

Fanconi syndrome after Ifosfamide exposure – case report

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ABSTRACT

Ifosfamide is an antineoplastic drug widely used in the treatment of paediatric malignancies. However, in up to 50% of patients, it is associated with nephrotoxicity ranging from asymptomatic tubulopathy to overt renal failure.

A two-year-old Caucasian boy was diagnosed with stage IV Burkitt lymphoma, with hepatic and renal and bone marrow involvement. Baseline evaluation showed GFR of 60 mL/min/1.73 m². He started chemotherapy with LMB 96 protocol group B with 5 courses of chemotherapy with vincristine, cyclophosphamide, doxorubicin, prednisone, and intrathecal administration of cytarabine and methotrexate. After the first chemo protocol, the patient was in remission and recovered normal renal function, but three months later he relapsed with involvement of the liver and kidneys. The patient initiated a salvage regimen with R-ICE (rituximab – ifosfamide, carboplatin, etoposide) intrathecal methotrexate and cytarabine and allogeneic stem cell transplantation was proposed. After achieving complete remission, he underwent allogeneic stem cell transplantation with busulfan and cyclophosphamide. Graft versus host disease prophylaxis was made with tacrolimus and methotrexate and infection prophylaxis with fluconazole and acyclovir.

However, during treatment of the relapse, the patient presented downward crossing of weight and height centiles without recovery after treatment terminus and, following transplantation, consecutive laboratory testing suggested tubulopathy. Upon nephrologist referral, he was diagnosed with Fanconi syndrome and adequate supplementation was initiated with improvement of the patient's general condition and slow centile catch up. After literature review, the most probable causing agent was determined to be ifosfamide, as the nephrotoxic effects of the other medications prescribed tend to be reversible after stopping.

Nephrotoxicity secondary to chemotherapy is a major cause of morbidity in paediatric cancer survivors. Our case represents a rare situation with unspecific clinical signs. Clinicians must be alert to the necessity of close monitoring to identify renal toxicity, mainly tubular dysfunction, as early as possible and allow adequate supplementation, which is crucial in preventing side effects.

Keywords: Ifosfamide, Nephrotoxicity, Fanconi Syndrome.

INTRODUCTION

Ifosfamide is an isomer of cyclophosphamide with considerable efficacy against a wide range of hematological and non-hematological neoplasms in children. However, it is associated with nephrotoxicity in up to 50% of patients, depending on the screening method.^{1,2} Ifosfamide nephrotoxicity may manifest abruptly or subclinically and belatedly several months or years after exposure, with different degrees of severity, ranging from asymptomatic tubulopathy to overt renal failure.¹⁻³ Important metabolic consequences include acidosis and electrolyte disorders, with the need for complex supplementation therapy, decreased quality of life, and also limitations on optimal antineoplastic treatment of relapses.⁴

Fanconi syndrome is a proximal tubulopathy characterized by proximal tubular loss of glucose, phosphate, bicarbonate, amino acid and proteins which may result in rickets and growth impairment.⁵ It has been described as a late effect of Ifosfamide in only 5 to 7% of patients treated.^{2,6}

In this case report the authors describe a case of Fanconi syndrome diagnosed 17 months after exposure to ifosfamide for Burkitt lymphoma treatment.

CASE REPORT

A 33-month-old boy, with unremarkable personal and family history, presented with dyspnea and abdominal distension with a palpable mass on the lower left abdominal quadrant. Thoracic, abdominal, and pelvic *computed tomography* was performed, showing: “large abdominal adenopathic conglomerate, retroperitoneal and mediastinal adenopathies, coexisting numerous cervical adenopathies (...) signs of probable splenic and renal involvement; ascites and bilateral pleural effusion.” The bone marrow examination revealed 6.4% of lymphoid cells with morphology compatible with Burkitt lymphoma. Lumbar puncture showed no central nervous system involvement. The patient was diagnosed with stage IV Burkitt lymphoma with hepatic, renal and

bone marrow involvement. Initial laboratory evaluation showed a creatinine of 0.71 mg/dL, corresponding to an estimated GFR (eGFR) of 51 mL/min/1.73 m², calculated with the Revised Schwartz formula

($eGFR = [\text{Height (cm)} \times 0.413] / \text{creatinine (mg/dL)}$) and normal urinalysis (Table 1). He received chemotherapy with LMB 96 protocol group B (according to the percentage of blasts in bone marrow) consisting of

Table 1

Laboratory findings during disease course.

