Neuropsychiatric Toxicity of Ifosfamide in Patients Admitted for Chemotherapy

Mohammadali Mashhadi,[1] Alireza Khosravi,[2]
[1]Hematology- Oncology Department, Zahedan University of Medical Sciences, Zahedan, Iran
[2]Neurology Department, Zahedan University of Medical Sciences, Zahedan, Iran

Corresponding Author: Mashhadi Mohammad Ali, MD, associated professor in Hematology- Oncology
Hematology- Oncology Department
Zahedan University of Medical Sciences
Zahedan, Iran
Tel. No.: 09153411445
E-mail: dralimashhadi@yahoo.com

Abstract

Introduction: Ifosfamide (IFO) is a potent drug that is used in cancer therapy. The major uses of IFO are: solid tumors especially, osteogenic sarcoma, other soft tissue sarcomas and hematologic malignancy, especially in lymphoma patients. The toxicity of IFO is very encompassing and includes: alopecia, nausea, vomiting, gastrointestinal, renal and neurological problems. Neuropsychiatric toxicities vary and include: fatigue, confusion, coma, and death. An early detection of the neurologic toxicities of IFO and discontinuation of the drug is the best way to manage these side effects.

Materials & methods: In a prospective study, on all admitted patients in our ward who had received Ifosfamide for chemotherapy and did not have any underlying disease. After a full physical examination and the performing of necessary paraclinical evaluations, information forms for all of the patients were filled out at admission and in follow up visits to be used in their final assessments. Neuropsychiatry examinations were performed with neuropsychiatric physician. The physician repeated their examinations at the end of treatment. If the patients had any symptoms or signs of neuropsychiatric problems the examinations were repeated examination and documented in their files.

Results: Sixty- six cases were male and 34 cases were female. The mean age was 36.4 years (18-49). The most common neuropsychiatric side effects were fatigue and delirium. Side effects were observed in 60% of the patients, and other toxicities included: somnolence (20%), confusion (10%), agitation (5%), extrapyramidal symptoms (5%), stupor (8%); and aphasia, seizures, mutism, coma, and death were not observed. All of the side effects ceased after 48- 120 hours cessation of treatment except fatigue which continued 7- 10 days after the cessation of therapy.

Conclusion: Ifosfamide has the power potential to produce both mild and severe neuropsychiatric side effects. A careful physical examination and early detection of these side effects can prevent major neuropsychiatric problems and rule out the necessity for specific treatment of those side effects and discontinuation of drug.

Keyword: Ifosfamide, Neuropsychiatry, Side effects

Received: 10, Feb., 2010
Accepted: 26, Sep., 2010

Introduction

Ifosfamide (IFO) is an alkylating agent that is used in the treatment of many solid and hematological malignancies.(1) Although IFO is an active, potent drug in the treatment of malignancies, it has many major, potentially life threatening toxicities that include: hematologic, nephrologic, renal, and neuropsychitric toxicity.(2)

The clinical manifestations of neuropsychiatric side effects vary. They range from: mild fatigue, somnolence and confusion to very severe toxicities such as coma, seizure, ataxia, aphasia and cerebellar abnormality and death.(3,4) The prevalence of these neuropsychitric toxicities are not clear and varyas to the route of administration of the drug and closed follow up and examination.(5,6) The assessment of neuropsychiatric toxicities is routinely based on conventional tests of neuropsychiatry function, such as exactly physical examination and the use of specific test.

Table- 1. The grading of IFO induced neuropsychiatric toxicities.

Grade	NCI neurocortical toxicity	Mean well
0	No deficits	Alert
1	Mild somnolence or agitation	Transient lethargy
2	Moderate symptoms	Somnolence < 50% of the time and/or mild to moderate disorientation
3	Severe symptoms, e.g. hallucination	Somnolence > 50% of the time and/or severe disorientation, echolalia, perseveration of writing, palilalia, logorrhoea, hallucinations or delusions
4	Coma or seizure	Coma

Table 2: Prevalence of Ifosfamide side effects in admitted patients in hematology & oncology ward of comparing with other studies

IFO side effect	Prevalence according to other studies	Prevalence in our study	
		Number	percent
Alopecia	Almost> 80-90%	70	70%
Nausea & Vomiting	Almost> 80%	60	60%
Hematuria	46%	12	12%
Hematuria (Gross)	12%	0	0
Hematuria (Microscopic)	common	12	12%
Decrease in serum electrolyte	common	0	0
CNS toxicity	Common	20	20%
Infection	12%	4	4%
Hepatotoxicity	Less common 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%

Materials& Methods

In a prospective study, we evaluated Ifosfamide with respect to the neuropsychiatric side effects in all admitted patients to the hematology & oncology ward who had been candidates for Ifosfamide treatment during 2003– 2007.

