Jurnal Ilmu Farmasi dan Farmasi Klinik
(Journal of Pharmaceutical Science and Clinical Pharmacy)
ISSN 1693-7899 (print) - 2716-3814 (online)
DOI: 10.31942/jiffk.v21i1.9529

Risk Factors for Ifosfamide-induced Encephalopathy: A Case Control Study at Dr. Kariadi Central General Hospital

Viren Ramadhan[1]*, Setiarsih[2], Essyah Prawitasari[1], Fuji Dora Amantara[1], Raguwan[1]

[1] Pharmacy Installation, Dr. Kariadi General Hospital, Semarang, Central Java, Indonesia
[2] Oncology Installation, Dr. Kariadi General Hospital, Semarang, Central Java, Indonesia

ABSTRACT: Ifosfamide is a cytotoxic agent used in chemotherapy, with neurotoxicity—particularly encephalopathy occurring in approximately 10–30% of patients. This study aims to identify the risk factors associated with ifosfamide-induced encephalopathy (IIE) to aid in its prevention. A case-control study was conducted using secondary data from electronic medical records at the Pharmacy Installation of Dr. Kariadi Central General Hospital between January and June 2024. A total of 48 cancer patients who received ifosfamide were included, comprising 19 patients in the case group (with encephalopathy) and 29 in the control group (without encephalopathy). The analysis revealed that a higher dose of ifosfamide (5000 mg/m^2) was significantly associated with increased risk of encephalopathy, with odds ratios ranging from 2.5 to 8.3 compared to a lower dose (1200 mg/m^2). Patients with no history of prior chemotherapy had 0.3 to 8.8 times higher odds of developing encephalopathy than those with previous chemotherapy exposure, suggesting potential adaptive tolerance or protective mechanisms. Neo-adjuvant treatment was also associated with an increased risk (OR 0.5 to 0.14) compared to adjuvant therapy, possibly due to differences in disease burden or patient condition at the time of treatment. Additionally, patients with impaired liver function showed substantially higher risk (OR 6.1 to 7.4), highlighting the liver's critical role in ifosfamide metabolism and neurotoxic metabolite clearance. High-dose ifosfamide, absence of prior chemotherapy, neo-adjuvant treatment, and impaired liver function are significant risk factors for ifosfamide-induced encephalopathy (IIE). These findings underscore the importance of individualized risk assessment before ifosfamide administration to improve patient safety and optimize therapeutic outcomes.

Keywords: Ifosfamide; cancer; encephalopathy; risk factors

*Corresponding author:
Name : Viren Ramadhan
Email : virenramadhan19@gmail.com
Address : The pharmacy installation, RSUP Dr. Kariadi Semarang, Central Java, Indonesia

Submitted: 16-02-2025; Received in Revised Form: 14-04-2025; Accepted: 18-05-2025

INTRODUCTION

Ifosfamide is a cytotoxic agent used in the treatmenr of various cancers, including sarcoma, acute lymphoblastic leukemia, and nasopharyngeal carcinoma (Brunello et al., 2007). Inclinical practice, ifosfamide is commonly used, particulary in soft tissue sarcomas, where it is part of standard regimens such as AIM (Adriamycin, Ifosfamide an and Mesna) or VAC (Vincristine, Actinomycin-D, and Cyclophosphamide/Ifosfamide). A retrospective study reported that up to 20-30% of sarcoma patients undergoing chemotherapy received ifosfamide-based regimens (Frezza et al., 2015).

Similary, data from the Pharmacy Installation of Dr. Kariadi Central General Hospital in 2023 showed that 48 patients per year received ifosfamide as part of their chemotherapy regimen. Most of these patients were diagnosed with soft tissue sarcoma, followed by testicular cancer and osteosarcoma. The majoruty of patients were male and within the age group of 20-50 years, which reflects the demographic most affected by these malignancies. This pattern underscores the significance of ifosfamide in the management of solid tumors within the institution.

