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Reminder of important clinical lesson

Ifosfamide induced Fanconi syndrome

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Summary

Ifosfamide (IFA) is a powerful chemotherapeutic drug that is active against a variety of paediatric malignancies. However, renal toxicities such as haemorrhagic cystitis and Fanconi syndrome are major hazards that hinder its use in clinical practice. The authors present a case of a patient treated for Wilms' tumour with IFA who developed rickets with Fanconi syndrome. Patients undergoing IFA treatment must be carefully monitored for the development of iatrogenic complications. Recent studies have improved our understanding of the underlying pathomechanism of IFA induced Fanconi syndrome, and selective renal protection against during chemotherapy with IFA may be possible soon.

BACKGROUND

There are multiple causes for renal injuries in children suffering from malignancies including the adverse effects of the therapies. Due to the grim prognosis of the malignant diseases without proper treatment, caretakers for these children have been compelled to administer chemotherapeutic agents with serious and toxic side effects. Attempts to reduce the dose and frequency have not been able to avoid all the unwanted toxic effects of these treatments. Ifosfamide (IFA) is an alkylating oxazophosphorine derivative of cyclophosphamide (CPA) that has been used widely in the treatment of a number of childhood tumors.[1] Although its use was initially restricted by the acute side effect on causing haemorrhagic cystitis, the availability of 2-mercapothenesulfonic acid (MESNA) has largely mitigated this limitation.[2] However, IFA continues to be one of the most important chemotherapeutic agents that is responsible for chronic renal toxicity.[3] Incidence of chronic renal injury secondary to IFA has been reported from 1.4 to 30%.[4–7] However, only about 5% of children will develop full Fanconi syndrome.[8–10] Fanconi syndrome is a global proximal tubulopathy of the kidney that results in wasting of glucose, amino acids, calcium, phosphate, uric acid, bicarbonate and many organic compounds in the urine.[8] Hypophosphatemic rickets is one of the major associated complications that have profound impact on children. It is imperative for physicians who take care of children with childhood malignancies to be aware of this potential side effects.[11]The case outlined below demonstrates the renal side effects of IFA treatment and the associated long-term complications of Fanconi syndrome.

CASE PRESENTATION

A 4-year-old Caucasian boy was diagnosed with Wilms tumour stage IV who presented with a mass on the left kidney and pulmonary metastasis. Initial laboratory investigations showed that he had a normal renal function and urinalysis. He underwent a left nephrectomy, chemotherapy (actinomycin-D, vincristine, cyclophophamide and adriamycin) and radiation therapy. After the initial treatment, the pulmonary metastasis persisted. After consulting the North American Wilms Tumour Study Group, therapy was then switched to IFA (a total dose of 117 grams per m^2), carboplatinum (a total dose of 2.275 grams per m^2) and etoposide (a total dose of 6.5 grams per m^2) for over a year. In view of the toxicities of this regimen, especially in a young child with unilateral nephrectomy, all the chemotherapies were administered in hospital and the patient was monitored closely by the oncology and nephrology teams throughout the therapy for potential complications related to the drugs. Besides intravenous fluid hydration and MESNA rescue, blood counts, electrolytes, renal and liver functions tests and urinalysis were monitored before each cycle and then every other days. Repeated lung biopsy after 5 weeks of treatment revealed residual metastasis. After thorough discussions with the family, it was decided to continue the regimen for a total of 13 cycles or until the patient could not tolerate the chemotherapy. In addition to the laboratory investigation as mentioned above, chest x-ray was performed at months 1, 2, 3, 6, 9 and 12 months. Other imaging investigations such as ultrasound and CT scan were also performed as indicated. Echocardiogram and audiometry were also done per our protocol. Other than the requirement of several platelet infusions and granulocyte colony stimulating factors injections, the patient was able to tolerate the 13 cycles of chemotherapy and achieve remission, without overt renal complications. However, nephrology team was urgently consulted about 2 years after he has finished his last dose of IFA, due to new onset metabolic acidosis and proteinuria. Laboratory investigations showed that his serum bicarbonate was 18 mmol/l. Other electrolytes including calcium and phosphorus were within normal range. Urinalysis confirmed the presence of glucose, protein and renal loss of bicarbonate. He was diagnosed to have Fanconi syndrome secondary to the IFA. The patient was started on citrate supplementation and ACE inhibitors. No phosphorus supplementation was given due to normal blood level at that time. He was clinically stable during follow-up. His potassium levels were stable enough that

