Case Report

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# Ifosfamide-Induced Encephalopathy in Relapsed Lymphoma: Report of Two Cases

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## Abstract

**Objective**: Ifosfamide is a chemotherapeutic drug available for various malignancy, including lymphoma. Ifosfamide has adverse effects including myelosuppression, nephrotoxicity, hemorrhagic cystitis, and neurotoxicity. Encephalopathy is a severe manifestation of neurotoxicity due to ifosfamide, with an incidence of 10–40%. This study aimed to report two cases of ifosfamide-induced encephalopathy.

**Case**: This case studies reported two relapsed lymphoma patients with almost similar characteristics who received ifosfamide chemotherapy. The first case of 48-year-old woman with relapsed High-Grade B-cell lymphoma stage IIIBE while the second case of 38-year-old woman with relapsed non-hodgkin lymphoma. The first case showed a good outcome with improvement in consciousness 48 hours after stopping ifosfamide and thiamine, while the second case experienced tumor lysis syndrome, leading to the death of the patient.

**Conclusion**: Mechanism of ifosfamide-induced encephalopathy remains unclear, with the hypothesis from the neurotoxic effects of the resultant metabolite chloracetyldehide. Radiology examination of the brain and electroencephalography is required to rule out other differential diagnoses. Early recognition of adverse effects, followed by immediate discontinuation of ifosfamide, administration of therapy, such as methylene blue and/or thiamine, and supportive treatment usually produced good outcomes.

**Keywords**: Encephalopathy, ifosfamide, lymphoma, thiamin

## Introduction

Ifosfamide is an alkylated oxazaphosphorin derivative with a structural formula that resembles cyclophosphamide. It has been used as chemotherapy for several types of tumors, including ovarian, testicular, cervical, head and neck cancers, lymphoma, and sarcoma.[1–4] Adverse effects of ifosfamide include myelosuppression, nephrotoxicity, hemorrhagic cystitis, and neurotoxicity.[3–5] Neurotoxicity may manifest as extrapyramidal disturbances disorientation, agitation, seizures, confusion, lethargy, and hallucinations, but rarely progresses to coma or causes permanent brain damage or death.[2,6] The incidence of ifosfamide-induced encephalopathy ranges from 10% to 40%.[4,6] These conditions can occur within 2 to 146 hours after intravenous ifosfamide administration and may improve within 48 to 72 hours after the discontinuation of therapy.[1,4,6] Poor performance status, renal impairment, high cumulative dose, history of brain metastases, and hypoalbuminemia are risk factors for neurotoxicity.[2,7,8]

The pathophysiology of the ifosfamide-

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induced encephalopathy remains unclear. Several theories suggest that the resultant products of ifosfamide metabolism, such as chloroacetaldehyde and chlorotilamine, act as neurotoxic agents capable of penetrating the blood-brain barrier.[6,9] Based on previous studies, methylene blue, thiamine, and albumin are the treatment options for this condition.[2,6,10] This study aims to report cases of ifosfamide-induced encephalopathy in patients with relapsed lymphoma.

## Case(s)

The first patient was a 48-year-old woman with relapsed high-grade B-cell lymphoma stage IIIBE. She had been diagnosed with lymphoma two years before. The patient underwent intra-abdominal tumor resection and colostomy, followed by the R-CHOP chemotherapy regimen (Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), achieving a complete response one year earlier. She was subsequently treated with the ICE chemotherapy regimen (ifosfamide, carboplatin, etoposide)The patient had a colostomy, and her vital signs and other physical examinations were within normal limits, with an Eastern Cooperative Oncology Group (ECOG) performance status of 2. Laboratory results indicated mild thrombocytopenia (Table 1), and chest x-rays were normal (Fig. 1).