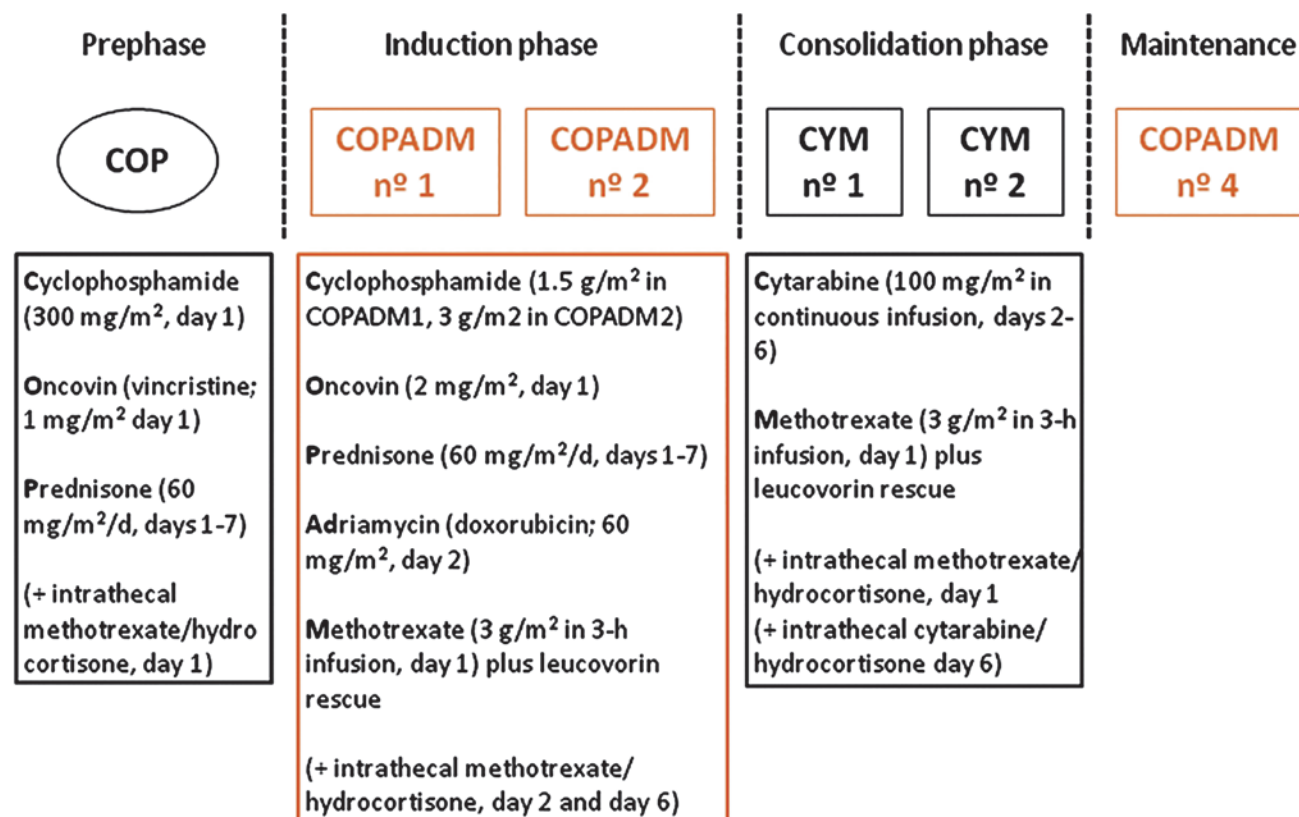
Age	At diagnosis of Burkitt lymphoma	After 1 st treatment (LMB 96 protocol group B – Fig. 1)	Relapse	After 2 nd treatment and before blood marrow transplant	After blood marrow transplant (R-ICE protocol – Fig. 2)	After tacrolimus suspension	At diagnosis of Fanconi syndrome (nephrology appointment)	Reference range
	2yr 9mo (33 mo)	2yr 11mo (35 mo)	3yr 3mo (39 mo)	3yr 7mo (43 mo)	3yr 8mo (44 mo)	4yr 11mo (59 mo)	5yr 4mo (64 mo)	
Peripheral blood								
WBC (/uL)	8440	1680	7030	5230	6670	10400	7340	5000 – 15000
Neutrophils (/uL)	4740	360	342	3870	6430	6540	3750	1500 – 8000
Hemoglobin (g/dL)	10.2	10.0	13.5	12.7	10.4	12.7	11.2	11.5 – 13.5
Platelets (/uL)	388 000	1 020 000	362 000	346 000	256 000	247 000	332 000	200000 – 450000
Glucose (mg/dL)	50	50		58	114	94	87	60 – 99
Urea (mg/dL)	24	24		26	11	39	35	15 – 36
Creatinine (mg/dL)	0.71	0.37	0.43	0.42	0.39	0.63	0.69	0.44 – 0.69
Uric acid (mg/dL)	3.8	3.7	5.2	2.6	<1	1.0	1.5	1.8 – 4.9
Sodium (mEq/L)	136	137	137	140	140	137	136	136 – 145
Potassium (mEq/L)	3.4	4.1	4.5	4.1	3.6	3.7	2.8	3.4 – 4.7