The patients were assessed during admission and in follow- up visits for neuropsychiatric side effects. We evaluated and examined them for fatigue, somnolence, confusion, disorientation,(7,8) hallucination, agitation, aphasia, seizure, asterixis, extrapyramidal symptoms, mutism, stupor, coma, and death.(9,10)

Patient information was written on data sheets for final assessment. Baseline laboratory tests were done for all patients who had entered this study: Complete blood cells count, Glucose, serum electrolytes, blood urea nitrogen, creatinine, GFR, uric acid, liver enzymes and bilirubine and urinolysis.

In all patients, a detailed assessment of neuropsychiatry function was carried out at the beginning of therapy. Neuropsychiatry function was reassessed before each subsequent cycle of the therapy. In patients who had demonstrated any abnormalities with the above parameters, additional determinations were performed, as necessary.

Patients were examined during every visit and were information on detecting neurotoxicity. Laboratory tests were repeated every week after the administration of Ifosfamide for the evaluation of hematologic and renal toxicities or other electrolyte imbalances that might be the causes of this situation.

Administration of the drug: After preparation of an IV-line, all patients received maintenance IV fluid. Other pretreatment medications were Kytril, Cholorpheniramine and Metoclopramide (10mg), intravenously, 30-60 minutes before the initiation of chemotherapy.

Chemotherapy was continued in cases that did not show nephrotoxicity or substantial neurotoxicity. Finally, data was analyzed using SPSS Ver 10 software.

Results

Overall, we evaluated 100 patients (66 male and 34 female cases). The patients, aged 12-57 years (the mean age was 32.6 years), were being treated for solid childhood tumors according to applicable chemotherapy protocols. 36 cases (28 males and 8 females) had non Hodgkin's lymphoma, 74 cases (26 females and 48 males) had osteosarcoma.

The Ifosfamide therapeutic dose was 2gr/m2/day in 1 liter normal saline and equal doses of Mesna during a 24 hour periodwhich was administered over a period of 3– 7 days for every cycle.

Neuropsychiatry toxicities often presented themselves during the period of administration or shortly after this administration.
The grading of IFO- induced neuropsychiatric toxicities is based on NCI and mean well grading (Table1).(11,12)
In our study, fatigue and confusion were the most common symptoms and signs that occurred in 60% of the patients. Other toxicities included: somnolence (20%) , confusion (10%), agitation (5%), extrapyramidal symptoms (5%), and stupor (8%). Aphasia, seizures, mutism, coma, and death were not observed (Table- 2).
The maximum grade of these toxicities was grade 1 and 2. Grade 3 toxicity occurred in only 2 cases. All of these side effects were resolved after 3-7 days of at the end of treatment. None of them needed specific treatment. Close follow- up and supportive care were the maximum management.
Our results are summarized in Table- 2.

Discussion

100 patients were treated with chemotherapy containing Ifosfamide. This drug was the sole drug or the main drug administered. The true percentage of neuropsychiatry toxicities of IFO varies based on different studies. One of these studies, in 2005, reported that the most common toxicity was confusion and occurred in 80% of patients. Another very common toxicities were hallucination or psychosis that occurred in 30 % of patients. The presence of incontinence and muscle twitching occurred in 9% of patients.(13) Other, less common and rare presentations were: extrapyramidal symptoms, cranial nerve palsy, seizures, mutism and asterixis.(14,15)
In our study, fatigue and confusion occurred in 60% of the patients. Other toxicities included: somnolence (20%), confusion (10%), agitation (5%), extrapyramidal symptoms (5%), stupor (8%). Aphasia, seizures, mutism, coma, and death were not observed.
The maximum grade of these toxicities were grade 1 and 2. Grade 3 toxicity occurred in 2 of the cases. All of these side effects were resolved after 3-7 days at the end of treatment. None of them needed specific treatment. Close follow- up and supportive care were the maximum management. In one case, cranial nerve palsy (Nerve VII) occurred. This problem was resolved in 7 days after the termination of therapy. All of these side effects occurred during the first and second cycles of treatment. These side effects were not observed during other cycles.
The Ifosfamide toxicity grading system is different in many studies. In one study which was done in 2004, the result was: 25% grade 1 NCI-CTC toxicity, 12 % grade 2, 44% grade 3, and 19% grade 4.(16) In this retrospective study, 16 patients with IFO encephalopathy were assessed.(16) In another study of 105 patients, encephalopathy occurred in 13 cases (5.4%), 3 cases had grade 1 toxicity (20%), 4 cases, grade 2 (27%), 6 cases, grade 3 (40%), and 2 cases, grade 4 (13%) toxicity.(17)
Another study performed by Watkin et al, revealed: 2 cases, grade 2 (11%), 14 cases, grade 3 (77%), and in 2 cases, grade 4 toxicity was observed.(18)
In our study, the maximum grade toxicity was grade 1 and 2. Grade 3 toxicity, occurred in one patient. There were no cases of grade 4 toxicity.
We evaluated and treated every problem that may have mimicked neuropsychiatrical manifestations such as: renal disorder and electrolyte imbalance (we did not observe these side effects that mimic neuropsychiatric symptoms).
When we evaluated the risk factors for neuropsychiatric side effects in patients that had been treated with IFO, a risk factor that we did observe in this prospective study was a low level of albumin (<3.5 gr/dl). In our study, more than 50% of the patients with neuropsychiatric manifestation had low albumin levels.
The incidence of these side effects in both genders was equal. Gender did not play a role in these toxicities.
This finding might be the result of the fact that our patients had not had renal or prior renal or neurologic problems.

