Case Report

iMedPub Journals
www.imedpub.com

Medical Case Reports
ISSN 2471-8041

2018
Vol.4 No.3:82

DOI: 10.21767/2471-8041.100118

# A Case of Ifosfamide Encephalopathy and its Literature Review

**Qiao-Ling Gong[1#], Pei Fen-Ma[1*] and Ye Chai[2#]**

[1]School of Nursing, Lanzhou University, Lanzhou, P.R China

[2]Department of Hematology, The Second Hospital of Lanzhou University, Lanzhou, P.R China

[*]**Corresponding author:** Pei-Fen Ma, Department of Hematology, The Second Hospital of Lanzhou, University, No. 82 Cuiyingmen, Lanzhou 730030, Gansu Province, P R. China, Tel: +8613893675190; E-mail: sherry_bb@163.com

**Received:** July 10, 2018; **Accepted:** July 24, 2018; **Published:** July 26, 2018

**Citation:** Gong QL, Fen-Ma P, Chai Y (2018) A Case of Ifosfamide Encephalopathy and its Literature Review. Med Case Rep Vol.4 No.3:82.

[#]These authors contributed equally to this work

## Abstract

Ifosfamide is a cytostatic drug commonly used in chemotherapy. One of the common adverse effects resulting from the treatment with ifosfamide is encephalopathy. Here we describe the case of a male patient was diagnosed of acute lymphoblastic leukemia. He had gone through chemotherapy six times, and achieved complete remission. On the second day of the seventh HR-2 regimen chemo treatment (0.5 g, 2.5 g, or 2 g methotrexate, 4 mg vindesine, 0.8 mg ifosfamide, Q12 h), he had convulsion and became unconscious. The epileptic symptoms are considered to be ifosfamide encephalopathy. According to the case report and the review of the relevant literature information demonstrated that any chemo regimens containing ifosfamide can not only lead to bone marrow inhibition and nephrotoxicity, but possible development of ifosfamide encephalopathy. Furthermore, risk factors that might induce ifosfamide encephalopathy should be avoided or eliminated as much as possible.

**Keywords:** Ifosfamide; Central Nervous System (CNS); Encephalopathy; Acute Lymphoblastic Leukemia (ALL)

## Introduction

Ifosfamide is an anti-cancer (anti-neoplastic or cyto-toxic) chemotherapy drug. It is an alkylating agent used in the treatment of germ-cell tumors, sarcomas and lymphomas. It is also used to treat different types of malignancies including ovarian, testicular, cervical cancers, lymphomas and sarcomas. Common adverse effects of Ifosfamide include bone marrow suppression, nausea and vomiting, hemorrhagic cystitis and encephalophathy. Here we describe the case of a male patient who was diagnosed of acute lymphoblastic leukemia.

## Case Presentation

A male patient, aged 15-years-old, came to our clinic in April 2016 with a chief complaint of intermittent headache and dizziness for 2 years. His other symptoms were fatigue and loss of appetite for 2 weeks. A routine blood test showed a white blood cell (WBC) count of 63.10 × 109/L, red blood cell (RBC) count of 2.21 × $10^{12}$/L, hemoglobin (Hb) levels of 78 g/L, and platelet (PLT) count of 33 × $10^{9}$/L. Bone marrow biopsy after admission showed active bone marrow hyperplasia; G=68%, E=1.00%, G/E=68:1. Granulocytic hyperplasia was seen, with 65% of cells being primitive cells. There was an increase in primary monocytes by 29%, and RBCs and lymphocytes significantly decreased in number. PLTs were rarely seen. A diagnosis of acute myelomonocytic leukemia was considered. Flow cytometry results showed that a total of 73.12% lymphocytes were atypical with expression of CD20, CD22, CD19, CD13, CD123, HLA-DR, CD10, CD79a; partial expression of CD9, CD33; and no expression of CD7, CD38, CD11b, CD15, CD4, CD34. The final diagnosis was B cell acute lymphoblastic leukemia/lymphoblastic lymphoma (B-ALL/LBL) with cross-lineage expression of CD13 and CD33. Acute myeloid leukemia prognosis-related gene mutation detection results showed no mutation of FLT3-ITD, C-kit/D816V, or NPM1/CEBPA. Chromosome examination results showed no clonal number or structural abnormalities. Hematological neoplasm-related gene examination results were negative for all 43 fusion genes in leukemia. Routine test and biochemical analysis of cerebrospinal fluid (CSF) were both normal with no immature cells detected. A diagnosis of ALL was confirmed. The patient was successively treated with the IA regimen (idarubicin and cytarabine), VDLP regimen (VCR [Vincrisstine], DNR [Daunomycin], L-ASP [L-Asparaginase], Prednisolone and Dexamethasone), clarithromycin (CAM) regimen, methotrexate (MTX) regimen, and HR-3 regimen, and achieved complete remission. He was admitted to our hospital again on November 1, 2016. Physical examination upon admission showed no enlargement of the superficial lymph nodes of the whole body; the neck was soft with no rigidity; and no obvious cardiac, pulmonary, or abdominal anomalies were detected. Physiological reflexes were present and pathological reflexes could not be elicited. Routine blood test showed a WBC count of 2.5 × 109/L, Hb levels of 124 g/L, and a PLT count of 133 × 109/L. Routine test and biochemical analysis of CSF were both normal with no immature cells detected. Head CT scan did not show any anomalies. Bone marrow biopsy suggested complete remission. The patient began HR-2 chemotherapy regimen (0.5