The patient began chemotherapy with 100 mg/m$^2$ of intravenous etoposide on the first day. On the second day, the patient received a second dose of 100 mg/m$^2$ of etoposide, along with 5 AUC of carboplatin and 5,000 mg/m$^2$ of ifosfamide, administered intravenously. The final dose of 100 mg/m$^2$ of etoposide was given on the third day. There were no signs of fever or seizures on the fourth day and thereafter. During treatment, indicators of tumor lysis syndrome were monitored, and the results were normal (Table 1). However, on the fourth day, the patient became somnolent and was moved to a semi-intensive care unit for treatment.

There were no focal neurological deficits noted during the physical examination. A head computed tomography (CT) scan with contrast revealed no structural abnormalities (Fig. 2). The patient received 100 mg of thiamine intravenously every 4 hours, without methylene blue (MB) administration due to its unavailability. She became fully conscious after 48 hours, on the seventh day of treatment. Unfortunately, the patient developed neutropenia as a side effect of chemotherapy. She subsequently experienced sepsis from pneumonia and died after two weeks of treatment due to respiratory failure.

The second patient, a 38-year-old woman diagnosed with relapsed non-Hodgkin lymphoma involving the kidneys and lungs, was admitted to the hospital with abdominal pain that had persisted for the last four months. She had previously undergone chemotherapy with the R-CHOP regimen (Rituximab, cyclophosphamide, doxorubicin, vincristine,

**Table 1 Laboratory Results (Patient No. 1)**

| Parameter | Day 1* | Day 4 | Day 7 |
|---|---|---|---|
| Hemoglobin (g/dL) | 11.2 | 9.6 | 8.5 |
| Hematocrit (%) | 34.2 | 29.9 | 26.3 |
| Leukocyte (/uL) | 8,830 | 10,210 | 12,000 |
| Platelet (/uL) | 118,000 | 131,000 | 97,000 |
| Absolute neutrophil (/uL) | 6,710 | 9,904 | 10,680 |
| Ureum (mg/dL) | 28.0 | 39.0 | 61.0 |
| Creatinine (mg/dL) | 1.11 | 0.88 | 1.21 |
| Uric acid | | 4.2 | 6.0 |
| Potassium (mEq/L) | | 4.6 | 3.6 |
| Calcium (mg/dL) | | 4.95 | 4.81 |
| Phosphor (mg/dL) | | 3.64 | 4.18 |

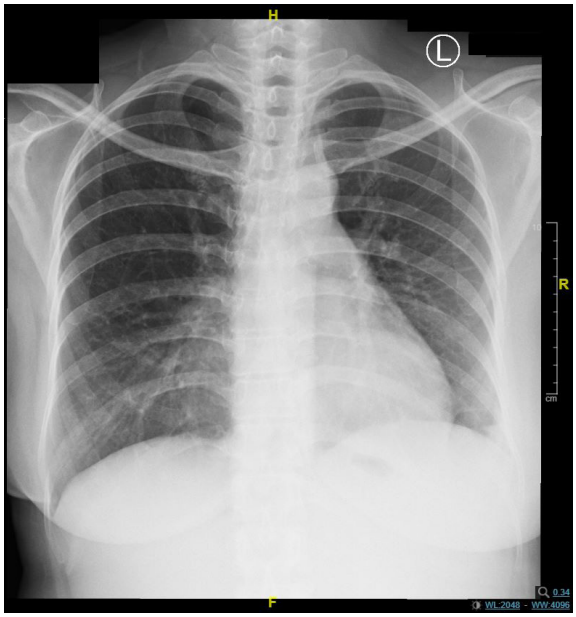


**Fig 1. Chest X-ray (Patient No. 1)**

and prednisone), achieving a complete response in 2019, and was scheduled to undergo chemotherapy with the ICE regimen. Upon admission, the patient had normal vital signs, but her ECOG performance status was rated at 2. She presented with anemia and a palpable abdominal mass. An abdominal CT scan revealed a mass measuring 20 cm in diameter (Fig. 3). Furthermore, she exhibited anemia and abnormal kidney function (Table 2), and a chest X-ray indicated features of pulmonary involvement (Fig. 4).