Chloride (mEq/L)	104	104	105	106	109	111	108	98 – 107
Phosphate (mg/dL)	5.7	5.7		4.9	2.7	2.1	1.8	4.1 – 5.9
Magnesium (mg/dL)	1.8	1.8		2.3	1.8	2.2	2.3	1.7 – 2.3
Calcium (mg/dL)	8	10		9.8	9.4	9.1	9.9	8.8 – 10.8
GFR* (mL/min/1.73m ²)	51	105	90	98	106	68	51	> 89
Vitamin D 1.25 (pg/mL)							13.60	19.6 – 54.3
Vitamin D25 (ng/mL)							17.7	30 – 100
Intact parathyroid hormone (pg/mL)							11.70	16.23 – 63.02
Aldosterone (ng/dL)							61.8	4 – 44
Active rennin (uUI/mL)							220.5	15.8 – 100.8
Acid base balance (capillary)								
pH							7.31	7.35 – 7.45
pCO2 (mmHg)							33.3	35 – 45
HCO3- (mmHg)							16.6	22 – 26
BE (mEq/L)							-9.7	-2.0 – 2.0
An Gap (mEq/L)							13	8 – 16
Urinalysis								
pH	5			5	8	7	7	5 – 8
Specific gravity	1013			1013	1010	1009		
Glucose	negative			Negative	50	1000	>1000 mg/dL	
Proteins	negative			negative	negative	30	50 mg/dL	
Tubular phosphate reabsorption (%)							53	> 85
Fractional excretion of potassium (%)							44.7	10 – 30%
Fractional excretion of uric acid (%)							61.1	16%
Albumin:creatinine ratio (mg/g)							470	< 30

