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ORIGINAL ARTICLE

Risk factors of ifosfamide-related encephalopathy in adult patients with cancer: A retrospective analysis

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Background/Purpose: Ifosfamide, a widely used chemotherapeutic agent, has been frequently associated with encephalopathy. A larger-scale study was conducted to identify risk factors of ifosfamide-related encephalopathy, including hepatic function.
Methods: Adult patients who had completed at least one cycle of ifosfamide between January 2008 and December 2010 were included. Those with renal failure or liver failure were excluded. Data were collected through chart review. Patients with encephalopathy and patients without encephalopathy were compared on age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), baseline serum creatinine (S_{Cr}) level, albumin level, white blood cell count, liver function, brain metastasis, and dosage of ifosfamide. Chi-square test or Fisher's exact test, Student *t* test, and univariate and multivariate logistic regressions were used for analysis.
Results: This study enrolled 337 patients. Thirty-eight patients (11%) had ifosfamide-related encephalopathy. They had poorer ECOG PS; higher S_{Cr} level, white blood cell count, and aspartate aminotransferase level; and lower serum albumin level compared with patients without encephalopathy. Ifosfamide dosage, brain metastasis, and age were not significant risk factors. Multivariate analysis indicated that only ECOG PS, S_{Cr} level, and albumin level contributed significantly to the risk.
Conclusion: To date, this is the largest-scale study to have analyzed the risk factors of ifosfamide-related encephalopathy. This study confirms that an ECOG PS of 2–4 and increased S_{Cr} level are significant risk factors of ifosfamide-related encephalopathy, whereas increased

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albumin level decreases the risk, consistent with previous reports. Higher aspartate aminotransferase levels have no significant impact. In contrast to previous studies, ifosfamide dosage and brain metastasis are not significant contributing factors.

Introduction

Ifosfamide is a cytotoxic agent that is widely used in the treatment of a wide range of malignant diseases (including sarcomas, lymphomas, and gynecologic diseases) at various doses and frequencies of administration. Ifosfamide is an oxazaphosphorine that acts as an alkylating agent. Approximately 50—80% of intravenous ifosfamide is oxidized by hepatic enzymes into its active forms (4-hydroxyifosfamide and aldofosfamide) and into other inactive dechloroethylated and carboxy metabolites. Most metabolites are excreted by the kidneys, with dechloroethylated and carboxy metabolites accounting for 50% of the drug excreted in urine. Hemorrhagic cystitis is a common adverse effect of ifosfamide that is related to one of its metabolites, acrolein. It is prevented by administering mesna.[1,2] Cases of ifosfamide-related encephalopathy have often been observed in clinical practice; symptoms include neuropsychiatric conditions such as confusion, disorientation, somnolence, agitation, hallucinations, lethargy, and seizures.[3—6] Symptoms usually manifest within 48 hours of initiation, and recovery occurs within 48—72 hours after the withdrawal of ifosfamide. The reported incidence of ifosfamide-related encephalopathy varies from 10—15% to 40%.[5,7—10] Although the exact etiology of this condition is unknown, inactive metabolites of ifosfamide (including chloroacetaldehyde) may be involved.[1] Methylene blue, thiamine, and albumin have been studied as reversing agents for this condition.[11—13]

With the widespread use of ifosfamide in oncology, its toxicity may pose a challenge to the treatment of patients with cancer. Clinical practitioners are often unable to identify high-risk patients prior to treatment; unexpected development of neurologic symptoms may cause treatment delay, treatment discontinuation, and subsequent disruption of treatment plans. Although toxicity is reversible in most cases, severe long-term complications (including coma and death) have been reported.[7]

Previously proposed risk factors include history of cisplatin use, poor Eastern Cooperative Oncology Group (ECOG) performance status (PS), renal dysfunction, high cumulative dose,[5,10] history of brain metastasis, and hypoalbuminemia.[7] Living in an area where hepatitis B virus is endemic, we were interested in determining whether liver dysfunction plays a role. To investigate the impact of liver function on ifosfamide-related encephalopathy and to further clarify risk factors within our patient population, we collected cases of adult patients who were treated with ifosfamide in a medical center and analyzed the pretreatment characteristics of these cases retrospectively.