The patient underwent chemotherapy at the same dose as patient No. 1. On the third day of chemotherapy, patient No. 2 became agitated and difficult to communicate with, but did not show seizures or overt focal neurological deficits. The patient continued treatment in the intensive care unit, receiving intravenous thiamine at a dose of 100 mg every

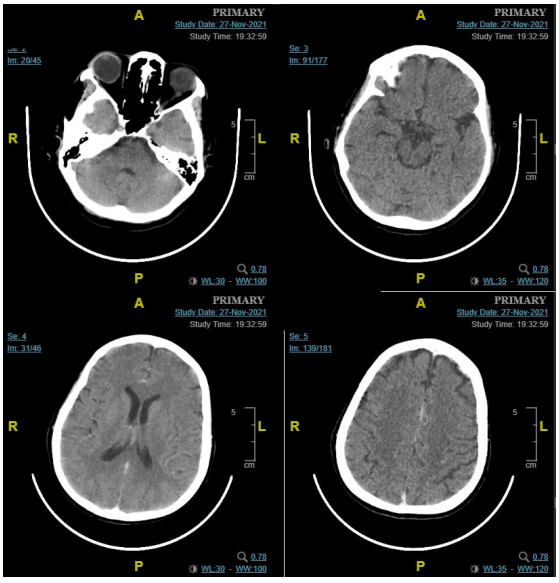


**Fig. 2 Head Computed Tomography (CT) with Contrast (Patient No. 1)**

**Table 2 aboratory Results for Second Patient**

| Parameter | Day 1* | Day 3 | Day 6 |
|---|---|---|---|
| Hemoglobin (g/dL) | 10.2 | | 7.2 |
| Hematocrit (%) | 30.9 | | 22.6 |
| Leukocyte (/uL) | 13840 | | 21030 |
| Platelet (/uL) | 328000 | | 344000 |
| Absolute neutrophil (/uL) | 11210 | | 20609 |
| Ureum (mg/dL) | 52.5 | 67.9 | 103.6 |
| Creatinine (mg/dL) | 2.52 | 1.69 | 1.88 |
| Uric acid | 3.6 | 4.8 | 8.4 |
| Potassium (mEq/L) | 3.6 | 4.7 | 6.1 |
| Calcium (mg/dL) | | 4.51 | 4.25 |
| Phosphor (mg/dL) | | 4.68 | 10.72 |