Like cyclophosphamide, Ifosfamide is often combined with other cytotoxic agents including doxorubicin, epirubicin, paclitaxel, carboplatin, and fluorouracil (Howell et al., 2008). One of the major limitations of ifosfamide use is its potential to induce neurotoxicity in the form of encephalopathy, which typically presents as confusion, somnolance, delirium, hallucinations, and coma. This adverse effect has been reported in approximately 10-30% of patients receiving intravenous ifosfamide, depending on dosage, combination therapy, and patient-specific factors (Furui et al., 2023; Kettle et al., 2010). Ifosfamide is a prodrug that is metabolized by the cytochrome P450 enzyme into an active metabolite so that it can act as an alkylating agent which is considered to be the cause of encephalopathy (Res et al., 2020).

This study was conducted at Dr. Kariadi central General Hospital, a national referral and academic hospital located in Semarang, Indonesia, which serves a large and diverse population from Central Java and surrounding regions. The hospital's role as a tertiary care center with comprehensive oncology services, along with a consistent annual caseload of ifosfamide-treated patients, make it an appropriate and strategic site for evaluating the incidence and risk factors of ifosfamide-induced encephalopathy (IIE) in real-world clinical practice.

The dose of ifosfamide is 1200-8000 mg/m^2 according to the protocol of chemotherapy regimen. A case report shown the incidence of ifosfamide-induced encephalopathy (IIE) occured in an initial dose of 5000 mg/m^2 within 24 hours of infusion (Menon et al., 2024). Tamma et al. (1994) reported an incidence of IIE ranging from 10%-30% with higher risk observed in patients with low serum albumin, renal dysfunction, or a history of central nervous system disorders. Ajithkumar et al. (2007) identified a possible association between the use aprepitant, a CYP3A4 inhibitor, and increased risk of IIE

Given these findings, the role of clinical pharmacists is essential in assessing risk factors, evaluating potential drug interactions, and implementing preventive measures to minimize the incidence of IIE. This study aims to further investigate a broader range of clinical and pharmacological risk factors that may influence the development of IIE in patients undergoing ifosfamide-based chemotherapy.

METHODS

The design of this study was a case-control that began with collecting cancer patients undergoing ifosfamide regimen. Data were obtained from integrated patient notes in electronic medical records and then looked back at the risk factors that influenced the occurrence of encephalopathy. Data collection was carried out on patients with first cycle in January to June 2024 period. This study was approved by the Ethics Committee of Dr. Kariadi Central General Hospital (No. 16218/EC/KEPK-RSDK/2024).

The population were cancer patients with chemotherapy in the oncology installation, Dr. Kariadi Central General Hospital with the following inclusion criteria: 1) Patients aged at least 17 years, 2) Diagnosed with cancer. 3) Completed first cycle of ifosfamide treatment. The exclusion criteria were: 1) Patients were transfered to intensive care, 2) Patients died after first cycle of ifosfamide treatment.

The data were analyzed using SPSS® *version 24*. The Odds Ratio (OR) test was used to assess the risk factors associated with the incidence of IIE, as it is appropriate for case-control study designs.

RESULT AND DISCUSSION

A total of 48 patients who received ifosfamide between January and June 2024 were included. Of these, 19 were identified with ifosfamide-induced encephalopathy and 29 were not. The patient characteristics are depicted in Table 1. The patients were dominated by male with 62.5% and around 85.4% were under 65 years. Patients underwent chemotherapy after surgery (Adjuvant) about 70.8% and A total of 56.3% of patients had received other chemotherapy regimens prior to the initiation of ifosfamide, including doxorubicin, cisplatin, paclitaxel, and gemcitabine. Only 8.4% of patients experienced decreased of kidney function but 27% of patients had liver problem. Seven patients (14.6%) experienced hypoalbuminemia and 40% of patients did not receive vitamin before ifosfamide infusion. To evaluate risk factors associated with the development of encephalopathy, several pre-treatment characteristics were included in a univariate analysis.

