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Editorial Comment

EDITORIAL COMMENT

The growing pains of ifosfamide

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ABSTRACT

Ifosfamide is a commonly used chemotherapeutic known to have numerous adverse kidney manifestations. In this issue of *Clinical Kidney Journal*, Ensergueix *et al.* report a multicentric observational retrospective French study on 34 adult patients with tubular dysfunction and /or kidney dysfunction following ifosfamide treatment. Of these patients, 18% had isolated proximal tubular dysfunction, 14% had isolated acute kidney injury (AKI), 18% had isolated chronic kidney disease (CKD) and 50% had a combination of proximal tubular dysfunction and AKI. Concomitant treatment with cisplatin was identified as a risk factor for the development of AKI, and cisplatin and age were associated with estimated glomerular filtration rate at last follow-up. Interestingly, the cumulative dose of ifosfamide was not associated with renal outcomes. This report highlights the need for additional studies on the prevalence, spectrum and management of ifosfamide-associated nephrotoxicity and clearly demonstrates that patients who received ifosfamide should be followed long term to detect proximal tubular dysfunction and CKD early.

Keywords: adults, Fanconi syndrome, ifosfamide, nephrotoxicity

Ifosfamide is an alkylating agent and a member of the nitrogen mustard family. It is a synthetic analogue of cyclophosphamide that is primarily excreted in the urine (80% of the total dose as unchanged ifosfamide). It is believed to act through interfering with DNA replication and RNA production, and is used to treat different types of cancers in adult and paediatric populations [1, 2]. Common side effects include hair loss, vomiting, nephrotoxicity, neurotoxicity (encephalopathy and peripheral neuropathy) and bone marrow suppression.

Ifosfamide is associated with numerous possible adverse kidney manifestations [3]: acute kidney injury (AKI) due to acute tubular necrosis (ATN) [4], Fanconi syndrome [4, 5], interstitial nephritis [6], glomerular disease [7] and haemorrhagic cystitis [8]. While both ifosfamide and cyclophosphamide can cause haemorrhagic cystitis, only ifosfamide is associated with Fanconi syndrome. The introduction of sodium 2-mercaptoethanesulphonate (mesna) has virtually eliminated haemorrhagic cystitis. However, mesna has no preventive effect on the tubular toxicity of ifosfamide [9, 10]. Ifosfamide-induced tubular toxicity can be associated with metabolic acidosis with a normal anion gap (hyperchloremic acidosis) due to Type 1 (distal) or, less frequently, Type 2 (proximal) RTA. Polyuria due to nephrogenic diabetes insipidus (i.e. resistance to antidiuretic hormone) appears to be relatively rare.

Several risk factors for ifosfamide-induced nephrotoxicity have been identified including pre-existing kidney disease, combination with platinum-based chemotherapy and /or other nephrotoxins, cumulative dose of ifosfamide (>119 g/m^2) and renal irradiation [11]. In a Dutch study, it was demonstrated that paediatric patients who received ifosfamide had a lower

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glomerular filtration rate (GFR) than patients with the same pathologies who did not receive this treatment [12]. The main risk factors for nephrotoxicity in children are a cumulative dose >45 mg/m^2, young age (<3 years), previous or concurrent cisplatin treatment, Wilms tumour and unilateral nephrectomy [13]. The incidence of Fanconi syndrome in treated patients has been estimated to be between 1.4% and 5% [9]. Most information on ifosfamide nephrotoxicity comes from studies in children, as its use in paediatric oncology is common [14–16]. In contrast, reports of ifosfamide-related Fanconi syndrome in adult patients are scarce [6, 17]. In a long-term assessment of ifosfamide-related renal toxicity in adult patients, Farry *et al.* [18] reported a steady decline in the estimated GFR (eGFR), although none of the patients progressed to end-stage renal disease. The mean eGFR fell from 82 to 67 mL/min/1.73 m^2 after 5 years; most of this reduction occurred during the course of chemotherapy (likely reflecting AKI), although renal function continued to decline thereafter. So the reduction in kidney function associated with ifosfamide administration occurs in a minority of patients, is permanent and progressive and can also occur long after exposure to ifosfamide [19].