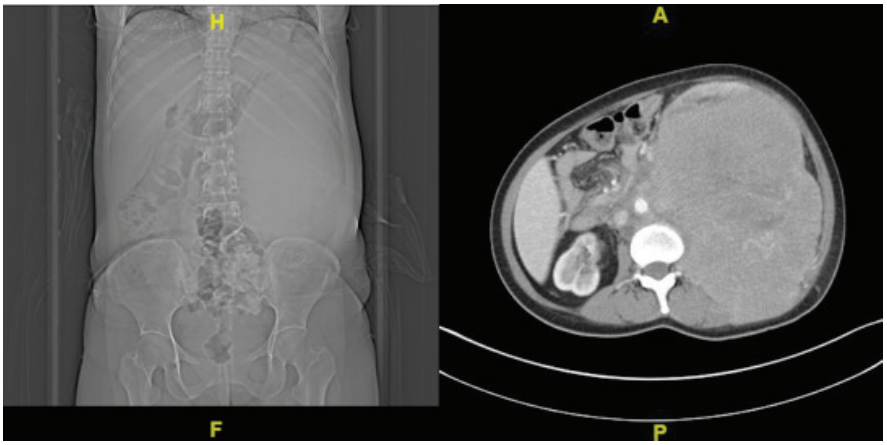


**Fig. 3 CT Abdomen with Contrast in Second Patient**

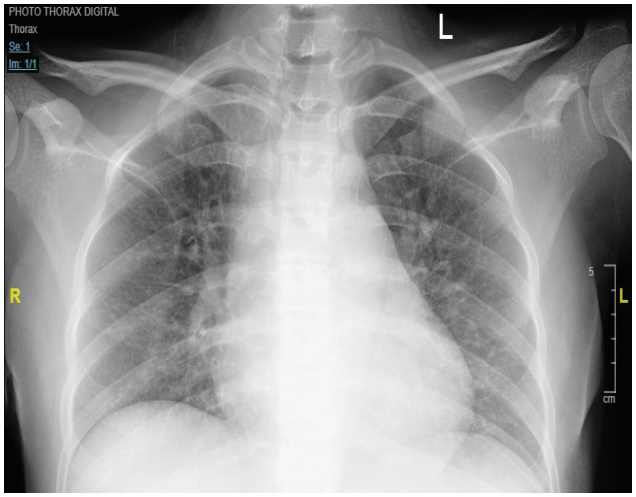


**Fig. 4 Chest X-ray (Patient No. 2)**

4 hours. Tumor lysis syndrome developed on the second day after chemotherapy. The patient's consciousness was comatose and did not improve; the patient died on the sixth day of hospitalization, following two days of thiamine administration and treatment for tumor lysis syndrome.

## Discussion

Ifosfamide metabolism occurs in the liver via cytochrome P450 (CYP450), producing cytotoxic metabolites. The pathophysiological mechanism of encephalopathy remains not fully understood. The neurotoxicity of ifosfamide is attributed to the resultant metabolites of chloroacetyldehyde and chlorotilamine.[6,9,10] Both of these metabolites can penetrate the blood-brain barrier and subsequently inhibit mitochondrial oxidative phosphorylation, reducing glutathione levels in the central nervous system and causing encephalopathy.[3] Tajino *et al*. demonstrated that the ifosfamide dose predisposes patients to a higher incidence of encephalopathy. In a recent study, Yin *et al*. found no significant difference in the incidence of ifosfamide-induced encephalopathy between daily and cumulative doses in patients.[2,7] Both cases in this case study received the same daily dose of ifosfamide and presented with nearly the same symptoms of neurotoxicity. Adverse effects on the central nervous system can occur 2 to 146 hours after ifosfamide administration.[4,6] The first patient showed symptoms of encephalopathy 72 hours after the first dose, while the second experienced encephalopathy 48 hours after the ifosfamide administration. Improvement can occur 48 to 72 hours after stopping therapy.[1,4] The first case showed significant improvement in consciousness 48 hours after discontinuation of therapy, whereas the second case showed no improvement until death. Ifosfamide-induced encephalopathy is a clinical diagnosis with differential diagnoses including infections, other metabolic disorders, and adverse drug interactions. The diagnosis is supported by normal brain radiology to exclude other causes of the patient's altered consciousness. Electroencephalography (EEG) examination reveals typical features of metabolic encephalopathy and correlates with severity. EEG changes can be detected 12–24 hours before symptoms of toxicity appear and improve 24–48 hours before clinical recovery occurs. [1,3,6] A head CT scan with contrast for the first patient was within normal limits; however, the second patient did not undergo brain examination. Decreased consciousness in the absence of obvious focal neurological deficits in a patient receiving ifosfamide is consistent with the clinical diagnosis of ifosfamide-induced encephalopathy.

EEG examinations should be performed routinely in patients with ifosfamide-induced encephalopathy. This condition can present with varying degrees of severity: grade 1 shows vague depressive affect, grade 2 is characterized by prolonged sleep periods, grade 3 includes stuporous consciousness, severe depression, or mild hallucinations, and grade 4 indicates severe hallucinations, seizures, or coma.[1,4,6] Agitation to the point of somnolence became a clear manifestation of grade 3 encephalopathy in both patients. Early evaluation of neurotoxicity after the administration of ifosfamide is needed to prevent the progression of encephalopathy. Several conditions can increase the risk of ifosfamide-induced encephalopathy. Risk factors include female sex, kidney and liver disorders, low albumin levels, a history of platinum consumption, large intra-abdominal tumors, and poor performance status.[1,3,6] Yin *et al*., showed performance status ≥2 and an increase of 1 mg/dL in serum creatinine increase the risk of ifosfamide-induced encephalopathy, whereas an increase of 1 g/dL in albumin reduces this risk.[2]

