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Review Article

Is continuous infusion of high-dose ifosfamide, a safe option? Drug review

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ABSTRACT

Higher doses of ifosfamide are required to treat Sarcoma, Bone sarcomas, germ cell tumours and lymphoma. Recent protocols are based on continuous infusion of ifosfamide for 5-14 days. But what is the evidence behind it? and experience?. We present a review of high dose ifosfamide and our small experience in giving ifosfamide, both as continuous infusion and as bolus dose, as per the respective protocol. We also report MESNA with its role in reducing the urotoxicity and required dose variation according to Ifosfamide dose. In children, however, we prefer bolus as compared to continuous infusion due to nephrotoxicity. In India, many oncologists prefer to give ifosfamide as bolus dose over 3-4 hr and the dose given is much lesser. Many a times they face myelotoxicity and other non haematological toxicities. This leads to negative impact on patient compliance and ultimately the treatment is not completed properly. If a proper dose infusion is planned, this toxicity may be reduced to some extent. We need an Indian data on continuous vs bolus dose ifosfamide. High dose ifosfmide is required for better treatment of soft tissue sarcoma.

Keywords: Ifosfamide, Continuous infusion, Sodium-2-mercaptoethanesulfonate, Myelotoxicity

INTRODUCTION

High-dose ifosfamide, by definition, is prescribing ≥10 g/m^2/dose of ifosfamide in any regimen.[1] Such a high dose of ifosfamide is prescribed in sarcoma (vincristine, ifosfamide, doxorubicin, and etoposide protocol, VIE, etc.) or germ-cell tumors (GCT) salvage regimen and lymphoma salvage regimens.

High-dose ifosfamide follows saturation kinetics, so any dose prescribed above a certain limit will have the same effect. This high dose also generates neurotoxic chloroacetaldehyde and urotoxic acrolein along with active pharmaceutical moiety – isophosphoramide mustard. To contain urotoxicity, we use sodium-2-mercaptoethanesulfonate (MESNA). MESNA was developed as a specific chemoprotective compound against acrolein-induced bladder toxicity, a dose-limiting side effect of both cyclophosphamide and ifosfamide.[2]

But what should be the dose of MESNA at such high production of acrolein is a subject of research. Moreover, its pharmacokinetics should not hamper the production of isophosphoramide mustard, an active pharmaceutical moiety. The dose of MESNA for ifosfamide up to 2.5 mg/m^2/dose is 60% of the total ifosfamide dose.[2]

MESNA

MESNA is a thiol compound, which functions as a regional detoxificant of urotoxic oxazaphosphorine cytostatic agents, ifosfamide, and cyclophosphamide. MESNA inactivates

alkylating metabolites by forming an inert thioether. On entering the bloodstream, MESNA is immediately converted to an inactive disulfide form and dithiodiethanesulfate (dimesna), which is subsequently filtered and secreted by the kidneys, where the enzymes thioltransferase and glutathione reductase reduce dimesna back to MESNA.

The free sulfhydryl (thiol) groups of MESNA combine directly with a double bond of acrolein and with other urotoxic 4-hydroxyoxazaphosphorine metabolites (4-hydroxycyclophosphamide and 4-hydroxyifosfamide) to form stable, non-toxic compounds. The metabolite acrolein has been implicated as the major causative agent in oxazaphosphorine-induced urothelial toxicity.

MESNA IN HIGH-DOSE IFOSFAMIDE

Although MESNA has been given in dosages equivalent to 60–160% of the ifosfamide daily dosage, safety and efficacy of dosages exceeding 60% of the ifosfamide daily dosage have not been established, and dosages exceeding 120% of the ifosfamide daily dosage may be associated with increased gastrointestinal toxicity.

In patients receiving high-dose ifosfamide, the American Society of Clinical Oncology (ASCO) states that more frequent and prolonged MESNA dose regimens may be required for maximum protection against urotoxicity since the elimination of ifosfamide is dose-dependent.

In the intravenous (IV) and oral regimen recommended by the manufacturer and ASCO guidelines for prophylaxis of ifosfamide-induced hemorrhagic cystitis, MESNA generally is given in a dosage equivalent to 100% of the ifosfamide daily dosage when the ifosfamide dosage is <2 g/m^2 daily. In this regimen, an initial dose of MESNA equivalent to 20% of the ifosfamide daily dosage is given by IV injection at the time of administration of the ifosfamide dose; this dose is followed by two oral doses, each equivalent to 40% of the ifosfamide daily dosage, administered as tablets at 2 and 6 h after the ifosfamide dose [Table 1].