Treatment-related characteristics are depicted in Table 2. To identify differences between patients who experienced IIE and those who did not. Among ifosfamide dose, previous other regimen, type of chemotherapy, and liver function were found to be significantly different ($p<0.05$). Kidney function, hypoalbuminemia, and vitamins were similar between the two groups. This study showed a dose of 5000 mg/m^2 had 2.5 risk and 8.3 odds higher to experienced of IIE compared to a dose of 1200 mg/m^2 (p=0.003; 95% CI; 2.1-32.3). A case control study by Kettle, et al. In 2010 there was no significant difference between ifosfamide doses of 2200 mg/m^2/day and 2800 mg/m^2/day in influencing of IIE (Kettle et al., 2010). Likewise, a study in Taiwan found no significant difference in cumulative doses and cycles in ifosfamide infusion (Lo et al., 2016). However, a study in Japan found that patients who received ifosfamide doses 2000 mg/m^2 above had 2.14 risk higher compared to doses less than 2000 mg/m2 (p=0.00045; 95% CI; 1.37-3.34) (Shimada et al., 2019).

The findings of this study align with the results reported by Ajino et al. (2010), who demonstrated that encephalopathy occurred predominantly at ifosfamide doses ≥5 g/m^2 and was more severe (grade 3) at doses ≥9 g/m^2. Our study similarly found a statistically significant association between a 5000 mg/m^2 dose of ifosfamide and the occurrence of

encephalopathy (p = 0.003; RR 2.5; OR 8.3), reinforcing the role of cumulative dose as a major risk factor.

Table 1. Patient characteristics

Patient characteristics	n	%	*P*
Gender			
Male	30	62.5	< 0.05
Female	18	37.5	
Age			
< 65 years	41	85.4	< 0.05
> 65 years	7	14.6	
IIE			
Yes	19	40	< 0.05
No	29	60	
Ifosfamide dose			
5000 mg/m^2	24	50	< 0.05
1200 mg/m^2	24	50	
Chemotherapy history			
Yes	27	56.3	< 0.05
No	21	43.7	
Type of chemotherapy			
Adjuvant	34	70.8	< 0.05
Neo-adjuvant	14	29.2	
Liver function			
Decreased	4	8.4	< 0.05
Normal	44	91.6	
Kidney function			
Decreased	13	27	> 0.05
Normal	35	73	
Hypoalbuminemia			
Yes	7	14.6	> 0.05
No	41	85.4	
Vitamins			
No	19	40	> 0.05
Yes	29	60	

Moreover, Shimada et al. (2019) emphasized the role of ifosfamide metabolites—such as chloroacetaldehyde—in neurotoxicity. This supports our findings that liver dysfunction, which may impair metabolite clearance, was significantly associated with encephalopathy (p = 0.02; OR 7.4; CI= 1.3-41.2). This is consistent with previous observations that impaired hepatic metabolism may exacerbate neurotoxic effects.

Unlike some studies which reported hypoalbuminemia as a strong predictor of ifosfamide neurotoxicity (due to increased free drug concentration), our results did not reach statistical significance (p = 0.097), although a trend was noted (RR 3.8). This discrepancy may be due to our limited sample size or differences in patient population characteristics.

Finally, no significant association was observed in our study between kidney function or vitamin supplementation and encephalopathy, which is in line with certain reports, though other studies suggest a protective role of thiamine and methylene blue against

neurotoxicity—highlighting the need for further controlled investigations. Therefore, drug monitoring was very important to detect early sign and symtomps of encephalopathy.

