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*Original Article*

# Renal side effects of Ifosfamide in patients admitted for chemotherapy

*Mohammad Ali Mashhadi**

## Abstract

**BACKGROUND:** Ifosfamide (IFO) is an alkylating cytostatic agent with nephrotoxic properties. Most often it causes disturbances in proximal tubular function manifesting as glycosuria, albuminuria, hyperphosphaturia with hypophosphatemia, tubular acidosis, and hypokalemia. Impairment of renal glomerular function is less frequent and manifests as reduced glomerular filtration or distal tubulopathy along with the symptoms of diabetes insipidus. A significant percentage of patients also develop neurotoxic side effects. The aim of this study was to assess the incidence of side effects in patients treated with IFO for neoplastic diseases.

**METHODS:** This was a prospective study on all admitted patients that received Ifosfamide for chemotherapy. After full physical examination and performing necessary paraclinical examinations (sodium, potassium, calcium, BUN, creatinine, uric acid, SGOT, SGPT, bilirubin and ECG), information forms for all of them were filled out at admission and in follow up visits to be used in final assessment. Renal function was assessed at the beginning of chemotherapy and then regularly during subsequent cycles.

**RESULTS:** Sixty-six cases were male and 34 cases were female. Mean age was 36.4 years. Alopecia was recorded in 70 cases (70%) and nausea and vomiting in 43 cases (43%). Nephropathy (increased BUN and creatinine, gross hematuria, phosphaturia, glucosuria) was not observed in any patient. In 8 patients, microscopic hematuria was detected. Twenty-three patients had bone marrow suppression, and 7 cases showed severe neutropenia and broad spectrum antibiotics were prescribed for them. I did not find any culture positive infection. Serum electrolyte imbalance, diarrhea and severe allergic reactions were not observed.

**CONCLUSIONS:** Ifosfamide may potentially produce both mild and severe renal side effects. Side effects of IFO should be evaluated in different populations with different genomic profiles.

**KEYWORDS:** Ifosfamide, nephropathy, side effects.

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Ifosfamide (IFO) is an alkylating cytostatic agent with significant clinical activity against a wide variety of hematological malignancies, sarcomas and carcinomas in adults and children. For the first time, this drug was used in the treatment of neoplasms in the 1970's, but it was soon withdrawn because of frequent occurrence of acute hemorrhagic cystitis. In the late 1980's, owing to the use of protective factors like uromitexan (mesna), this cytostatic agent was reintroduced into chemotherapy protocols.[1-4] Nephrotoxicity and neurotoxicity are two most major clinical side effects of IFO. Evaluation of renal function is essential during IFO treatment, especially in children, to minimize the risk of severe chronic morbidity, such as that caused by Fanconi syndrome.[1,5] The character, localization, and extent of kidney damage by IFO are considerably varied. Proximal tubular dysfunction is common manifesting as glycosuria, albuminuria, hyperphosphaturia with hypophosphatemia, tubular acidosis, and hypokalemia, in different combinations including full Fanconi syndrome.[1,2,6,7] Distal tubular and collecting duct injuries may also develop, but a reduction

*Assistant Professor, Department of Hematology & Oncology, Hematology Oncology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. E-mail: dralimashhadi@yahoo.com

in the glomerular filtration rate (GFR) of more than 20% is rare. Considerable patient variation in nephrotoxic response to IFO has been reported. In most studies, however, renal function was measured at least 6 months after IFO chemotherapy, and many patients had also received cisplatin.[2,3] Assessment of nephrotoxicity is routinely based on conventional tests of renal function, such as blood urea nitrogen, plasma electrolytes, and creatinine, and the urinary excretion of low molecular weight proteins and renal tubular enzymes.[1,5] The frequency of IFO nephrotoxicity has been estimated by various authors ranging from 1.4 to 60%.[8] IFO administration has been associated with a number of acute side effects that often seen with antineoplastic agents. These include neutropenia, thrombocytopenia, nausea, vomiting, alopecia and hypersensitivity reactions. With conventional doses of IFO, these side effects are usually mild. IFO is also responsible for more specific toxicities such as hemorrhagic cystitis, nephropathy, encephalopathy and cardiac toxicity. Bladder toxicity, due to the urotoxin acrolein, is easily prevented by the use of mesna, a thiol compound that binds to the toxin.[9] Since the efforts are focused on diminution of side effects and improving quality of life of patients with cancer, the aim of this study was to assess the incidence of side effects in patients treated with IFO for neoplastic diseases in the department in 3 years.