no supplementation was required. However, at his visit 4 years (patient was at the age of 8) after the initial diagnosis of his Wilms tumour, he began to experience difficulty in running due to muscle weakness (myopathy possibly secondary to vincristine) and had obvious knock-knees. His body length was between the 10th and 25th percentiles, while it was along the 50th percentile a year before. His body weight percentile had not changed and was along the 75th percentile. Laboratory investigations revealed hypophosphatemia with normal calcium level. His serum creatinine level was 75 µmol/l. Urine examinations confirmed that he had excessive loss of phosphorus. An x-ray of the wrists and knees confirmed the diagnosis of rickets, and he was started on vitamin D and phosphorus supplementations. At his subsequent follow-up, his knee pain resolved and his serum phosphate and bicarbonate levels were well controlled. However, at age of 10, the patient suffered from an episode of acute rise in serum creatinine level to 185 µmol/l secondary to poststreptococcal acute glomerulonephritis. His ACE inhibitor was discontinued at that time, and his serum creatinine subsequently returned to 120 µmol/l after supportive management.

OUTCOME AND FOLLOW-UP

At his last visit at the age of 22, he had normal blood pressure of 123/68 mm Hg. His body weight and length were 73 kg and 161.5 cm, respectively. He still required phosphorus and vitamin supplementations for his Fanconi syndrome. His most recent blood works were: sodium 139 mmol/l (139 mEq/l); potassium 3.2 mmol/l (3.2 mEq/l); chloride 101 mmol/l (101 mEq/l); bicarbonate 28 mmol/l (28 mEq/l); blood urea nitrogen 5.9 mmol/l (35 mg/dl); creatinine 154 µmol/l (1.7 mg/l), glucose 4.9 mmol/l (88 mg/dl), calcium 2.45 mmol/l (9.8 mg/dl), phosphate 0.82 mmol/l (2.5 mg/dl), albumin 50 g/l (5 g/dl) and alkaline phosphatase at 100 U/l. He has recently finished his engineering degree and is adopting a healthy life style with exercise three times weekly in local gymnasium.

DISCUSSION

Fanconi syndrome is characterised by a global transport defect in the proximal tubules of the kidney. The spectrum of tubular dysfunction varies in different patients, ranging from a generalised proximal tubulopathy to partial reabsorption defects in sodium, potassium, glucose, amino acids, bicarbonate and phosphorus.[12] Medication is an important cause of acquired Fanconi syndrome (table 1). The combined use of IFA, carboplatinum and etoposide has been shown to be highly effective in inducing long-term remission among patients with soft tissue sarcomas that are resistant to other regimen. As the risks of renal tubular damage and haemorrhagic cystitis have been known for a long time, our institution had been adopting specific protocol to monitor and minimise the risks of such renal complications. Nephrotoxicity, including Fanconi syndrome, secondary to IFA therapy was first reported by van Dyk *et al* in 1972, and the findings were also observed and confirmed by others.[13] The mechanism by which IFA induces Fanconi syndrome has not been identified. As IFA is a prodrug and needs to be activated by the hepatic cytochrome oxidase systems before it can exert its effect, it has been proposed that the observed Fanconi syndrome was due to the one of its metabolic byproducts.[14] However, CPA, another commonly used antineoplastic drug and an isomer of IFA, only displays side effects of haemorrhagic cystitis but not other nephrotoxicities. As IFA and CPA are metabolised and converted to active compounds by the same P450 cytochrome systems, they both produce a number of alkylating substances. These toxic substances include acrolein, which is the primary toxic metabolite that causes haemorrhagic cystitis.[3] However, it has been shown that one of the other metabolites, chloroacetaldehyde (CAA), is able to induce Fanconi syndrome in isolated proximal tubular cells.[3 15 16] However, unlike CPA, IFA undergoes more extensive N-dechloroethylation and produces more CAA. As the metabolism of IFA produces more CAA than in CPA, it has been speculated that the differences in the production of CAA may lead to the observed differences in nephrotoxicity between IFA and CPA.[3] Nevertheless, the exact mechanism is still not yet elucidated. A recent study shows that IFA, rather than CPA, is selectively taken up by the organic cation transporter 2 (OCT2) receptor on the basolateral aspects of the proximal tubular cells and is likely to be the specific transport system that is responsible for IFA uptake.[17] Proximal tubular cells (isolated from mouse and human proximal tubules) with OCT2 expressions had significantly higher uptake of IFA. Since both IFA and CPA are highly hydrophilic and are not readily diffuse into the cells, the presence of such specific transporter may explain why only IFA can exert proximal tubular cell toxicity.[17] Interestingly, incubation of the human OCT2 cells with IFA together with cimetidine (a known substrate for human OCT2) completely suppressed the IFA induced toxicity. When dehydrogenase activity was measured as an index of cell vitality, the suppression of dehydrogenase activities by IFA was inhibited by the presence of cimetidine.[17] This finding sheds lights on the possibility of finding a selective kidney protection agent during chemotherapy. Further studies need to delineate the exact mechanisms and its clinical strategies. Other substances, including glycine, resveratrol (a natural phenol) and melatonin had also been studied and had various degrees of in vitro attenuation effects on renal toxicities in animal cells, but their clinical relevance is still doubtful.[18–20]