Conclusion

IFO has the potential to produce both mild and severe side effects. Neuropsychiatric side effects of IFO vary in different studies. The type and severity of these toxicities are different within different populations. The best management varies in every population. For this reason, the neuropsychiatric side effects of IFO should be carefully considered since every side effect is significant. The best management of these side effects is early detection. Cessation of treatment may be necessary in order to terminate these side effects.

References

1. Kerbusch T, de Kraker J, Keizer HJ, *et al*. Clinical Pharmacokinetics and Pharmacodynamics of Ifosfamide and its Metabolites. Clin Pharmacokinet 2001; 40: 41-62.
2. Nicolao P, Giometto B. Neurological Toxicity of Ifosfamide. Oncology, 2003; 65 (Suppl. 2): 11-16.
3. Dechant KL, Brogden RN, Pilkington and et al. IFO/mesna: A review of its Antineoplastic Activity, Pharmacokinetics

Properties and Therapeutic Efficacy in Cancer. Drugs, 1991; 42: 426-467.

4. Manegold C, Bischoff H and Fischer.JR. Oral Ifosfamide-Mesna: A Clinical Investigation in Advanced Non-small-cell Lung Cancer. Ann Oncol, 1992; 3: 723-726.

5. Pelgrims J, De Vos F, Van den Brande J, et al. Methylene Blue in the Treatment and Prevention of Ifosfamide-induced Encephalopathy: Report of 12 Cases and a Review of the Literature. Br J Cancer 2000; 82:291-294.

6. Mermisky O, Reider-Groswasser I, Wigler N, et al. Encephalopathy in Ifosfamide-treated Patients. Acta Neurol Scand 1992;86:521-525.

7. Kerdaudo C, Orbach D, Sarradet JL. Ifosfamide Neurotoxicity: An Atypical Presentation with Psychiatric Manifestation. Pediat Blood Cancer, 2005; 47: 100-102.

8. David KA, Picus J. Evaluation Risk Factors for the Development of Ifosfamide Encephalopathy. Am J Clin Oncol, 2005; 28: 277-280.

9. Nicolao P, Giometto B. Neurological Toxicity of Ifosfamide. Oncology, 2003; 65: S11-S16.

10. Hernandez R, Juan O, Alberola V. Ifosfamide Induced Psychosis. Acta Oncol, 2004; 43: 119-120.

11. David KA, Picus J. Evaluating Risk Factors for the Development of Ifosfamide Encephalopathy. Am J Clin Oncol, 2005; 28: 277-280.

12. Meanwell CA, Blake AE, Kelly KA, et al. Prediction of Ifosfamide/Mesna Associated Encephalopathy. Eur J Cancer Clin Oncol, 1986; 22: 815-819.

13. David KA, Picus J. Evaluating Risk Factors for the Development of Ifosfamide Encephalopathy. Am J Clin Oncol, 2005; 28: 277- 280.

14. Primavera A, Audenino D, Cocito L. Ifosfamide Encephalopathy and Nonconvulsive Status Epilepticus. Can J Neurol Sci, 2002; 29: 180- 183.

15. Meyer T, Ludolph AC, Munch C. Ifosfamide Encephalopathy Presenting with Asterixis. J Neurol Sci, 2002; 199: 85-88.

16. Rieger C, Fiegl M, Tischer J, et al. Incidence and Severity of Ifosfamide-induced Encephalopathy. Anticancer Drugs, 2004; 15: 347-350.

17. Matsumine AKI, Ieguchi M, Hirosima K, et al. Ifosfamide (IFM)-induced Encephalopathy in Bone and Soft Tissue Sarcoma Patients. Proc Am Soc Clin Oncol, 2001; 20: 1454-1457.

18. Ajithkumar T, Parkinson C, Shamshad F, et al. Ifosfamide Encephalopathy. Clin Oncol (R Coll Radiol). 2007; 19 (2): 108-114.