* Calculated with the Revised Schwartz Equation for Glomerular Filtration Rate (GFR): $GFR = [\text{Height (cm)} \times 0.413] / \text{creatinine (mg/dL)}$

Legend: yr – years; mo – months; GFR – Glomerular filtration rate

Figure 1

LMB 96 protocol group B



one course with cyclophosphamide, vincristine and prednisone; 2 courses with vincristine, cyclophosphamide, doxorubicin, prednisone and high-dose intrathecal methotrexate (3 g/m² over 3 hours); and 2 courses of intrathecal methotrexate and continuous infusion cytarabine (Figure 1). Subsequently, he achieved remission and there was improvement of renal function with normalization of eGFR.

Three months later, the disease relapsed again with hepatic renal and bone marrow involvement. The thoracic, abdominal, and pelvic *computed tomography* showed: "lower mediastinal adenopathic conglomerate with about 60 mm; a voluminous lesion with a soft tissue component in the right chest wall (70x82mm), with an under and extrathoracic component, extending along the costophrenic sinus to the homolateral diaphragm pillar with extensive pre-foraminal paravertebral component and pleural infiltration; there are aspects compatible with renal relapse translated by the presence of several cortical nodular structures, (...)". The patient, then aged 3 years and 2 months old, was started on a salvage course of chemotherapy with ifosfamide, carboplatin, etoposide and rituximab (R-ICE), intrathecal administration of methotrexate and cytarabine (Figure 2), and allogeneic stem cell transplantation was proposed. Baseline analyses revealed an eGFR of 88 mL/min/1.73 m² and normal urinalysis. A total cumulative dose of 45 g/m² of Ifosfamide was administered and adequate hyperhydration and Mesna were used. He achieved remission after five cycles of R-ICE (five months later).

At the age of 3 years and 7 months, the patient underwent allogeneic stem cell transplantation with busulfan and cyclophosphamide. Graft versus host disease prophylaxis was made with tacrolimus and methotrexate and fluconazole and acyclovir were administered for infection prophylaxis. Serum creatinine before transplant was 0.42 mg/dL, corresponding to an eGFR of 88 mL/min/1.73m², and urinalysis was normal. No transplant related complications were registered.

During the relapse treatment, the patient presented downward crossing of weight and height centiles without recovery after treatment terminus (Figures 3 and 4). Following transplantation, consecutive laboratory workup showed low plasma levels of uric acid and