Tabel 2. Treatment-related characteristics

Encephalopathy	Yes	No	Sig. *(p-value)*	*RR; OR; CI*
Ifosfamide Dose				
5000 mg/m^2	15	9	0.003	2.5 ; 8.3 ; 2.1-32.3
1200 mg/m^2	4	20		
Chemotherapy history				
No	15	7	0.002	0.3 ; 8.8 ; 2.3-33.2
Yes	4	22		
Type of chemotherapy				
Neo-adjuvant	9	25	0.01	0.5 ; 0.14 ; 0.03-0.5
Adjuvant	10	4		
Liver function				
Decreased	4	1	0.02	6.1 ; 7.4 ; 0.8-72.9
Normal	15	28		
Kidney function				
Decreased	6	7	0.814	1.3 ; 1.45 ; 0.4-5.2
Normal	13	22		
Hypoalbuminemia				
Yes	5	2	0.097	3.8 ; 4.82 ; 0.8-28.1
No	14	27		
Vitamins				
No	9	10	0.555	1.3 ; 1.7 ; 0.5-5.5
Yes	10	19		

Sig: significant; RR: Relative risk; OR: Odds ratio

Patients who are undergoing ifosfamide infusion for the first time without previous regimens had 0.3 risk and 8.8 odds compared to patients who have undergone other chemotherapy regimens before ifosfamide. In accordance with previous studies, patients have cisplatin before ifosfamide can increase the incidence of IIE (Szabatura et al., 2014). The mechanism causing this incident is related to damage of renal tubulus due to cisplatin, resulting in impaired elimination of ifosfamide from the patient. Neo-adjuvant chemotherapy had 0.5 risk and 0.14 odds compared tp adjuvant. Patients with decreased liver function shown 6.1 risk and 7.4 odds compared to normal condition to increasing the incidence of IIE. Previous studies have reported that decreased the kidney function is a risk factor for IIE (Kettle et al., 2010) (Lo et al., 2016)(Szabatura et al., 2014).

The results of this study are consistent with prior research that identifies high-dose ifosfamide as a significant risk factor for encephalopathy. Ajino et al. (2010) reported that neurotoxicity was frequently observed at doses ≥5 g/m^2 and became more severe at ≥9 g/m^2. In alignment with this, our study demonstrated a significant association between ifosfamide 5000 mg/m^2 and encephalopathy (p = 0.003; OR 8.3).

Additionally, liver dysfunction was also significantly associated with encephalopathy in our study (p = 0.02; OR 7.4). This supports the findings of Shimada et al. (2019), who highlighted the role of hepatically generated toxic metabolites such as chloroacetaldehyde in ifosfamide-induced neurotoxicity.

In contrast, our results differ slightly from those of Szabatura et al. (2014), who found a statistically significant difference in serum creatinine between patients with and without encephalopathy. While our study observed a trend, kidney function did not show a significant association with encephalopathy (p = 0.814). Similarly, both studies agree that hypoalbuminemia was not statistically significant, although a trend toward increased risk was observed in our analysis (p = 0.097; OR 4.82).

The inconsistency across studies may be due to differences in patient populations, sample sizes, co-administered medications, or supportive treatments (e.g., hydration, vitamin supplementation).

CONCLUSION

This study provides information that the doses 5000 mg/m^2 of ifosfamide, first undergoing chemotherapy, type of neo-adjuvant chemotherapy, and decreased liver function are risk factors that influence the incidence of IIE. Meanwhile, decreased kidney function, hypoalbuminemia, and failure to provide vitamin prophylaxis are not influential factors.

ACKNOWLEDGMENT

The author may express gratitude to pharmacy installation, oncology installation, and the research team of Dr. Kariadi Central General Hospital who have provided a lot of assistance or funding during the research.

AUTHOR CONTRIBUTION

VR: Concepts or ideas; design; definition of intellectual content; literature search; experimental studies; data analysis; manuscript preparation.
SA: definition of intellectual content; literature search; experimental studies; data analysis.
EP: Manuscript editing; manuscript review.
FDA: Definition of intellectual content; literature search.
RG: Manuscript editing; manuscript review

ETHICS APPROVAL

The study had been approved by the ethics commission of Dr. Kariadi Central General Hospital, with the number of 16218/EC/KEPK-RSDK/2024.

