

# Side Effects of Ifosfamide

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## Key Words

Ifosfamide · Side effects · Toxicity

## Abstract

Ifosfamide is relatively well tolerated but it can be associated occasionally with life-threatening complications such as arrhythmias and heart failure, severe encephalopathy and hemorrhagic cystitis. Mesna administration can control the urothelial toxicity of ifosfamide, but it is without effect on the other complications. Other preventive measures, such as amifostine or methylene blue administration, have not yet been adequately evaluated in a sufficient number of patients. Clinicians prescribing ifosfamide, especially in high doses, should be watchful for early signs of toxicity in order to discontinue ifosfamide administration soon enough to avoid development of major toxicity.

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## Introduction

Ifosfamide administration has been associated with a number of acute toxic effects, that are also seen with many other antineoplastic agents: neutropenia, thrombocytopenia, nausea, vomiting, alopecia and hypersensitivity reactions. With conventional doses of ifosfamide, these adverse reactions are usually relatively mild. The prophylac-

tic and therapeutic approaches for their control have been well described; they are not different from the measures recommended for other cytostatic agents and are often very successful.

Ifosfamide has also been responsible for a series of more specific, potentially life-threatening toxicities: hemorrhagic cystitis, nephropathy, encephalopathy and cardiac toxicity. This review will focus on these specific aspects of ifosfamide-related toxicity, with a special emphasis on data recently published in the literature.

## Hemorrhagic Cystitis

This potentially severe complication is due to a metabolite of cyclophosphamide and ifosfamide, which is generated in the liver and acts as an urotoxin: acrolein. Ifosfamide has a greater tendency than cyclophosphamide to produce this complication possibly because of the generally higher doses administered, which result in higher amounts of acrolein and the additional excretion of chloroacetaldehyde. Mesna, a thiol compound, binds acrolein and other oxazaphosphorine metabolites, thus preventing bladder toxicity. It is routinely recommended to protect against urothelial toxicity associated with the administration of ifosfamide and high-dose cyclophosphamide [1].

Treatment of hemorrhagic cystitis, which causes diffuse bleeding, requires evacuation of clots and continuous bladder irrigation; instillation of 1% alum, prostaglandins

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0030-2414/03/0656-0007\$19.50/0

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E<sub>2</sub> and F<sub>2</sub> or high-dose tranexamic acid have been tried with varying, often disappointing, results. For intractable bleeding, patients may require hypogastric artery embolization, cutaneous ureterostomy or total cystectomy [2]. Bladder bleeding may also occur as a result of concomitant radio- or chemotherapy, viral infection (adenovirus, polyoma virus) or thrombocytopenia; these conditions increase the risk of bleeding induced by ifosfamide and make its treatment more difficult.

### **Nephrotoxicity**

Ifosfamide-induced nephrotoxicity has been described mostly in children; it can be seen in up to 30% of children treated with the drug. Even though ifosfamide can induce toxicity in any segment of the nephron, proximal tubulopathy characterized by tubular wasting of glucose, phosphates, bicarbonates, amino acids and protein – a Fanconi-like syndrome – is the most frequent presentation of ifosfamide-induced nephropathy [3].

The cause of ifosfamide-induced tubulopathy is not fully elucidated. Several risk factors appear to predispose to it: concomitant administration of other nephrotoxic drugs (e.g. cisplatin or aminoglycoside antibiotics), young age and higher cumulative dose of ifosfamide [4]. In contrast to hemorrhagic cystitis, mesna cannot overcome ifosfamide-induced nephrotoxicity and most of it persists after cessation of ifosfamide treatment [5]. Simultaneous administration of cisplatin appears to increase the risk of delayed or persistent renal tubular dysfunction, while concomitant use of carboplatin seems to induce more frequently acute tubulopathy, in comparison with ifosfamide alone [6].

Amifostine has been tried to reduce the nephrotoxicity of cisplatin/ifosfamide-based chemotherapy. In 31 patients with solid tumors, Hartmann et al. [7] have evaluated the glomerular and tubular functions in two groups of patients treated with or without amifostine (1,000 mg given by short infusion prior to chemotherapy). In the amifostine-treated patients the glomerular function was almost completely maintained, whereas in the control group a 30% reduction of the glomerular filtration rate was observed. The patients receiving amifostine also had less tubular damage compared to the controls. However, in two other studies in children, receiving ifosfamide-containing regimens [8, 9], no protection by amifostine of proximal tubular cells or against reduction of creatinine clearance was detected, casting some doubt on the reproducibility of the observation.

### **Encephalopathy and Neuropathy**

Ifosfamide and its metabolites penetrate the blood-brain barrier well after systemic administration, with central nervous system (CNS) toxicity occurring in 10–40% of the patients receiving high doses of the drug. Ifosfamide-induced encephalopathy is manifested by cerebellar ataxia, mental confusion, complex visual hallucinations, extrapyramidal signs, seizures and/or mutism. Less common CNS manifestations of ifosfamide are asterixis [10], non-convulsive status epilepticus [11], manic episodes [12] or cerebellar and temporo-frontal cortical degeneration [13].