## Methods

In a prospective study, I evaluated IFO side effects in all admitted patients in Hematology and Oncology ward who were candidate for IFO treatment during 2003-2006. The patients were assessed during admission and in follow up visits for side effects. I evaluated them for nausea, vomiting, anorexia, malaise, fatigue, alopecia, hematuria, CNS toxicity, fever, nervousness, diarrhea and allergic reactions. Patient's information was recorded in data sheets for final assessments. The following baseline laboratory tests were done for all patients: complete blood cells count, urinalysis, serum electrolytes, blood urea nitrogen, creatinine, GFR, uric acid, liver enzymes and bilirubin. Careful history (with special attention on drug history) and physical examination were done for all patients. My intention was to find out drugs with renal side effect in patients' past history. All included patients had no history of taking drugs with renal toxicity. In all patients, a detailed assessment of renal function was carried out at the beginning of treatment. It included assessments of creatinine clearance, urinanalysis (for glycosuria, albuminuria, hyperphosphaturia, tubular acidosis), sodium, potassium, creatinine, BUN and phosphate in blood serum. Renal function was reassessed before each subsequent cycle of the treatment. This assessment was performed in every male patient through the following formula: (140-age/72 × creatinine) × weight. In women, this formula was multiplied by 0.85. In patients who demonstrated abnormal renal function, additional determinations of 24-h urinary excretion of protein, phosphate and bicarbonate, gasometry and creatinine clearance were performed if necessary. Laboratory tests were repeated before every cycle of treatment and then weekly after IFO administration for evaluation of hematologic and renal toxicities. Duration of follow up was at least 6 months after termination of treatment. All patients received maintenance IV fluid after preparing IV-line. Other pretreatment medication was Kytril, intravenously, 30-60 minutes before initiation of chemotherapy. Chemotherapeutic regimen for all patients included IFO, 2 g/m$^2$/day in 1 liter normal saline plus equal dose of Mesna during 24 hours for 3-7 days in every cycle; 3 days for lymphoma patients with ICE protocol (IFO, Carboplatin, Epirubicin) and 7 days for patients with osteogenic sarcoma without any other drug. If nephrotoxicity (30% increase in serum creatinine or 30% decrease in creatinine clearance) were detected in follow-up laboratory results, subsequent course of treatment would be stopped till normal renal test results were achieved. Chemotherapy was continued in cases that didn't show nephrotoxicity or substantial neurotoxicity. Finally, data were analyzed with SPSS, version 10.

## Results

Overall, I evaluated 100 patients; 66 cases were male. They aged 12-57 years (mean age, 32.6

years), and were treated for solid childhood tumors according to the applicable chemotherapy protocols. Thirty-six cases (28 males) had non-Hodgkin lymphoma (NHL) and 74 cases (48 males) had osteosarcoma. IFO therapeutic dose was 2 g/m$^2$ in 1 liter normal saline which was administered along with equal dose of Mesna during 4 hours for all patients. Analyzed data showed no overt nephrotoxicity, gross hematuria, proteinuria or phosphaturia. In only 8 patients, microscopic hematuria (hemorrhagic cystitis) was detected. This side effect was resolved with conservative treatment. The most common complication was alopecia that observed in 70 cases (70%); 42 cases (42%) complained from nausea and vomiting, which continued for a maximum duration of 48 hours. Twenty-three patients showed bone marrow suppression; the most common toxicity was leucopenia. No significant anemia and thrombocytopenia was observed. None of the patients showed serum electrolyte imbalance, seizure, diarrhea, severe allergic reactions and chest pain. All laboratory tests especially BUN, creatinine, potassium, sodium, phosphate, fasting blood sugar, magnesium, and urinanalysis results of glucosuria, phosphaturia, hematuria or albuminuria were evaluated, and showed no abnormality except microscopic hematuria. These tests were repeated every month after termination of chemotherapy to assess delayed abnormalities reported by many studies. The results of current study are summarized in table 1.