REFERENCES

Ajino, T. A. T., Ikuchi, S. H. I. N. I. K., Amada, H. I. Y., Akeda, A. K. T., & Onno, S. H. I. N. I. K. (2010). *Ifosfamide encephalopathy associated with chemotherapy for musculoskeletal sarcomas : incidence , severity , and risk factors*. 104–111. https://doi.org/10.1007/s00776-009-1431-y

Brunello, A., Basso, U., Rossi, E., Stefani, M., Ghiotto, C., Marino, D., Crivellari, G., & Monfardini, S. (2007). Ifosfamide-related encephalopathy in elderly patients: Report of five cases and review of the literature. *Drugs and Aging*, *24*(11), 967–973. https://doi.org/10.2165/00002512-200724110-00008

Furui, Y., Komori, K., Kurata, T., & Sakashita, K. (2023). *Ifosfamide-Induced Encephalopathy Successfully Prevented by Methylene Blue : A Pediatric Case Report and Review of the Literature*.

15(6), 15–19. https://doi.org/10.7759/cureus.40213

Howell, J. E., Seung, A. H., Bcop, P., Nesbit, S. A., & Bcps, P. (2008). *Characterization of the occurrence of ifosfamide-induced neurotoxicity with concomitant aprepitant*. 157–162.

Kettle, J. K., Grauer, D., Folker, T. L., O'Neal, N., Henry, D. W., & Williams, C. B. (2010). Effectiveness of exogenous albumin administration for the prevention of ifosfamide-induced encephalopathy. *Pharmacotherapy*, *30*(8), 812–817. https://doi.org/10.1592/phco.30.8.812

Lo, Y., Shen, L. J., Chen, W. H., Dong, Y. H., & Wu, F. L. L. (2016). Risk factors of ifosfamide-related encephalopathy in adult patients with cancer: A retrospective analysis. *Journal of the Formosan Medical Association*, *115*(9), 744–751. https://doi.org/10.1016/j.jfma.2015.07.016

Menon, A., Enunwa, C. A., Read, W. L., & James, K. P. (2024). Rare Delayed Ifosfamide Encephalopathy: A Case Report of Chemotherapeutic Neurotoxicity. *Case Reports in Oncology*, 202–207. https://doi.org/10.1159/000535952

Res, S., Hamilton, J. E., Alexander, M., & Kelleher, F. C. (2020). Ifosfamide - induced encephalopathy : the EEG with frontal intermittent delta activity , and rapid resolution with methylene blue : A case report. *Clinical Sarcoma Research*, 1–4. https://doi.org/10.1186/s13569-020-00147-3

Richards, A., Marshall, H., & McQuary, A. (2011). Evaluation of methylene blue, thiamine, and/or albumin in the prevention of ifosfamide-related neurotoxicity. *Journal of Oncology Pharmacy Practice*, *17*(4), 372–380. https://doi.org/10.1177/1078155210385159

Shimada, K., Hasegawa, S., Nakao, S., Mukai, R., Matsumoto, K., Tanaka, M., Uranishi, H., Masuta, M., Nishida, S., Shimizu, S., Hayashi, Y., Suzuki, A., & Nakamura, M. (2019). Adverse event profiles of ifosfamide-induced encephalopathy analyzed using the Food and Drug Administration Adverse Event Reporting System and the Japanese Adverse Drug Event Report databases. *Cancer Chemotherapy and Pharmacology*, *84*(5), 1097–1105. https://doi.org/10.1007/s00280-019-03949-5

Szabatura, A. H., Cirrone, F., Harris, C., McDonnell, A. M., Feng, Y., Voit, D., Neuberg, D., Butrynski, J., & Fisher, D. C. (2014). An assessment of risk factors associated with ifosfamide-induced encephalopathy in a large academic cancer center. *Journal of Oncology Pharmacy Practice*, *21*(3), 188–193. https://doi.org/10.1177/1078155214527143

This page has been intentionally left blank.