Methods

The protocol used in this study was approved (approval number 201308057RINC) by the Research Ethics Committee of National Taiwan University Hospital (NTUH). The requirement for informed consent was waived by the aforementioned committee. No funding in any form was necessary for this study.

Study population

We screened patients who were prescribed ifosfamide between January 2008 and December 2010 at the NTUH, a 2500-bed medical center with $>$ 160 ifosfamide-treated patients per year. This study included patients aged at least 20 years who initiated ifosfamide treatment at the NTUH between January 2008 and December 2010 and had completed at least one cycle of ifosfamide treatment. Patients whose treatment began at other sites or before January 2008, those with end-stage renal disease who were receiving renal replacement therapy, those with Child—Pugh Stage C liver cirrhosis, and those who had completed less than one cycle of ifosfamide treatment were excluded from our study.

Collection of data

Medical records were reviewed. The following data were collected for each patient: age, sex, diagnosis, concomitant cytotoxic agents, ifosfamide dose per square meter per day, ifosfamide dose per square meter per cycle, cumulative ifosfamide dose per square meter, cumulative ifosfamide dose per square meter at the onset of neurologic symptoms, presence or absence of brain metastasis, and presence or absence of ascites. ECOG PS, complete blood cell count, differential blood cell count, and levels of serum creatinine (S_{Cr}), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and serum albumin (determined at the initiation of ifosfamide treatment and at the onset of neurologic symptoms) were collected.

"Patients with ifosfamide-related encephalopathy" were defined as patients who were diagnosed as having this condition and patients who had any of the following neuropsychiatric symptoms that were attributed to ifosfamide upon occurrence: delirium, disorientation, change or disturbance in conscience, hallucinations, somnolence, confusion, seizure, poor response, dizziness, agitation, behavior or personality change, and involuntary movement.

Patients who were treated with ifosfamide during the same time period, were not diagnosed as having

encephalopathy, and were clear of any neuropsychiatric symptoms were included in the nonencephalopathy group. "No encephalopathy" was recorded if there were no recorded neurologic or psychiatric symptoms upon assessment of toxicity after ifosfamide treatment.

Data analysis

Descriptive analyses of patients included age, sex, diagnosis, mean dose per square meter per cycle, and mean cumulative dose per square meter. Patients in the encephalopathy group and patients in the nonencephalopathy group were compared on age, baseline ECOG PS (0/1 or 2–4), baseline creatinine level, baseline albumin level, baseline white blood cell (WBC) count, ifosfamide dose per square meter per day, ifosfamide dose per square meter per cycle, and cumulative dose per square meter. Chi-square test was used for categorical variables (Fisher's exact test was used for expected values < 5). Student t test was used for between-group comparisons of continuous variables. Daily ifosfamide doses were grouped into four levels: Level 1, < 2 g/m^2; Level 2, 2–2.5 g/m^2; Level 3, 2.6–3 g/m^2; Level 4, > 3 g/m^2. To compare the incidence of encephalopathy, we formed the following subgroups: ECOG PS (0/1 and 2–4), liver transaminase levels (AST or ALT $>$100 U/L and AST and ALT $\leq$100 U/L), total bilirubin level ($>$ 3 mg/dL or $\leq$3 mg/dL), and the aforementioned dose levels.

Univariate logistic regression was used to identify and assess potential risk factors. In addition, multivariate analysis was performed to determine independent risk factors; covariates that were significant on univariate regression were incorporated into multivariate analysis. All statistics were calculated using the statistical software SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). In our dataset, the estimated risk of encephalopathy among patients taking ifosfamide was 10%. Assuming an odds ratio of 2.0 and an R^2 of 0.5 for covariates, a study population of 337 patients would have a power of $\geq$ 80% at an α level of 0.05.

