storage and chronological exclusion of 22 patients from any analysis were intended to provide accuracy of assessment. With this exclusion, there is a theoretical possibility of selection bias though it is unlikely to influence the outcome in view of subsequent complete inclusion over a number of years.

Our study suggests late onset and a progressive nature of glomerular dysfunction. Five of six affected children had normal glomerular function at the end of therapy and raised P_{cr} values were first recorded several months later (Fig. 2). Furthermore, median follow-up duration in affected children was significantly longer (41.5 vs. 19 months, $P = 0.04$) then the rest, suggesting that the longer

TABLE III. Comparison of Glomerular Impairment Group With the Rest

	Normal glomerular function	IFO-induced glomerular toxicity
1. Number of patients (%)	29 (82.9)	6 (17.1)
2. Age at study (years) Median (range)	9.5 (3.25–18.5)	13.7 (6.9–17.5)
3. Age at IFO treatment (years) Median (range)	6.08 (0.75–14)	8.37 (2.25–14.58)
4. Follow-up (months) Median (range)	19 (6–67)	41.5 (17–68)*
5. Cumulative IFO dose (g/m^2) Median (range)	54 (18–135)	93.7 (36–121)
6. Infusion schedule		
Fractionated (no. of patients)	13	2
Continuous (no. of patients)	16	4
7. Pretreatment nephrectomy (no. of patients)	1	1
8. Preexisting renal tract disease (no. of patients)	3	1[a]
9. Nephrotoxic anticancer agents (no. of patients)	5	0
10. Amphoterecin B/intravenous acyclovir (no. of patients)	5	0
11. Number of patients with toxic serum levels of aminoglycosides, vancomycin	1	0
12. Abdominal radiotherapy	4	1

[a]GFR at diagnosis was normal (123 $ml/min/m^2$).
*Significantly (P value 0.04) longer follow-up in the affected group; difference between no other factor reached statistical significance. Statistical analysis: Mann-Whitney median rank test for rows 2–5; chi-square test for 6–12.

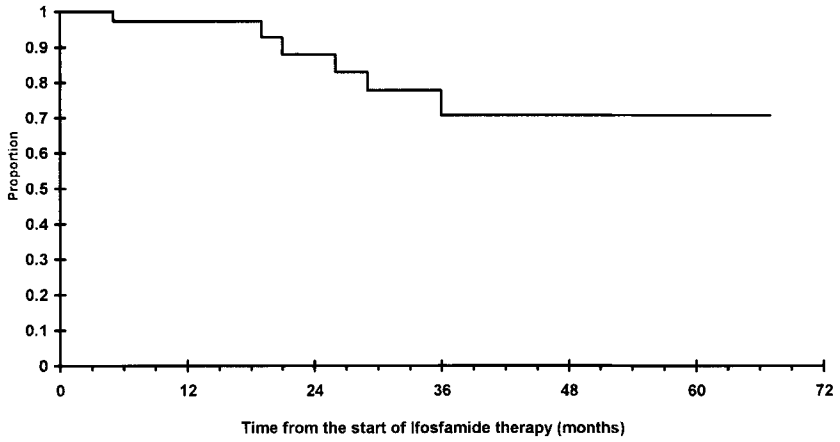

Fig. 2. Proportion of children without glomerular impairment from the start of IFO therapy (Kaplan-Meier plot).

these children are followed up, the higher might be the incidence of glomerular impairment. The argument for later onset and progressive nature is further strengthened by the fact that two of the children with clinical glomerular impairment were part of our previously published report [8]. They showed evidence of subclinical glomerular impairment by SDS-PAGE urine protein electrophoresis [29], 6 and 7 months after the end of therapy. Median follow-up in previous studies [26,27] was considerably less than ours and this may be a reason for their lower incidence.

Children with glomerular impairment were compared with those without, to identify possible predisposing factors (Table III). Although statistically not significant, af-

fected children were older. An older age is in sharp contrast to a generally recognized [13,26] association between younger age and tubular toxicity of this drug. Compared to the rest of the group, affected children received nearly twice the total amount of IFO, though this difference did not reach statistical significance. Infusion schedules were similar in the two groups. Ratios of actual weight, height, and BMI and respective age and sex appropriate 50th centile values were similar in the two groups. Lack of statistical difference between the two groups in relation to pretreatment nephrectomy, preexisting renal tract disease, use of other nephrotoxic anticancer drugs, intravenous amphotericin or acyclovir, or to antibiotic toxicity may be due to small numbers.

Nephrectomy has been suggested as a possible predisposing factor [14,26] but in our study there were too few nephrectomies to make any meaningful correlation. Nevertheless, the patient who developed the earliest toxicity had a nephrectomy. Increased risk following nephrectomy may be explained by the "higher single-nephron load" theory, which was developed from the study of cisplatin toxicity in a rat model [30]. All children with glomerular impairment in our study had coexistent tubulopathy which invariably developed prior to the glomerulopathy and suggests a characteristic pattern of IFO nephrotoxicity.

Glomerular impairment is likely to be underestimated in IFO-treated patients because of inherent flaws in the methods commonly used. Although P_{cr} values are universally used and commonly accepted as a test of glomerular function, there are certain limitations. In a study of 23 children with moderately low GFR (40–70 ml/min/1.73 m^2) measured by DTPA clearance, as many as 35% had a normal P_{cr} value [31]. P_{cr} value has been shown to be reduced by as much as 40% in situations where muscle mass is low, e.g., malnutrition [32], anorexia [33], and paraplegia and quadriplegia [34]. Furthermore, children with cancer are undernourished [35], a finding supported by our own analysis of BMI. Using P_{cr} values alone, as was the case with most Phase II studies, one would underestimate glomerular impairment. Indirect estimation of creatinine clearance (Schwartz's formula) [33] from P_{cr} level and body height, which has been used in another IFO follow-up study [26], also suffers from the same drawback of overestimating the GFR in undernourished children [33]. Tc-99m DTPA and Cr-51 EDTA clearances, which are used as standard tests for glomerular assessment in many centers [36], may overestimate GFR in the presence of tubulopathy because of partial leak of isotope from the damaged tubules resulting in faster clearance. This is particularly important in IFO-treated children as they have been shown to have coexistent tubulopathy. We recognize the weakness of using P_{cr} value in differentiating between normal and impaired glomerular function in our study, and it is possible that some of the children in the unaffected group may have abnormal glomerular function despite normal P_{cr} values. But that inaccuracy will, if anything, lead to a decrease in the calculated incidence of glomerular impairment and therefore will support our argument that glomerular impairment is underestimated.

Evidence of frequent (17.1%) and progressive glomerular impairment following IFO therapy in this study is a real cause for concern, as chronic renal insufficiency can have serious and long-term consequences. Owing to the limitations of tests routinely used, it is possible that this problem is underestimated. It is extremely important to assess renal function comprehensively in all children who have received IFO.

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