Cancer Chemother Pharmacol (1989) 23: 329–330

Cancer Chemotherapy and Pharmacology

Severe renal failure following high-dose ifosfamide and mesna

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Summary. A 62-year-old woman developed subacute renal failure after the repeated administration of ifosfamide (IFX), despite its combination with continuous sodium 2-mercaptoethane sulfonate (mesna) infusion. Biopsy findings, the possible underlying mechanism, and the existing literature are discussed.

Introduction

Increased doses of the cyclophosphamide analog ifosfamide (IFX) given as a 24-h infusion have resulted in improved response rates in a number of solid tumors, including testicular carcinoma, pediatric tumors, and soft-tissue sarcomas. The simultaneous administration of the sulfur-containing compound mesna (sodium 2-mercaptoethane sulfonate) prevents the urothelial toxicity of this oxazaphosphorine, thus enabling the use of higher doses of IFX over shorter time intervals; this approach has altered the toxicity pattern of IFX. Tubular damage has been described in pediatric patients, especially after previous treatment with the nephrotoxic drug cisplatin [4]; in these patients, a Fanconi-like syndrome occurred with aminoaciduria, renal tubular acidosis, and enhanced excretion of tubular enzymes such as *N*-acetyl-glucosaminidase. A rise in serum creatinine has also been described in six patients receiving a combination of cisplatin and IFX [3]. In a previous study, two patients died of acute renal failure, with a clinical picture of "acute tubular necrosis" [11], after receiving IFX doses of 5–8 g/m^2 over 24 h. Therefore, there is no doubt that higher doses of IFX may lead to tubular and possibly also glomerular damage despite the use of a detoxifying agent, which usually prevents urothelial damage. We report the case of a patient who manifested subacute tubular necrosis during IFX administration.

Case report

A 62-year-old woman was treated for a stage III ovarium carcinoma with multiagent therapy consisting of cyclophosphamide, hexamethylmelamine, adriamycin, and a 5-day cisplatin combination (CHAP-5). After six courses the patient achieved a complete remission but suffered from grade I sensory neuropathy. There was some regression of renal function at that time, serum creatinine levels being 85 μmol/l and creatinine clearance, 85 ml/min. After 58 months she underwent a tumor relapse, heralded by a rise in the serum marker CA 125; a 6-cm recurrence was seen on the computed tomogram, lying anteriorly against the diaphragm and abdominal wall. Radical surgical resection appeared impossible at laparotomy and the patient received IFX at a dosage of 5 g/m^2 over 24 h q 4 weeks, together with 5 g/m^2 mesna.

After three cycles there was a rise in serum creatinine up to 120 μmol/l; nevertheless, the patient received the full dose of the fourth treatment cycle. Her general practitioner reported a longer and more severe bone marrow suppression 15 days after this dose, with a leukocyte nadir of 0.3, a thrombocyte count of 128, and cystitis, for which she received sulfamethizole-trimetoprim. The patient was admitted for the next cycle 5 weeks after treatment. She had a puffy face and finger edema, and severe renal insufficiency was diagnosed, with the following values: serum urea, 12.2 mmol/l; creatinine, 1,240 μmol/l; and creatinine clearance, 2–3 ml/min. Her blood pressure was 160/90 mm Hg.

The urinary sediment revealed no leukocytes, erythrocytes, or bacteria but a diuresis of about 1,000 ml with 1.6 g protein/24 h. There was no ureteral obstruction on the ultrasonographic scan, on which the tumor nodule was hardly seen, and the serum levels of the marker CA 125 had normalized. A renal biopsy was carried out; a total of 13 glomeruli could be evaluated, 8 of which were hyalinized and the others, normal. Focal tubular atrophy and interstitial fibrosis together with some lymphocytic infiltration accompanied the glomerular scarring; there was also a more diffuse interstitial fibrosis with collapsed tubuli, which had no apparent relationship to the glomerular scarring. There were no signs of interstitial nephritis or recent tubular necrosis. Immunofluorescence studies of immunoglobulins and complement were negative.