Results

Four hundred and eighty-eight patients were prescribed ifosfamide between January 1, 2008, and December 31, 2010. Among them, 151 were excluded for the following reasons: age ($n = 88$), previous ifosfamide therapy ($n = 51$), noncompletion of the first cycle for various reasons ($n = 7$), Child–Pugh Stage C liver cirrhosis at the start of therapy ($n = 3$), and cancellation (and thus nonadministration) of ifosfamide treatment ($n = 2$). Three hundred and thirty-seven patients met the criteria for analysis. Among these, 38 patients (11%) either were diagnosed as having ifosfamide-related encephalopathy or developed related neurologic symptoms. Compared with the nonencephalopathy group, the encephalopathy group had a higher proportion of patients with higher ECOG PS (2–4), mean creatinine level, WBC count, and AST level, but lower mean albumin level (Table 1).

The proportion of patients with encephalopathy in the subgroups specified previously is presented in Table 2. The rate of encephalopathy was significantly higher in patients with poorer ECOG PS (2–4) and in patients with total bilirubin levels $>$ 3 mg/dL. The rate of encephalopathy was not significantly different among the groups given different doses, between patients with brain metastasis and patients without brain metastasis, or between patients with AST and ALT levels of $\leq$ 100 U/L and patients with AST or ALT levels $>$ 100 U/L.

Univariate logistic regression was applied to significant variables, including ECOG PS (0/1 or 2–4), total bilirubin level ($\leq$ 3 mg/dL or $>$3 mg/dL), albumin level, S_{Cr} level, AST level, and WBC count. Poor ECOG PS, a total bilirubin level $>$ 3 mg/dL, and increased AST level, S_{Cr} level, and WBC count increase the odds of ifosfamide-related encephalopathy, whereas an increase in albumin level decreases the odds of adverse events. Multivariate analysis showed that only ECOG PS, S_{Cr} level, and albumin level are significant independent covariates (Table 3).

After other covariates had been controlled for, a patient with an ECOG PS of 2–4 had 5.15 times as much risk of developing encephalopathy as a patient with an ECOG PS of 0/1. A 1-mg/dL increase in S_{Cr} level increases this risk to 15.42 times, whereas a 1-g/dL increase in serum albumin decreases the chance of encephalopathy by 67% (odds ratio, 0.33).

Patients with ifosfamide-related encephalopathy and their characteristics are listed in Table 4. Encephalopathy occurred after the first cycle of treatment in 20 of 38 cases. In these patients, baseline data and data at the onset of symptoms were virtually the same; as a result, nearly all comparisons between pretreatment and symptom onset were not significantly different on various statistical tests performed. As a group, only S_{Cr} level was significantly higher at the onset of symptoms than at baseline (1.23 vs. 1.18, $p = 0.037$, paired t test). Five patients experienced worsening ECOG PS; however, after they were stratified by ECOG PS (0/1 or 2–4; as with baseline data), this was no longer statistically significant ($p = 0.25$, McNemar test for related samples). Hence, only baseline data were utilized in our analysis.

Discussion

To date, this is the largest-scale study to have analyzed the risk factors involved in ifosfamide-related encephalopathy. Most previous studies were small-scale observations (with sample size ranging from 61 patients to 237 patients) and usually evaluated each risk factor individually.[5,7–9] A study by Tajino et al[5] recruited 61 patients (17 cases and 44 controls) who received cisplatin and high-dose ifosfamide ($>$ 5 g/m^2) and identified use of cisplatin and a dose $>$ 9 g/m^2 per cycle as risk factors. They did not include patients with S_{Cr} levels $>$ 1.5 mg/dL or patients with serum albumin levels $<$ 3.5 g/dL; thus, they could not evaluate these as possible risk factors. Sweiss et al[7] enrolled only 19 patients (8 cases and 11 controls) who received high-dose (6–25 g/m^2 per cycle) ifosfamide and indicated female sex, low total bilirubin level, low albumin level, low hemoglobin level, and obesity as risk factors. A study by Reiger et al[8] enrolled only 60 patients (16 cases and 44 controls) and did not

Table 1 Patient characteristics.