g, 2.5 g, or 2 g methotrexate, 4 mg vindesine, 0.8 mg ifosfamide, Q12 h) on November 4. An appropriate dose was given to the patient according to his height, body mass, and body surface area. On the second day of chemotherapy, the patient suddenly had convulsion of the limbs and transient loss of consciousness, which lasted for about 1 minute. Ten minutes later, he presented with unconsciousness, flexion rigidity, and convulsion of the upper limbs, which lasted for about 2 minutes. Physical examination showed a heart rate of 130/min, respiration rate of 39/min, and blood pressure of 150/92 mmHg. The patient became unconscious. His bilateral pupils were dilated with insensitive light reflex, tendon hyperreflexia of the four limbs were observed, and pathological reflexes on both sides were positive. Symptomatic treatment including dehydration to reduce the intracranial pressure, sedation, anti-convulsion, and oxygen inhalation were administered. Subsequently, the patient's vital signs gradually returned to normal. Five hours later, the patient fell into a coma with obvious glossoptosis and dyspnea, so endotracheal intubation and mechanical ventilation were immediately performed, and the chemotherapy regimen was suspended. The next day, the patient regained consciousness and tracheal extubation was performed after proper assessment. A re-examination of routine blood tests revealed a WBC count as low as $0.1 \times 10^9$/L, a RBC count of $2.14 \times 10^{12}$/L, Hb levels of 68 g/L, and low PLT levels of $70 \times 10^9$/L. After leukocyte enhancement therapy together with intermittent blood and PLT transfusion, the patient's hemogram returned to normal. Subsequently, the patient remained in good general condition and never had convulsions again, and magnetic resonance imaging of the head did not show significant anomalies.

On the second day of the patient's first HR-2 chemotherapy regimen, he had convulsion and loss of consciousness. He had no previous history of epilepsy. Possible disorders that might lead to epileptic manifestations, such as central nervous system leukemia and cerebral hemorrhage, were ruled out. After a review of the literature and the drug information for ifosfamide, central nervous system toxiciry induced by ifosfamide was highly suspected. After suspension of HR-2 chemotherapy regimen, the patient did not experience convulsions or any other encephalopathic manifestation. With no ifosfamide in previous and later chemotherapy regimen, the patient had never presented with convulsions, syncope, or any other symptoms of neurotoxicity. Therefore, the epileptic symptoms of this patient during treatment were considered to be ifosfamide encephalopathy.

## Discussion

Ifosfamide is a cell cycle non-specific drug. To exert its effects, ifosfamide is mainly hydrolyzed, by the phosphoamidase or phosphatase inside the liver or tumor, into active phosphoramide mustard. Adverse drug reactions of ifosfamide are mainly bone marrow inhibition, nephrotoxicity, and CNS toxicity. Since 1989, CNS toxicity induced by ifosfamide has been called ifosfamide encephalopathy, which has a reported incidence of about 10–30%. The major clinical manifestations of ifosfamide encephalopathy include somnolence, insanity, and hallucination. Within 2 hours of taking ifosfamide, the patient may develop unconsciousness, hallucination, cerebellar symptoms, disturbance of consciousness, and seizure. These symptoms are often reversible and symptomatic, and supportive treatment can be administered until complete disappearance of these symptoms [1]. There was also a reported death due to ifosfamide encephalopathy [2]. Since 1996, there have been a few reports of ifosfamide encephalopathy in China [3].

Currently the exact mechanisms underlying ifosfamide encephalopathy have not been clear. It has been postulated that ifosfamide may crosslink with DNA to inhibit the synthesis of DNA or interfere with RNA functions. There is also a possible correlation between ifosfamide encephalopathy and ifosfomide metabolites [4]. What is known is that the definitive risk factor for ifosfamide encephalopathy is a previous history of taking cisplatinum, which can aggravate the neurotoxicity of this drug. The occurrence of ifosfamide encephalopathy involves its dosage. Cohe et al. [5] reported that ifosfamide encephalopathy mainly develops among patients taking over 5 g/m$^2$ ifosfamide. However, Rieger et al. [6] stated that there is no significant correlation between the dosage of ifosfamide and ifosfamide encephalopathy. Other factors such as hyponatremia, hypoproteinemia, poor general condition, and previous history of nephrectomy might all increase the risk for ifosfamide encephalopathy [7], albeit not in a statistically significant manner.