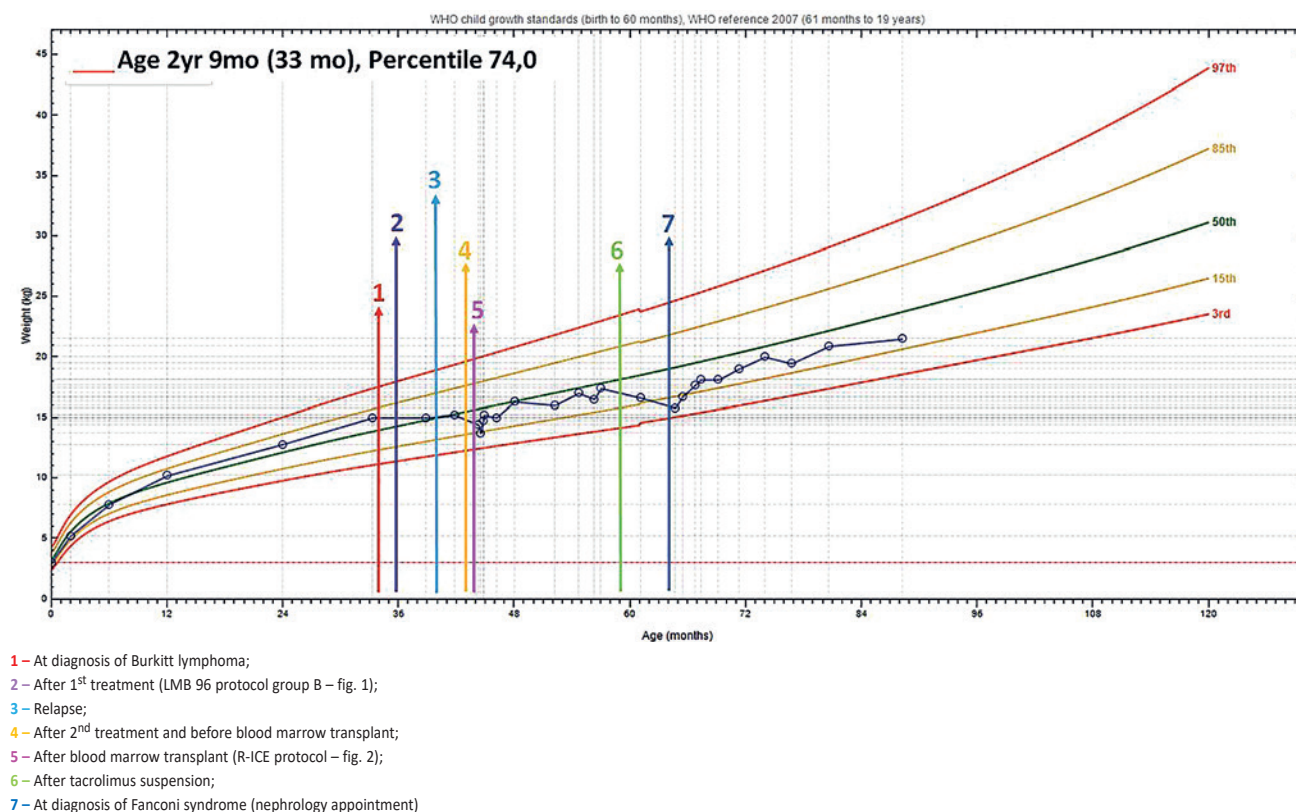
Figure 2

R-ICE treatment protocol.

	Day					
	1	2	3	4	7	14
Rituximab 375mg/m ²	+				+	+
Ifosfamide 2 g/m ²		+	+	+		
+ mesna		+	+	+		
Etoposide 75 mg/m ²		+	+	+		
Carboplatine AUC 5 (maximum 350 mg/m ²)		+	+	+		

Figure 3

Weight growth chart.



phosphate, glycosuria and proteinuria. Remarkably, these abnormalities didn't resolve after discontinuation of immunosuppressive therapy, which occurred 1 year and 7 months later, when the patient was 5 years old.

At the age of 5 years and 4 months, upon suspicion of renal tubulopathy, the patient was referred to the nephrology unit for further evaluation. He was 16 Kg (6th centile) and 102.5 cm (2nd centile), with normal blood pressure (50th-90th centiles). He complained of asthenia, but physical examination was otherwise unremarkable. Laboratory investigation showed an eGFR of 62 mL/min/1.73 m², non-anion gap metabolic acidosis, hypophosphatemia with low tubular reabsorption of phosphorus, hypokalaemia with high fractional excretion of potassium, normal magnesium, low plasma levels of uric acid with high fractional excretion of uric acid, proteinuria and glycosuria on urinalysis and albuminuria (Table 1). Ophthalmological evaluation revealed no cystine deposits.

Therefore the patient was diagnosed with Fanconi syndrome secondary to ifosfamide treatment. He started treatment with potassium and aliskiren (to help reduce the need for potassium supplementation), bicarbonate and phosphate supplements; indomethacin was also prescribed, to reduce renal tubular losses. Later he needed bicarbonate and 1,25-dihydroxycholecalciferol supplementation, due to low 25 and 1,25 vitamin D. After adequate supplementation the patient's

general condition and appetite improved with slow centile recovery (Figures 3 and 4).

Currently, the patient is 7 years and 7 months old and he is under regular follow up. It was possible to stop indomethacin, phosphate and 1,25-dihydroxycholecalciferol supplementation, but the patient maintains some features of Fanconi syndrome (acidosis, hypokalemia, glycosuria and proteinuria).