	With encephalopathy (n = 38)	Without encephalopathy (n = 299)	All patients (N = 337)	p
Age (y)	52.8 ± 12.8	48.8 ± 13.1	49.2 ± 13.1	0.071
Sex				
Female	16 (42.1)	124 (41.5)	140 (41.5)	0.940
Male	22 (57.9)	175 (58.5)	197 (58.5)	
ECOG PS				
0/1	16 (42.1)	243 (81.3)	259 (76.9)	<0.001[a]
2–4	22 (58.9)	56 (18.7)	78 (23.1)	
Concurrent cisplatin	1 (2.63)	25 (8.36)	26 (7.72)	0.335
Daily dose (mg/m^2)	2347.4 ± 729.1	2329.0 ± 1073.1	2331.1 ± 1039.2	0.891
Dose per cycle (mg/m^2)	5544.7 ± 1595.3	5603.4 ± 1949.4	5596.8 ± 1910.8	0.859
Cumulative dose (g/m^2)	19.02 ± 34.02	21.70 ± 23.55	21.39 ± 24.90	0.533
Laboratory data				
WBC count (×1000 cells/mm^3)	12.4 ± 9.36	8.70 ± 7.98	9.12 ± 8.21	0.026[b]
Platelets (×1000 cells/mm^3)	256.9 ± 147.1	278.7 ± 129.0	276.2 ± 131.1	0.335
S_{Cr} (mg/dL)	1.18 ± 0.52	0.92 ± 0.24	0.94 ± 0.30	0.004[b]
AST (U/L)	43.2 ± 34.7	33.1 ± 27.6	34.2 ± 28.6	0.039[b]
ALT (U/L)	39.1 ± 34.6	33.1 ± 38.1	33.7 ± 37.1	0.353
Total bilirubin (mg/dL)	1.49 ± 2.85	0.67 ± 0.63	0.76 ± 1.15	0.091
Albumin (g/dL)	3.72 ± 0.77	4.18 ± 0.50	4.14 ± 0.54	0.002[b]

Data are presented as mean ± SD or n (%).
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECOG = Easter Cooperative Oncology Group; PS = performance status; S_{Cr}, serum creatinine; WBC, white blood cell.
[a] Statistically significant on Chi-square test. P values <0.05 are considered to be statistically significant.
[b] Statistically significant on Student t test. P values <0.05 are considered to be statistically significant.

identify any risk factor. A study by David and Picus[9] recruited 237 patients (38 cases and 199 controls) and identified low albumin level and high S_{Cr} level as risk factors. In contrast to previous studies, we simultaneously assessed the effects of various risk factors on the multivariate logistic regression model. Because of the high prevalence of hepatitis B virus carrier status in Taiwan (estimated to be 15–20%, with a lower prevalence in young adults and children),[14,15] the initial aim of the study was to explore whether hepatic abnormality is a risk factor of ifosfamide-related encephalopathy. Although we found that hepatic abnormality was not a risk factor, we confirmed the involvement of other factors. The occurrence rate of encephalopathy among our study participants who initiated ifosfamide treatment within the study period was 11%. The factors contributing most to the risk of ifosfamide-related encephalopathy include poor PS and an increase in S_{Cr} level, whereas an increase in serum albumin level decreases the risk, consistent with previous reports.[7,9]

In contrast to the research conducted by Tajino et al,[5] which indicated that ifosfamide dosage may predispose patients to a higher risk of encephalopathy, our study showed that dose, dose level, and cumulative dose were not significant contributing factors because both groups of patients received similar dosages and cumulative doses. It is possible that some physicians tended to prescribe relatively lower doses to patients who appeared weaker; hence, we were unable to determine whether patients with encephalopathy received higher doses. It is also possible that ifosfamide treatment was discontinued prematurely among patients with encephalopathy, which could have resulted in lower cumulative doses for patients with encephalopathy; however, several patients developed encephalopathy late in their treatment course with very high cumulative doses, resulting in a mean cumulative dose similar to that in patients who did not develop encephalopathy.

