ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.ijmio.com

International Journal of Molecular and Immuno Oncology

Review Article

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

Mukul Arvind Gharote

Mukta Cancer Clinic, Nashik, Maharashtra, India.

***Corresponding author:**
Dr. Mukul Arvind Gharote, Mukta Cancer Clinic, Bunglow No-61, Teerthroop Bunglow, Sundarban Colony, Near Deccan Petrol Pump, Nashik - 422 009, Maharashtra, India.

mukul.gharote@gmail.com

Received : 22 November 2019
Accepted : 19 December 2019
Published : 13 May 2020

DOI
10.25259/IJMIO_21_2019

Quick Response Code:

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

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Cerny T, Leyvraz S, von Briel T, Küpfer A, Schaad R, Schmitz SF, *et al*. Saturable metabolism of continuous high-dose ifosfamide with mesna and GM-CSF: A pharmacokinetic study in advanced sarcoma patients. Swiss group for clinical cancer research (SAKK). Ann Oncol 1999;10:1087-94.
2. Carless PA. WHO EML Final Report MESNA (Sodium 2-mercaptoethane Sulfonate) February 2008. Geneva: 17th Expert Committee on the Selection and Use of Essential Medicines; 2009.
3. Güllü I, Yalçin S, Tekuzman G, Barişta I, Alkiş N, Celik I, *et al*. High-dose ifosfamide by infusion with mesna in advanced refractory sarcomas. Cancer Invest 1996;14:239-42.
4. Eilber FC, Eilber FR, Eckardt JJ, Rosen G, Forscher C, Maki RG, *et al*. Impact of ifosfamide-based chemotherapy on survival in patients with primary extremity synovial sarcoma. J Clin Oncol 2004;22 Suppl 14:9017.
5. Palumbo R, Palmeri S, Antimi M, Gatti C, Raffo P, Villani G, *et al*. Phase II study of continuous-infusion high-dose ifosfamide in advanced and/or metastatic pretreated soft tissue sarcomas. Ann Oncol 1997;8:1159-62.
6. Cerny T, Castiglione M, Brunner K, Küpfer A, Martinelli G, Lind M. Ifosfamide by continuous infusion to prevent encephalopathy. Lancet 1990;335:175.
7. Sanfilippo R, Bertulli R, Marrari A, Fumagalli E, Pilotti S, Morosi C, *et al*. High-dose continuous-infusion ifosfamide in advanced well-differentiated/dedifferentiated liposarcoma. Clin Sarcoma Res 2014;4:16.
8. Zhang J, Tian Q, Chan SY, Li Sc, Zhou S, Duan W, *et al*. Metabolism and transport of oxazaphosphorines and the clinical implications. Drug Metab Rev 2005;37:611-703.
9. Kerbusch T, Mathôt RA, Keizer HJ, Kaijser GP, Schellens JH, Beijnen JH. Influence of dose and infusion duration on pharmacokinetics of ifosfamide and metabolites. Drug Metab Dispos 2001;29:967-75.
10. Boddy AV, Yule SM, Wyllie R, Price L, Pearson AD, Idle JR. Comparison of continuous infusion and bolus administration of ifosfamide in children. Eur J Cancer 1995;31A:785-90.
11. Lorigan P, Verweij J, Papai Z, Rodenhuis S, Le Cesne A, Leahy MG, *et al*. Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: A European organisation for research and treatment of cancer soft tissue and bone sarcoma group study. J Clin Oncol 2007;25:3144-50.
12. Anderson H, Hopwood P, Prendiville J, Radford JA, Thatcher N, Ashcroft L. A randomised study of bolus vs continuous pump infusion of ifosfamide and doxorubicin with oral etoposide for small cell lung cancer. Br J Cancer 1993;67:1385-90.
13. Loehrer PJ, Gonin R, Nichols CR, Weathers T, Einhorn LH. Vinblastine plus ifosfamide plus cisplatin as initial salvage therapy in recurrent germ cell tumor. J Clin Oncol 1998;16:2500-4.
14. Kondagunta GV, Bacik J, Donadio A, Bajorin D, Marion S, Sheinfeld J, *et al*. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol 2005;23:6549-55.
15. Juergens C, Weston C, Lewis I, Whelan J, Paulussen M, Oberlin O, *et al*. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. Pediatr Blood Cancer 2006;47:22-9.
16. Moskowitz CH, Nimer SD, Zelenetz AD, Trippett T, Hedrick EE, Filippa DA, *et al*. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory hodgkin disease: Analysis by intent to treat and

development of a prognostic model. Blood 2001;97:616-23.
17. Kewalramani T, Zelenetz AD, Nimer SD, Portlock C, Straus D, Noy A, *et al*. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2004;103:3684-8.
18. Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008;113:573-81.
19. Antman K, Crowley J, Balcerzak SP, Rivkin SE, Weiss GR, Elias A, *et al*. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol 1993;11:1276-85.
20. Antman K, Crowley J, Balcerzak SP, Kempf RA, Weiss RB, Clamon GH, *et al*. A southwest oncology group and cancer and leukemia group B phase II study of doxorubicin, dacarbazine, ifosfamide, and mesna in adults with advanced osteosarcoma, ewing's sarcoma, and rhabdomyosarcoma. Cancer 1998;82:1288-95.
21 Elias A, Ryan L, Sulkes A, Collins J, Aisner J, Antman KH. Response to mesna, doxorubicin, ifosfamide, and dacarbazine in 108 patients with metastatic or unresectable sarcoma and no prior chemotherapy. J Clin Oncol 1989;7:1208-16.
22. Bacci G, Briccoli A, Rocca M, Ferrari S, Donati D, Longhi A, *et al*. Neoadjuvant chemotherapy for osteosarcoma of the extremities with metastases at presentation: Recent experience at the rizzoli institute in 57 patients treated with cisplatin, doxorubicin, and a high dose of methotrexate and ifosfamide. Ann Oncol 2003;14:1126-34.
23. Singh AS, Sankhala K, Mukherjee A, Narasimha V, Chmielowski B, Quon D, *et al*. 14 day continuous infusion ifosfamide in advanced refractory sarcomas. Sarcoma Res Int 2015;2:1010.
24. Martin-Liberal J, Alam S, Constantinidou A, Fisher C, Khabra K, Messiou C, *et al*. Clinical activity and tolerability of a 14-day infusional ifosfamide schedule in soft-tissue sarcoma. Sarcoma 2013;2013:868973.
25. Jiang Q, Huang H, Liu Q, Sun J, Zhou H, Fan Z, *et al*. Continuous IV infusion of MESNA can prevent hemorrhagic cystitis in HSCT and retain MESNA concentration in urine. Bone Marrow Transplant 2015;50:1490-2.
26. Babu KG, Patidar R, Kuntegowdanahalli CL, Dasappa L, Jacob LA, Babu S, *et al*. Metastatic synovial sarcoma: Experience from a tertiary care center from India. Indian J Med Paediatr Oncol 2019;40 Suppl S1:95-8.
27. Pai VR, Parikh DM, Mazumdar AT, Rao RS. Phase II study of high-dose ifosfamide as a single agent and in combination with cisplatin in the treatment of advanced and/or recurrent squamous cell carcinoma of head and neck. Oncology 1993;50:86-91.

How to cite this article: Gharote MA. Is continuous infusion of high-dose ifosfamide, a safe option? Drug review. Int J Mol Immuno Oncol 2020;5(2):62-6.