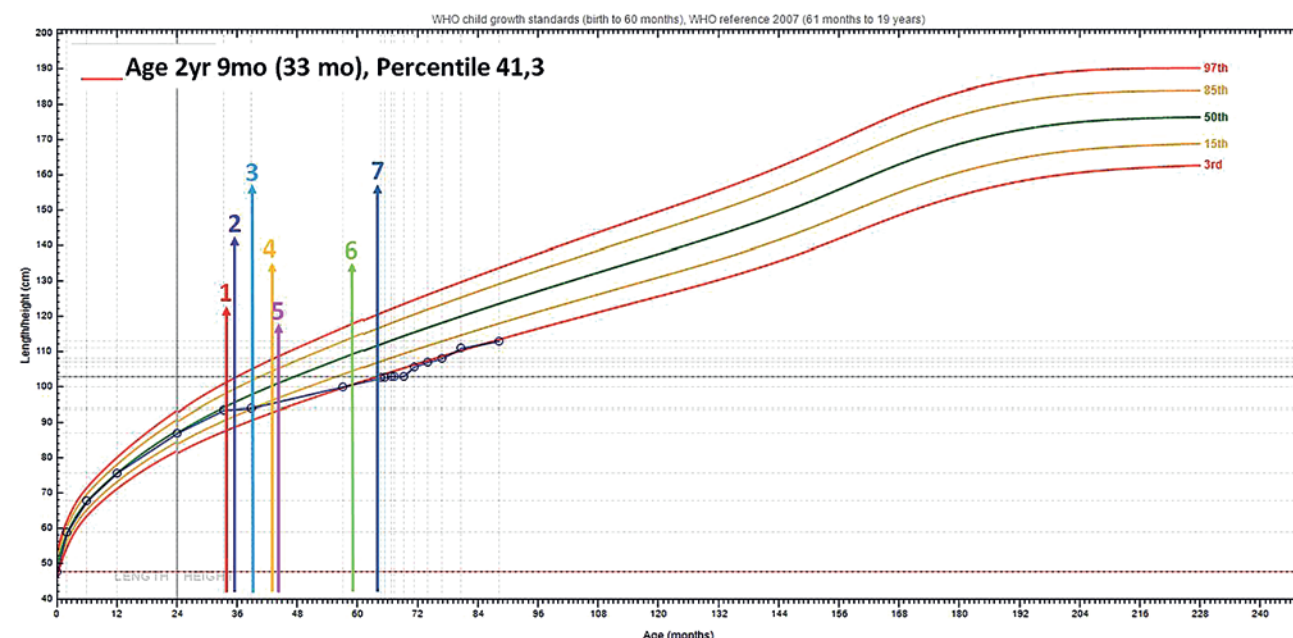
DISCUSSION

Fanconi syndrome is a proximal tubule defect consisting of a generalized loss of reabsorption capacity, resulting in wasting of glucose, sodium, potassium, bicarbonate, phosphate, amino acids and proteins, in different degrees of severity⁵. It can lead to rickets and growth impairment and has been described as occurring in 5 to 7% of paediatric patients treated with ifosfamide.^{2,6}

Our patient presented with metabolic acidosis, hypophosphatemia, hypokalemia, hypouricemia, proteinuria and glycosuria. Further testing showed low tubular reabsorption of phosphorus and high fractional excretion of potassium and uric acid, thus confirming the diagnosis of Fanconi syndrome. Some features of Fanconi syndrome (hyperchloremia – possibly indicating non-anion gap acidosis – glycosuria,

Figure 4

Height growth chart.