HIGH-DOSE IFOSFAMIDE

Ifosfamide, even if given at doses as high as 3 g/m^2, is not promising in second-line sarcoma, so a higher dose is required.[3,4] Better tolerability has been reported for continuous infusion high-dose ifosfamide,[5,6] especially in pre-treated cases of sarcoma. Continuous infusion of ifosfamide for 3–4 days is associated with better tolerability and less incidence of myelosuppression, renal failure, neurotoxicity, etc.[7] We at our centre give continuous high dose ifosfamide (ciHDIFX) in ewings sarcoma, recurrent sarcoma and in relapsed Lymphoma.

Many others tend to give Ifosfamide in a period of 3-6 hr infusion. This leads to saturation of ifosfamide metabolism, resulting in toxicity. Besides mesna has a different pharmacokinetic as compared to ifosfamide.

We tend to give ifosfamide in a period of 3–6 h infusion. This leads to a saturation of ifosfamide metabolism, resulting in toxicity. Besides, MESNA has a different pharmacokinetic as compared to ifosfamide.

Pharmacokinetics of high-dose ifosfamide

Here, we need to understand the pharmacokinetics of ifosfamide; ifosfamide is a prodrug with four metabolites. It is mainly metabolized by CYP3A4 and CYP2B6. This metabolism of ifosfamide can be affected by autoinduction, coprescription, and/or polymorphisms of genes encoding enzymes that metabolize and transport ifosfamide.[8]

The rate by which autoinduction of the metabolism of ifosfamide developed was found to be significantly dependent on the infusion schedule. The rate was 52% lower with long infusion durations compared with short infusion durations.[9] Autoinduction led to less than proportional increase in the area under the ifosfamide plasma concentration-time curve area under the curve (AUC) and more than proportional increase in metabolite exposure with increasing ifosfamide dose. As against long infusion durations, dose-corrected exposures (AUC/D) were significantly decreased for ifosfamide and increased for 3-dechloroethylifosfamide compared with short infusion durations.[9]

At present, it is believed that a dose of ifosfamide >10.5 g/m^2/day cannot be considered standard.

As Grades 3 and 4, hematological and non-hematological toxicity was seen in this large Phase II trial of the European Organization for the Research and Treatment of Cancer and Soft Tissue and Bone Sarcoma Group, in which 124 advanced soft-tissue sarcoma patients were treated with 12 g/m^2 of ifosfamide as a 3-day continuous infusion every 3 weeks.

However, it is not clear whether continuous infusion or 3 h infusion of ifosfamide is better. The dose more than 12 g/m^2 per cycle does not yield increased response. The reason for this being saturated pharmacokinetics of ifosfamide and perhaps the inhibition of metabolism at a very high dose.[1]

In children, however, bolus infusion of ifosfamide seems to be better than continuous IV infusion, the reason being, there was up to 70% less of the dechloroethylated metabolites in plasma following bolus administration compared to continuous infusion. Dechlorethylated metabolites are responsible for nephrotoxicity.[10]

In adults, there is no difference in continuous dose ifosfamide and 3 h infusion of ifosfamide in a case of sarcoma, as far as, progression-free survival, overall response rate, and side effect profile are considered.[11] In an older randomized study, done in small cell carcinoma of the lung, continuous

infusion of ifosfamide was associated with less myelotoxicity as compared to bolus infusion ($P = 0.04$).[12]

Although there is no consensus on bolus versus continuous dose ifosfamide, the majority of trials in sarcoma and bone sarcoma give continuous dose ifosfamide (5–14-day continuous infusion see Table 2).[7,23,24]

Even MESNA can be given at 100% of the dose of ifosfamide as a continuous infusion; continuous infusion of MESNA also reduces the incidence of hemorrhagic cystitis.[25]

We usually give a continuous infusion of ifosfamide in Ewing's sarcoma, GCT (relapsed), and sarcoma at our center, we did not get much myelotoxicity. Of total 12 cycles of continuous infusion high-dose ifosfamide, prescribed in two patients, not a single episode of myelotoxicity, neurotoxicity, and nephrotoxicity due to continuous dose of ifosfamide were experienced, even though the dose was higher [see Table 3].

We avoided a continuous dose of ifosfamide only in case of relapsed GCT and Ewing's sarcoma, due to the risk of nephrotoxicity. However, out of 18 cycles given in three patients, we experienced Grade 4 neutropenia in 2 cycles and neurotoxicity in 1 cycle of short infusion ifosfamide (2–4 h) [see Table 3].