In this issue of *Clinical Kidney Journal*, Ensergueix *et al.* [20] report a multicentric observational retrospective study of 34 adult patients from six French nephrology departments with tubular dysfunction and /or kidney dysfunction following ifosfamide treatment. Of these patients, 18% had isolated proximal tubular dysfunction, 14% had isolated AKI, 18% had isolated chronic kidney disease (CKD) and 50% had a combination of proximal tubular dysfunction and AKI. eGFR decreased progressively in 16 of 34 patients, 10 patients progressed to CKD Stage 5, and 6 patients required haemodialysis. Six patients died during follow-up and at the end of follow-up, only 5 of 34 patients were alive without CKD. Concomitant treatment with cisplatin appeared to be a risk factor for the development of AKI, and cisplatin and age were associated with eGFR at last follow-up. Interestingly, the cumulative dose of ifosfamide was not associated with renal outcomes.

Proximal tubular dysfunction is the most common ifosfamide-associated nephrotoxicity. Tubular involvement is generally very prolonged, potentially progressive and may lead to advanced CKD [20, 21]. Ifosfamide-induced proximal tubular toxicity is characterized by aminoaciduria (28%), glucosuria (90%), low molecular weight proteinuria, Fanconi syndrome (1–7%), hypophosphataemia, proximal RTA, hypokalaemia, phosphaturia and, more rarely, calciuria, magnesiuria and natriuria [13]. In the study of Ensergueix *et al.*, the most common finding of proximal tubular dysfunction was hypokalaemia, followed by metabolic acidosis, hypophosphataemia, low molecular weight proteinuria, TmPO4^{2-}/eGFR <0.8, hypuricaemia and UAFE >10%. Distal tubular toxicity has also been reported with Type 1 RTA, a defect in urine concentration and nephrogenic diabetes insipidus. Ifosfamide can induce SIADH characterized by hyponatraemia, plasma hypo-osmolality and inadequate urinary osmolality [22, 23]. Rossi *et al.* [9] performed a follow-up study of 75 patients who had received ifosfamide for various malignancies. Over 31 months of follow-up, five patients developed renal Fanconi syndrome as demonstrated by the presence of hyperaminoaciduria, phosphaturia, glucosuria and low serum bicarbonate [9]. Seven patients developed generalized subclinical tubulopathy, which was defined as an impairment of three or all four parameters of proximal tubular solute transport (amino acids, phosphate, glucose and sodium) in the absence of acidosis or metabolic bone disease [9]. They reported that generalized subclinical tubulopathy occurred before the development of Fanconi syndrome in all five cases, and moderate reduction in creatinine clearance was also reported in them [9].

Ifosfamide is more nephrotoxic than cyclophosphamide and this is due to selective uptake of ifosfamide in proximal tubular cells through the organic cation transporter-2 (Figure 1) [24]. Ifosfamide undergoes substantial metabolization with the production of acrolein (responsible for bladder irritation and haemorrhagic cystitis) and chloro-acetaldehyde (responsible for the development of proximal tubulopathy). Studies in rats showed that chloro-acetaldehyde (CAA) causes renal injury by inhibiting nicotinamide adenine dinucleotide (reduced):ubiquinone oxidoreductase (Complex-1; C-I), one of the enzymes in the oxidative phosphorylation pathway [25]. CAA inhibits