- 1 – At diagnosis of Burkitt lymphoma;
- 2 – After 1st treatment (LMB 96 protocol group B – fig. 1);
- 3 – Relapse;
- 4 – After 2nd treatment and before blood marrow transplant;
- 5 – After blood marrow transplant (R-ICE protocol – fig. 2);
- 6 – After tacrolimus suspension;
- 7 – At diagnosis of Fanconi syndrome (nephrology appointment)

hypophosphatemia and hypouricemia) appeared after blood marrow transplant, and, so, after treatment with ifosfamide and carboplatin (Table I and Figure 1), but the full picture was only evident at the first nephrology appointment.

It is difficult to assume a direct causative relation for renal damage in patients with complex clinical situations and exposure to different nephrotoxic agents. In our patient, we assumed the Fanconi syndrome to be secondary to chemotherapy because no other causes of renal damage were apparent.

Although cystinosis is the most frequent aetiology of Fanconi Syndrome in children, corneal cystine crystal are present in all patients after the age of 1 year old and Fanconi syndrome is present in virtually all patients at the age of 6 months.⁷ Our patient, not only had a normal ophthalmological exam without complaints of photophobia, but also Fanconi syndrome was not present at the time of Burkitt lymphoma diagnosis (33 months old) leading us to believe that cystinosis is not the cause for his renal dysfunction.

Of note, the patient presented with renal involvement with decreased GFR at the time of Burkitt lymphoma diagnosis. However, after achieving remission, renal function normalized and severe deterioration was apparent only after the second chemotherapy protocol.

Amongst the chemotherapy agents used, ifosfamide, carboplatin, methotrexate and tacrolimus have all been implicated in tubular nephrotoxicity.

Ifosfamide is an alkylating synthetic analog of cyclophosphamide and both can cause hemorrhagic cystitis. The use of Mesna has reduced the occurrence of hemorrhagic cystitis.⁸

Ifosfamide is transformed to its active metabolites mainly by cytochrome P450 and is excreted in urine predominantly as acrolein and inactive metabolites; 20% of the administered dose is excreted as unchanged ifosfamide.⁹

The antineoplastic effect of ifosfamide is exerted only by its active alkylating metabolites, ifosfamide mustard and acrolein, which result from hydroxylation of ifosfamide. Besides hydroxylation, the oxazaphosphorine ring of ifosfamide undergoes side chain dealkylation, that produces 2- and 3-dechloroethylifosfamide (non-toxic) and chloroacetaldehyde, which is the presumed causative agent of ifosfamide nephrotoxicity.⁹

The exact pathologic mechanisms of Ifosfamide renal damage remain unknown, but there are several pathophysiological mechanisms that can explain ifosfamide nephrotoxicity: 1) binding toxic metabolites of ifosfamide to mitochondrial DNA, causing depletion of ATP; 2)

binding to nuclear DNA, leading to blockage of cell regeneration; 3) inhibition of sodium-dependent phosphate co-transport in kidney cells by ifosfamide metabolites chloroacetaldehyde, 4-hydroperoxyifosfamide and ifosfamide mustard.⁹ However, further investigation is needed to confirm the exact cellular and molecular mechanisms of ifosfamide renal damage to allow the development of kidney protective protocols. Meanwhile, there is no proven strategy to minimize ifosfamide tubular toxicity.^{10,11}

Ifosfamide nephrotoxicity may manifest with variable clinical features in different degrees of severity and incidence rates. According to literature the following manifestations have been described: 1) Glomerular toxicity (1-4%), manifested either as acute or chronic renal failure; 2) Proximal tubular toxicity, either as complete Fanconi syndrome (1-7% of children) or isolated defects of tubular reabsorption – aminoaciduria (28%); glycosuria (28%), impairment of phosphate reabsorption (20-30%), hypophosphatemia and hypophosphatemic rickets, low molecular weight proteinuria, calciuria, magnesuria and natriuria; 3) Distal tubular toxicity, presenting as subclinical impairment of urinary concentration (30%), distal renal tubular acidosis or nephrogenic diabetes insipidus; 4) Renal toxicity – proteinuria and hypertension.⁹ Chronic tubular dysfunction persisting over a period of 5 years has been found in 25-47% of children treated with ifosfamide.¹⁰

All the above mentioned acid-base and hydroelectrolytic disturbances may contribute to growth failure in children⁹, especially chronic renal disease, hypophosphatemic rickets and renal tubular acidosis.