Both patients had almost the same characteristics, women with a history of intraabdominal tumors and low serum albumin levels (<3.5 g/dL).[1] Patients were managed for ifosfamide-induced encephalopathy by immediately stopping ifosfamide administration, followed by supportive care that included fluid hydration, electrolyte and albumin correction, and the discontinuation of other drugs with potential CNS side effects. Most cases can improve on their own, but healing can be accelerated by the administration of methylene blue (MB) and thiamine. Previous studies have identified MB as therapy and prophylaxis for ifosfamide-induced encephalopathy.[3,4,6] MB acts as a substitute for the electron transport enzyme flavoprotein, restores the oxidative function of nicotinamide adenosine hydrogen dinucleotide (NADH) in the liver, and inhibits the oxidation of monoamine chlorethylamine to chloroacetyldehyde outside the liver.[11] The administration of MB before ifosfamide is crucial as prophylaxis for ifosfamide-induced neurotoxic encephalopathy. Monitoring for MB's adverse effects, such as anaphylactic

shock, Heinz body hemolytic anemia, or serotonin syndrome, is also necessary. Serotonin syndrome caused by MB can lead to disturbances of consciousness that resemble ifosfamide encephalopathy, but it can be differentiated through a thorough examination of the patient's history, physical examination, and the Hunter Serotonin Toxicity Criteria.[4,12–14] The patients in this case study did not receive MB as prophylaxis for ifosfamide-induced encephalopathy because it was not available at Dr. Hasan Sadikin General Hospital in Bandung, Indonesia.

Ifosfamide-induced encephalopathy has features similar to Wernicke's encephalopathy, a syndrome caused by severe thiamine deficiency. Thiamine is considered a therapeutic option and may be used alone or in combination with MB for either treatment or prophylaxis.[15] Chloroacetyldehyde interferes with the function of thiamine pyrophosphorylase (TPP) by preventing TPP from binding to its receptors, without decreasing serum thiamine levels. Thiamine administration is expected to improve the balance of enzyme function in thiamine triphosphate (TPP) and its active form. Thiamine is the treatment of choice for ifosfamide-induced encephalopathy in patients, with thiamine administered at a dose of 100 mg intravenously every 4 hours. Buesa *et al*. explained that thiamine, at doses used in both cases of this study, was the second choice of therapy when MB was unavailable or when there was unresponsiveness after MB administration. [15]

The two cases had different outcomes. The first patient showed an improved response to full consciousness after a single 48-hour thiamine administration, while the second case worsened to death. The clinical worsening of the second case could be due to extensive brain damage due to ifosfamide or tumor lysis syndrome as another side effect of chemotherapy.

Evaluation of the signs and symptoms of acute neurological deficits in patients receiving ifosfamide is particularly important for diagnosing ifosfamide-induced encephalopathic neurotoxicity. Early recognition of the adverse effects of ifosfamide requires immediate management, including discontinuation of the drug and supportive therapy. The clinical diagnosis of ifosfamide-induced encephalopathy is supported by normal brain imaging and EEG showing metabolic encephalopathy, which helps rule out other causes. A routine EEG examination is recommended for diagnosis. Thiamine administration has been shown to provide better outcomes and improve consciousness more quickly. This study has a limitation in that it only discusses two cases of encephalopathy in relapsed lymphoma patients induced by ifosfamide.

In conclusion, the mechanism of ifosfamide-induced encephalopathy remains unclear, with a prevailing hypothesis regarding the neurotoxic effects of the resultant metabolite, chloracetaldehyde. Radiologic examination of the brain and electroencephalography are required to rule out other differential diagnoses. Early recognition of adverse effects, followed by immediate discontinuation of ifosfamide, administration of therapies such as methylene blue and/or thiamine, and supportive treatment usually produce good outcomes.

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