The exact pathophysiological mechanisms responsible for the development of ifosfamide-induced encephalopathy are not known, but one hypothesis is that chloroethylamine – an ifosfamide metabolite – may be the principal neurotoxin involved. Chloroethylamine can induce the formation of thialysine ketimine, which can also inhibit the electron-binding flavoproteins in the mitochondrial respiratory chain. Another important pathway may be mediated by monoaminoxidase, which can be inhibited by methylene blue [14]. A recent series confirms previous observations that methylene blue (4–6 × 50 mg, i.v.) is an effective treatment for ifosfamide-induced encephalopathy [15].

Peripheral neuropathy has been described – seldom after ifosfamide administration, particularly in patients with pre-existing axonal peripheral neuropathy [16]. Therefore, one might fear that the combination of ifosfamide with a potentially neurotoxic agent like cisplatin, paclitaxel or vinorelbine could lead to severe progressive neurotoxicity. A recent study of ifosfamide with vinorelbine, in patients with ovarian cancer, previously treated with cisplatin or carboplatin and paclitaxel, demonstrated that ifosfamide plus vinorelbine was a reasonably safe therapy for those patients, since severe, progressive neurotoxicity was not observed [17]. Along the same line, ototoxicity, in patients treated with cisplatin-ifosfamide regimens, is not exacerbated [18].

### **Cardiac Toxicity**

Arrhythmias have been reported with various antineoplastic drugs, namely anthracyclines, 5-fluorouracil and ifosfamide; however, the cardiotoxicity of these drugs is mainly myocardial or ischemic. Hypotension, resulting from cancer treatment, has been most often associated with reversible congestive heart failure with ifosfamide [19] or cardiomyopathy, induced by anthracyclines.

Cyclophosphamide and ifosfamide have little cardiac toxicity at standard doses. However, at high doses such as those used for bone marrow ablation, these drugs are known to cause severe myocarditis, exudative pericarditis, myocardial depression, arrhythmias and congestive heart failure [20]. The total dose, that has caused myocardial injury, usually has been far in excess of 1,000 mg/m<sup>2</sup> of ifosfamide and these patients usually develop cardiac toxicity within 2 weeks of receiving the drug; congestive heart failure associated with ifosfamide is often reversible. Hemorrhagic myocarditis has been associated mainly with high-dose cyclophosphamide therapy; although ifosfamide is related structurally to cyclophosphamide, hemorrhagic myocarditis has not been documented [19].

Radiation therapy can affect all structures of the heart, including the coronary arteries and the valves, but especially the myocardium and pericardium, resulting in clinical disease.

Dexrazoxone is a derivative of EDTA that chelates intracellular iron and reduces doxorubicin-related cardiotoxicity. There is no convincing evidence that it can protect against cyclophosphamide or ifosfamide-related heart disease.

Since therapy in severe chemotherapy-induced cardiopathy is often disappointing, early diagnosis might be essential: a recent report indicates that myocardial injury, due to high-dose chemotherapy, including ifosfamide-containing regimens, can be revealed by elevated plasma troponin I levels [21].

### **Interactions of Ifosfamide with Other Drugs**

Because of the structural similarity and comparable mechanism of action of ifosfamide and cyclophosphamide, similar interactions can occur. As already mentioned, patients who receive ifosfamide after cisplatin or carboplatin have a significantly higher risk of nephrotoxicity. A potentiation of ifosfamide-related CNS toxicity and hematological toxicity, by prior cisplatin therapy, was also reported [22]. Although ifosfamide is not ototoxic, it may exacerbate cisplatin-induced hearing deficits when both drugs are given together [23].

Docetaxel, when given prior to ifosfamide 24 h infusion, appears to decrease the area under the curve (AUC) of ifosfamide, resulting from an increased clearance of ifosfamide. The reverse sequence does not cause any alteration of AUC. It is unclear whether this increased clearance of ifosfamide is due to docetaxel or to the pre-treatment with corticoids [24].

Drugs like phenobarbital, phenytoin and rifampicin, known to induce hepatic microsomal activation, have been reported to increase metabolism of ifosfamide, under experimental conditions. The clinical significance of that phenomenon is unknown, although a case of ifosfamide/mesna-related encephalopathy, with a possible role of phenobarbital in enhancing neurotoxicity, has been described.

Three cases of serious disturbance of anticoagulant control with warfarin, while the patients were receiving ifosfamide-containing chemotherapy, have been reported. Close monitoring of anticoagulation control is recommended during co-administration of these drugs [25, 26].

### **Conclusions**

Chemotherapy is now prescribed to an increasing number of patients, including older patients who can be compromised not only by their neoplastic disease but also by many concurrent illnesses. Therefore, it is of paramount importance for the oncologist to be aware of the possible side effects of all antineoplastic agents and their potential interaction with other morbid conditions and other medications.

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