Table 1 Medications associated with drug-induced Fanconi syndrome (adapted from)[8]

Antiretrovirals	
Nucleoside reverse transcriptase inhibitors	Lamivudine, stavudine, didanosine (ddI)
Acyclic nucleoside phosphonates	Cidofovir, adefovir, tenofovir
Antibiotics	
Aminoglycosides	Gentamicin, amikacin, tobramycin
Tetracyclines	Tetracycline, doxycycline
Chemotherapies	
Alkylating and platinum agents	Ifosfamide, cisplatin, carboplatin, steptozocin
Antimetabolites	Azacitidine, mercaptopurine
Antiparasitic drugs	Suramin
Antiepileptic drugs	Valproic acid
Histimine2-blocking agents	Ranitidine, cimetidine
Carbonic anhydrase inhibitor	Acetazolamide
Salicylate intoxication	Aspirin
Iron-chelating treatment	Deferasirox
Psoriasis treatments	Fumaric acid
Spasmolytic drugs	Methyl-3-chromone

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As specific renal protective agent against IFA induced toxicity is currently not available, it is imperative for caretakers to identify patients who are at risk. It has been shown that those children at young ages (less than 3), had previous or concurrent treatment with cisplatinum, had nephrectomy or pre-existing renal impairment, and who had received a cumulative dose of more than 45 grams per m^2 of IFA are particularly susceptible to develop renal toxicity.[21 22] These patients should be monitored more closely for renal side effects. Urinalysis (presence of glucosuria and proteinuria) and blood work (levels of calcium, phosphate, bicarbonate and alkaline phosphatase) should be monitored before treatment and repeatedly during the course of treatment in order to determine any changes in renal function. Early identification of renal toxicity allows supplementation, which is crucial in preventing side effects such as those seen in the patient. Our patient received a very high dose of IFA (a total of 117 grams per m^2) due to the persistence of his pulmonary metastasis after initial therapy, and thus was particularly prone to develop renal tubulopathy. Although the decision to continue the aggressive chemotherapy was supported by the North American Wilms Tumour Study Group and the family in our situation and the patient was able to achieve remission, most patients are not able to tolerate such high doses. However, our patient did not show any laboratory evidence of tubulopathy until almost 2 years post-therapy suggests that patients with exposure to IFA, especially when the dose is high, need to be followed closely for prolong period of time even after finishing the chemotherapy. As in our patient, despite his Fanconi syndrome and rickets are adequately controlled by prolonged supplementations with phosphorus and vitamin D, the defect is very likely to be permanent and irreversible. Hence, IFA therapy is associated with significant morbidity and specific renal protection agent, like MESNA against hemorrhagic cystitis, is needed.

In conclusion, although IFA is an effective drug against many childhood malignancies, the nephrotoxic effects in children are still common and substantial and these renal injuries may be permanent and irreversible. Caretakers for these children should bear in mind these potential consequences and be vigilant in assessing the risks before treatment, as these complications may be easily underestimated and even overlooked. However, recent studies may shed new lights on selective renal protection during chemotherapy with IFA, but clinical use of these agents is not recommendable at this point.

Learning points

- Nephrotoxicity secondary to chemotherapy has significant morbidity.
- Some signs of nephrotoxicity may be subtle and require high index of suspicions.
- New therapy to avoid Fanconi syndrome in patients treated with IFA may be available in the near future.

Competing interests None.

Patient consent Obtained.

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