In view of the normal tubules present, the overall picture fits better with subacute tubular damage than with clear-cut, acute tubular necrosis. However, during the following 3 weeks, the renal-function disturbances gradually deteriorated and stabilized at a serum creatinine value of about 1,800 μ*M* and serum urea level of 38 mmol/l. The patient remained in a labile condition after the diagnosis of renal failure and died of tumor recurrence 12 months later.

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Discussion

Following the administration of high-dose IFX, over a period of 5 weeks this patient developed progressive renal failure, which was irreversible over an observation period of 12 months. Her presentation is in contrast to the acute tubular necrosis after IFX described in the literature [11], since this patient manifested a gradual onset of uremic symptoms 5 weeks after exposure to the drug. Slowly progressive glomerular failure has been described [8] after the induction of an adult Fanconi syndrome by IFX.

The renal biopsy showed considerable atrophy, which partly appeared to be ischemic in origin, judging from the type of glomerular scarring. There were no signs of interstitial nephritis, but diffuse interstitial fibrosis with collapsed tubuli occurred instead. Subacute tubular damage is probably the clue to the slow deterioration of renal function. The presence of urinary tract infection and the administration of sulfamethizole may have contributed to the toxic effects of IFX. The renal histopathology related to the clinical syndrome of acute tubular necrosis found by others after IFX has not been described in detail. Chronic toxicity studies in dogs have shown some "renal changes" [5], and Klein et al. [6] have found tubular necrosis and interstitial bleeding in mice receiving 600 mg/kg IFX (LD_{10}); this renal damage in mice could be completely prevented by mesna. In human studies, mesna has also appeared to prevent the renal toxicity of IFX at doses of up to 80 mg/kg daily for 5 days [5–7].

The occurrence of some (or even severe) renal tubular damage was described as early as 1972 [12]. Such reports have become more frequent, since higher doses of IFX are now given over shorter periods of time. The administration of higher doses has been enabled by the concomitant use of mesna, which prevents the urothelial toxicity of oxazaphosphorines. The occurrence of urothelial damage due to oxazaphosphorines seems to be dose-dependent, the active 4-hydroxy metabolites being less easily taken up by urothelial cells at a lower pH (around 5.0) than at higher ones [1].

However, we could find no evidence in the literature as to the effect of pH on the binding of acrolein by mesna or the prevention of intrinsic renal toxicity. Direct renal toxicity due to mesna itself does not seem very likely, although the doses given nearly reached the maximum tolerated dose previously described for healthy human volunteers [2, 9, 13]. The main side effects of mesna are gastrointestinal symptoms. A review of the available literature indicates that severe renal toxicity after IFX seems to occur especially during the use of the high-dose 24-h schedule; during the formerly used 5-day schemes, it was observed only when IFX was given without mesna [12].

Enhancement of urothelial toxicity has been described in previous studies [8], in which IFX was given together with other alkylating agents such as melphalan, a compound that may either interfere with the activation of mesna by glutathione within the tubular cells or directly inactivate mesna by covalent binding. The combination of IFX and cisplatin given by Einhorn [3] may cause renal damage by a cumulative toxic effect on the kidney, leading to mutually diminished clearance and enhanced nephrotoxicity. Tubular toxicity may also compromise the kidneys' potential to activate the disulfide form of mesna within the tubular cells.

It is both tragic and instructive that the high dose given in the present study, which probably resulted in high blood levels as a result of compromised renal function, led to a complete clinical response, a rather rare event in relapsing ovarian cancer.

In conclusion, IFX doses of $\geqslant 5\ g/m^2$ per day may be nephrotoxic, especially after or during treatment with other nephrotoxic compounds such as cisplatin. When IFX is combined with other alkylating agents such as melphalan, its urothelial toxicity may be enhanced. Care must be taken to protect the kidney before and during treatment with this compound by using sufficient fluids and inducing the proper urinary pH, preferably pH <6 [1]. In case of elevated serum creatinine values, the IFX dose should be accordingly adapted.

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Received February 29, 1988/Accepted November 8, 1988