Usually the symptoms of ifosfamide encephalopathy are reversible and disappear after withdrawal. Regarding its treatment, in 1994, Kupfer et al. [8] used methylene blue for the treatment of ifosfamide encephalopathy. There has also been an increasing number of reports on methylene blue for the prevention and treatment of ifosfamide encephalopathy, possibly due to the fact that methylene blue can counteract some metabolic pathways of ifosfamide, thereby decreasing the plasma concentration of its active metabolites and reducing its toxicity [9]. Currently the recommended treatment for ifosfamide encephalopathy includes immediate withdrawal of ifosfamide once ifosfamide encephalopathy is suspected and intravenous administration of methylene blue [10]. However, some researchers have questioned the validity of using methylene blue for treating ifosfamide encephalopathy. One study [11] reported that severe encephalopathy could last as long as 20 days without methylene blue before the development of encephalopathy. There have also been reports on other prevention and treatment measures including albumin [4], glucose [12], and vitamin B1 transfusion. A second ifosfamide chemotherapy is not an absolute contraindication, but intravenous administration of methylene blue (every 6 h, 50 mg each time) is needed as prophylactic treatment. The patient in the present report developed epileptic symptoms after approximately 2 days of ifosfamide chemotherapy. Ifosfamide encephalopathy was highly suspected and chemotherapy was immediately suspended. He was only given symptomatic treatment without methylene blue, which led to symptom remission the next day.

## Conclusion

This case report and a review of the relevant literature demonstrated that chemotherapy regimens containing ifosfamide can lead to bone marrow inhibition and nephrotoxicity. In addition, the possible development of ifosfamide encephalopathy should be monitored. Furthermore, risk factors that might induce ifosfamide encephalopathy should be avoided or eliminated as much as possible.

## Acknowledgements

We express our heartfelt thanks for the strong support of the Second Hospital of Lanzhou University.

## References

1. Lin JK, Chow DS, Sheu L, Rehani B (2017) Wernicke-like encephalopathy associated with ifosfamide. J Neurohospitalist 7: 49-50.
2. Bozcuk H, Ozdogan M (2011) The predictors of the efficacy of high-dose chemotherapy and stem cell support in the management of metastatic germ cell cancer. Bratisl Lek Listy 112: 296-304.
3. Wang ZQ, Yu H, Zhu XJ, Lin L, Sun XM (2015) Ifosfamide induced encephalopathy: A case report and a literature review. Journal of Clinical Hematology 4: 623-625.
4. Shin YJ, Kim JY, Moon JW, You RM, Park JY, et al. (2011) Fatal ifosfamide-induced metabolic encephalopathy in patients with recurrent epithelial ovarian cancer: Report of two cases. J Cancer Res Treat 43: 260-263.
5. Cohen MH, Creaven PJ, Tejada F, Hansen HH, Muggia F, et al. (1975) Phase I clinical trial of isophosphamide (NSC-109724). J Cancer Chemother Rep 59: 751-755.
6. Rieger C, Fiegl M, Tischer J, Ostermann H, Schiel X (2004) Incidence and severity of ifosfamide-induced encephalopathy. J Anti-Cancer Drugs 15: 347-350.
7. Kocabay G, Karabay CY (2011) Iopromide-induced encephalopathy following coronary angioplasty. J Perfusion 26: 67-70.
8. Kupfer A, Aeschlimann C, Wermuth B, Cerny T (1994) Prophylaxis and reversal of ifosfamide encephalopathy with methylene-blue. J Lancet 343: 763-764.
9. Jack CI, Leikin JB (2016) Methylene blue. Am J Ther 10: 289-291.
10. Barthelemi L, Bara E, Descoeur J, Sirvent N (2015) Ifosfamide-induced encephalopathy: symptoms and efficacy of methylene blue (MB) in the treatment and prevention of this adverse effect. J Fundam Clin Pharmacol 29: 24-24.
11. Filhon B, Lacarra B, Hervouet C, Jaffray M, Schneider P, et al. (2016) Ifosfamide-induced encephalopathy due to a novel formulation of ifosfamide. Pediatric Blood & Cancer 63: 372-373.
12. Krouwer HGJ, Wijdicks EFM (2012) Neurologic complications of hematopoietic stem cell transplantation. Eur Assoc Neurooncol Mag 2: 233-252.