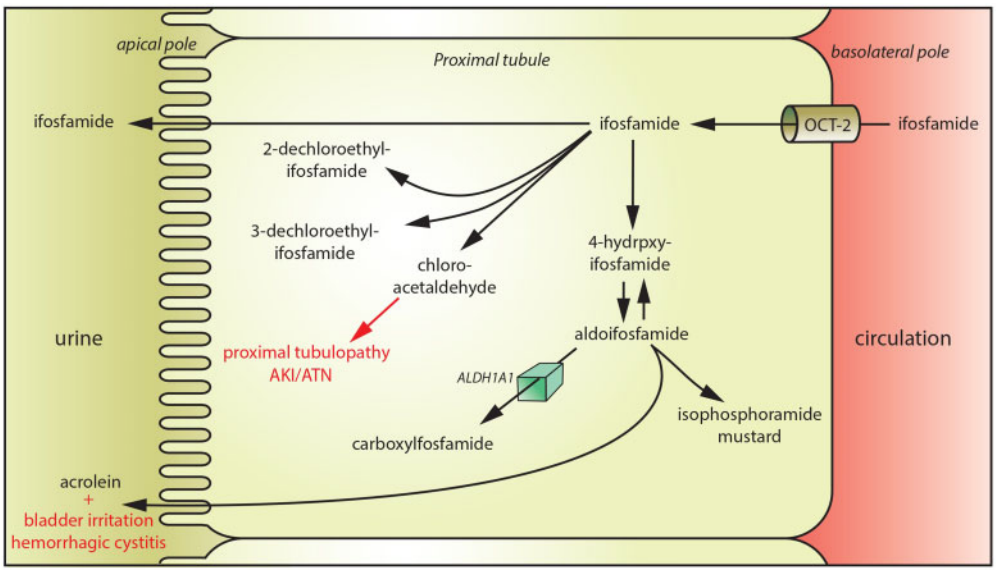

FIGURE 1: Mechanism of ifosfamide-associated tubular toxicity. Ifosfamide is transported in the proximal tubular cells through organic cation transporter-2. Ifosfamide undergoes substantial metabolization with the production of acrolein (responsible for bladder irritation and haemorrhagic cystitis) and chloro-acetaldehyde (responsible for the development of proximal tubulopathy). ALDH1A1: aldehyde dehydrogenase 1A1.

endocytosis in the rat proximal tubules [26]. This inhibition was attributed to a decrease in adenosine triphosphate (ATP) levels and inhibition of Vacuolar-type H^+-ATPase induced by CAA [26]. In the current study, 14 biopsies were available, 3 including electron microscopic evaluation. Histology findings included signs of ATN, vacuolation of epithelial cells and nuclear atypia. Moreover, most biopsies also showed interstitial inflammation and fibrosis. Electron microscopic analysis showed, in addition, evidence of severe mitochondrial abnormalities including irregular mitochondria and attenuation of mitochondrial ridges.

The limitations of this study are numerous. First of all, only 34 patients are reported in this study. While ifosfamide is a widely used chemotherapeutic and nephrotoxicity is observed in a significant subset of patients, the data remain limited. Secondly, based on the data of Ensergueix *et al.*, it is impossible to establish the prevalence of ifosfamide-associated nephrotoxicity in adults. The study period is very long (1995–2016), and treatment changes have occurred during this time period regarding type and dosing of concomitant chemotherapeutics, which may have impacted the occurrence of nephrotoxicity in these patients. Fifteen patients (44.1%) received cisplatin treatment in addition to ifosfamide chemotherapy. Cisplatin is well-known nephrotoxic drug, making it difficult to attribute kidney dysfunction to ifosfamide in these patients. However, combining chemotherapeutics is a reality in cancer patients, making these data helpful anyway. Finally, only limited histology data are available in this study, with only three patients undergoing electron microscopic evaluation. Although tempting, we need to be very careful regarding the mitochondrial abnormalities observed and putting this forward as the mechanism of action of ifosfamide-associated nephrotoxicity.

In conclusion, Ensergueix *et al.* report 34 adult patients with ifosfamide-associated nephrotoxicity. The most common forms of ifosfamide-associated nephrotoxicity are proximal tubular dysfunction and AKI. eGFR decreased progressively in 16 of 34 patients, 10 patients developed Stage 5 CKD, 6 required haemodialysis and 6 died. Only five were still alive without CKD at the end of a mean follow-up of 41.8 months. Histologic evaluation in three patients suggests mitochondrial damage as a possible mechanism of ifosfamide-associated nephrotoxicity. Although the data presented in the article do not allow for definite conclusions, ifosfamide was likely an important contributor to the kidney damage in these patients. Patients eligible for ifosfamide treatment should be informed regarding the possibility of irreversible kidney damage. This report highlights the need for additional studies on the prevalence, spectrum and management of ifosfamide-associated nephrotoxicity, and clearly demonstrates that patients who received ifosfamide should be followed long term to detect proximal tubular dysfunction and CKD early. More general, in cancer patients, kidney function should be assessed regularly during but also after treatment, as kidney injury is both common and an important determinant of long-term outcome. The field of onconephrology is relatively new and still developing. Reports like the one of Ensgerueix *et al.* highlight the importance of a close collaboration between nephrologists and oncologists to improve long-term outcomes in cancer patients.

CONFLICT OF INTEREST STATEMENT

B.S. is a senior clinical investigator of the Research Foundation Flanders (F.W.O.; 1842919N).

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