Table 1: Various doses of ifosfamide and MESNA.

S. No.	Dose of ifosfamide	MESNA with ifosfamide infusion	4 h after (% of ifosfamide)	6 h after (% of ifosfamide)	Remark
1.	1.2 g/m^2/day	240 mg/m^2 IV bolus	480 mg/m^2 PO	480 mg/m^2 PO	Manufacturer recommendation
2	Up to 2 g/m^2/day	20% bolus IV/40% PO	40% PO	40% PO	American Society of Clinical Oncology guidelines
3.	3–5 g/m^2/day	50–100% IV infusion	25–40% PO	25–40% PO	Safety profile not established? Gastrointestinal toxicity

MESNA: Sodium-2-mercaptoethanesulfonate, IV: Intravenous

Table 2: High-dose ifosfamide protocols.

S. No.	Protocols	Days	Continuous infusion/ bolus infusion	Reference
1.	VEIP	5	1200 mg/m^2 bolus over 3–4 h	Loehrer *et al.*[13]
2.	TIP	4	1500 mg/m^2 bolus over 3–4 h	Kondagunta *et al.*[14]
3.	Vincristine, ifosfamide, doxorubicin, and etoposide	3	3000 mg/m^2 over 1–3 h	Juergens *et al.*[15]
4.	ICE/R-ICE	1	5000 mg/m^2 continuous infusion	Moskowitz *et al.*[16]/ Kewalramani *et al.*[17]
5.	AIM	3	1500–5000 mg/m^2 continuous infusion	Pervaiz *et al.*[18]
6.	MAID	3	2000 mg/m^2 over 24 h/2500 mg/m^2 continuous infusion r	Antman *et al.*;[19] Antman *et al.*[20]/ Elias *et al.*[21]
7.	Ifosfamide/cisplatin/doxorubicin/HDMT regimen	5	3000 mg/m^2 continuous infusion	Bacci *et al.*[22]

Table 3: Our experience with various doses of ifosfamide either bolus or continuous infusion.

Pt.	Indication	Protocol	Dose of ifosfamide	Rate of infusion	Grade 4 myelotoxicity toxicity reported	Non-hematologic toxicity	Number of cycles
1	Ewing's sarcoma	VIDE	1.5 g/m^2	4 h	2 cycles	Nil	6
2	Ewing's sarcoma	VIDE	1.5 g/m^2	4 h	Nil	1	6
3	Germ cell tumor relapsed	VEIP	1.2 g/m^2	2 h	Nil	Nil	6
4	Adenosarcoma of uterus	AIM	3 g/m^2	24 h	Nil	Nil	6
5	Soft-tissue sarcoma–relapsed	AIM	3 g/m^2	24 h	Nil	Nil	6

VIDE: Vincristine, ifosfamide, doxorubicin, and etoposide

CONCLUSION

Although there is no consensus on bolus versus continuous dose of ifosfamide, we prefer continuous dose ifosfamide in patients at low risk of nephrotoxicity. However, we give a bolus dose of ifosfamide in children and in the patient at risk of nephrotoxicity, especially in relapsed GCT post platinum cases. Regarding MESNA, we prefer to give MESNA to the tune of 160% of total ifosfamide if the dose of ifosfamide is >2.5 g/m^2, but in a lower dose, we give 60% of total ifosfamide.

More detail studies are required to administer high-dose ifosfamide in a relatively safe way; the question remains are continuous infusion ifosfamide a safe option? Because if it is a safer option, then drug compliance will increase and effective treatment of sarcoma and Ewing's sarcoma and other malignancies can be offered.

In India, the dose of ifosfamide is much lesser than the Western counterpart. In one of the study published, the dose of ifosfamide was 1.8 g/m^2 (day 1–3) in combination with doxorubicin (75 mg/m^2).[26] In another study, done on 152 patients of head and neck squamous cell carcinoma, the dose given was 1.5 g/m^2 over half-hour.[27] No data on chemotherapy tolerance were published.[26] The main reason for low-dose ifosfamide in Indian scenario is that the majority of Indians are protein deficient, comorbidity, and poor socioeconomic status.

Limitations of our study is that our data is of only 5 patients, but its very encouraging, as far as toxicity profile is concerned. Our method of administration of ifosfamide was different. Further studies are warranted as far as ifosfamide is concerned, we need to give higher dose for better results in soft tissue sarcoma.

Declaration of patient consent

Not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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