Renal toxicity can manifest after conclusion of ifosfamide therapy; consequently, patients should be followed up closely for a protracted period of time, even after finishing chemotherapy,^{9,12} especially when a higher cumulative dose was used. Carboplatin is a cisplatin analog, with a spectrum of activity similar to cisplatin, but is less nephrotoxic as it is not transformed into toxic metabolites by renal tubule cells.¹⁰ Rarely, it may cause reduction in GFR and hypomagnesemia; but the risk of renal lesion and tubulopathies is higher with combination therapy with carboplatin and ifosfamide.¹⁰

High-dose methotrexate is responsible for a decline in GFR in about 1.8% of patients. The low solubility in acid pH causes precipitation of the drug and metabolites within the renal tubular lumen, with subsequent obstruction, reduction of GFR and tubular cell death. Methotrexate-related nephrotoxicity appears to be entirely reversible after drug suspension, with a median time to recovery of renal function of 16 days.¹⁰

Tacrolimus produces an imbalance between vasoconstrictor factors (endothelin, thromboxane and activation of the renin-angiotensin system) and decrease of vasodilator agents (prostaglandin E2, prostacyclin, and nitric oxide), thus causing vasoconstriction of the afferent arteriole, which induces an acute reversible impairment of renal function and also acute reversible tubular dysfunction.⁸

As previously mentioned, our patient was medicated with several nephrotoxic drugs and sometimes more than one of these agents were used concomitantly. Nevertheless, ifosfamide is the most frequently implied in complete full Fanconi syndrome and may be

irreversible. In contrast, nephrotoxicity caused by the other agents is described as reversible upon treatment terminus.^{1,3,10,12}

While specific protective treatment protocols are not available, it is important to identify patients at increased risk of ifosfamide nephrotoxicity. Currently proven risk factors include higher cumulative doses (> 45 mg/m²), previous nephrectomy and concomitant administration of cisplatin or carboplatin. Younger age at treatment has been reported by some groups to be relevant; however other studies showed no independent effect and further investigation is needed.^{3,4,10,12-14} Remarkably, nephrotoxicity can occur even in children who do not have any of the established risk factors, which has been proposed to be due to specific pharmacogenetic differences between individuals.³

This patient was three years old when he was exposed to ifosfamide, had simultaneous treatment with carboplatin and was treated with a cumulative dose of 45 g/m² of ifosfamide. He was maintained under clinical and analytical surveillance, which at one point revealed renal damage that did not resolve after ending treatment with all nephrotoxic drugs. Upon suspicion of a tubulopathy, he was referred to the Nephrology team and diagnosed with Fanconi syndrome 1 year and 5 months after ifosfamide treatment. Upon adequate supplementation, the patient recovered appetite, wellbeing and started to show centile recovery.

Our case represents a rare situation with nonspecific clinical signs and highlights the need for close monitoring of child cancer survivors in order to identify renal toxicity and allow timely supplementation. Although some large follow-up studies have shown recovery of tubular function in some patients³ our patient maintains the need for complex supplementation 2 years after diagnosis.

In conclusion, nephrotoxicity secondary to chemotherapy is a major cause of morbidity in paediatric cancer survivors, limiting life quality and the delivery of further optimal antineoplastic treatment. Our case highlights the necessity of close monitoring of these patients to identify renal toxicity as early as possible and allow adequate supplementation. Follow up must include detailed recordings of the chemotherapy protocols administered, clinical evaluation with growth and blood pressure measurement, and, finally, laboratory surveillance of renal damage with measurement of serum creatinine, urea, electrolytes and urinalysis.

Disclosure of potential conflicts of interest: none declared.

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