**Table 1.** Prevalence of Ifosfamide side effects in admitted patients in hematology and oncology ward compared with other studies.

| IFO side effect | Prevalence according to other studies | Prevalence in current study | |
|---|---|---|---|
| | | Number | Percent |
| Alopecia | Almost > 80-90% | 70 | 70 |
| Nausea & Vomiting | Almost > 80% | 42 | 42 |
| Hematuria | 46% | 8 | 8 |
| Gross Hematuria | 12% | 0 | 0 |
| Microscopic Hematuria | Common | 8 | 8 |
| Decrease in serum electrolyte | Common | 0 | 0 |
| CNS toxicity | Common | 14 | 14 |
| Infection | 12% | 0 | 0 |
| Hepatotoxicity | Less < 3% | 0 | 0 |
| Anorexia | Less common | 0 | 0 |
| Phlebitis | Less common | 0 | 0 |
| Fever | Less common | 7 | 7 |
| Allergic reaction | Rare | 0 | 0 |
| Cardiac toxicity | Rare | 3 | 3 |
| Bone marrow suppression | Common | 23 | 23 |

## Discussion

I described 100 patients with NHL and osteosarcoma, treated with IFO chemotherapy, who did not show nephrotoxicity. Nephrotoxicity is the most important side effect of IFO, especially because it may lead to chronic kidney damage, and even chronic renal failure in some cases. Some investigators believe the problem is very serious and recommend reconsideration of using this cytostatic agent in pediatric oncology and its replacement by less toxic cyclophosphamides in appropriately high doses.[10] Nephropathy among the patients in this study was not observed and this finding was against similar studies. Some reports emphasized on even higher rates of nephrotoxicity of the drug, finding some signs of renal function impairment in almost all patients after using very sensitive methods of assessment.[6] On the other hand, it is difficult to explain the fact of the very low incidence of nephropathy reported by other authors[1,11] given that irrespective of the method of assessment, some patients demonstrate overt tubulopathy and/or glomerulopathy, which can be diagnosed with simple laboratory tests. In 8 patients in this study, microscopic hematuria was diagnosed. The preliminary diagnosis was

usually based on routine laboratory test (urinalysis). Further assessment included determination of 24-h urinary loss of protein, phosphate, potassium, bicarbonates, calcium and magnesium, creatinine clearance and GFR. No increases in urinary calcium, magnesium and potassium loss in 24-h urine were detected in any patient.[2,8,12] The risk factors for the development of nephropathy after IFO treatment include high dose of the chemotherapeutic regimen (exceeding 80 g/m$^2$), age less than 3 years, previous treatment with cisplatin, unilateral nephrectomy, previous renal damage or involvement by the neoplastic process, and radiotherapy of the abdominal cavity.[2,10,12] Some reports do not confirm increased risk of IFO-related nephropathy in the age group below 3 years.[8,13] All patients with diagnosed nephropathy and other patients treated with IFO require further observations. It is known that the lack of signs of renal damage immediately after treatment does not allow exclusion of the toxic effect of the cytostatic agent and that the symptoms may develop gradually after completion of the therapy.[3,10,11,14] Alopecia is the most common side effect of IFO (almost 100 %). Its prevalence in this study was 70%. The risk of developing chronic nephropathy after IFO treatment is still unknown; therefore, systematic monitoring of the patient's renal function is necessary after the completion of chemotherapy.

## Conclusion

IFO has the potential power to produce both mild and severe side effects. Renal side effects of IFO are varied in different studies and the type and the severity of these toxicities are different in different populations and the best management is varied in every population. For this reason, renal toxicity of IFO should be carefully considered. The best management of these side effects is early detection. Cessation of treatment may be necessary to terminate these side effects. These toxicities should be revised in different populations with different genomic patterns and different races.

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