Similarly, age was not a significant contributor; it remains unknown whether the exclusion of patients younger than 20 years affected the results. In addition, the incidence of encephalopathy among patients with brain metastasis was not higher than that among patients without brain metastasis, as physicians may attribute the development of neuropsychiatric symptoms in these patients to brain metastasis rather than to ifosfamide treatment. Other pre-existing neurologic deficits or diseases that may have confounded our results were not assessed in this study.

Total bilirubin level was used as a variable because a previous review recommended adjusting ifosfamide dosage when the total bilirubin level was > 3 mg/dL, and we were interested in determining the impact of the total bilirubin level on the risk of encephalopathy.[16] However, after controlling for other covariates, we found that it was not an independently significant contributor.

Additional factors reported previously were not assessed in this study. The influence of previous cisplatin use was not assessed because some patients did not receive chemotherapy in our hospital but may have been treated elsewhere; thus, their information was irretrievable. For similar reasons, we excluded patients who had

Table 2 Risk of encephalopathy for different groups.

Subgroups	*n*	Encephalopathy group, *n* (%)	Odds ratio (95% CI)	*p*
ECOG PS				
0/1	259	16 (6.2)	Ref	<0.001[a]
2–4	78	22 (28.2)	5.97 (2.94–12.1)	
Daily dose				
Level 1 (<2 g/m^2)	101	7 (6.9)	NA	0.150
Level 2 (2–2.5 g/m^2)	118	17 (14.4)		
Level 3 (2.6–3 g/m^2)	91	13 (14.3)		
Level 4 (>3 g/m^2)	27	1 (3.7)		
Brain metastasis				
Yes	30	4 (13.3)	1.24 (0.41–3.75)	0.761
No	307	34 (11.1)		
Liver transaminases				
AST & ALT ≤100 U/L	315	34 (10.8)	Ref	0.292
AST or ALT >100 U/L	22	4 (18.2)	1.84 (0.59–5.75)	
Total bilirubin				
≤3 mg/dL	329	34 (10.3)	Ref	0.007[a]
>3 mg/dL	8	4 (50.0)	8.68 (2.08–36.28)	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; NA = not available; PS = performance status; Ref = reference.
[a] Statistically significant.

received ifosfamide treatment before the study period. Similarly, electrolyte imbalance, which was reported in earlier studies, was not assessed because of incomplete records and large amounts of missing data. Furthermore, we did not include patients younger than 20 years because of local regulations and differences in the assessment of pediatric patients.

We are aware that S_{Cr} level may not be an accurate indicator of renal function. Because most of our study participants did not perform a 24-hour urine collection, creatinine clearance had to be retrospectively estimated, which proved difficult because of inconsistent weight records. We decided to use S_{Cr} level as a variable because it was measured and was more reliable.

Concurrent medications may confound the results of this study. Concomitant opioids have been reported as a significant risk factor.[10] We assessed the impact of concomitant cisplatin, which did not contribute significantly probably because only a few patients received cisplatin with ifosfamide. Noncytotoxic medications that may contribute to neuropsychiatric symptoms were not assessed because of difficulty retrieving complete information. Future studies could be designed to include assessment of concurrent medications that affect the central nervous system.

The retrospective nature of this study has certain limitations. First, as information was limited to medical records, we could not assess the severity of each encephalopathy case with formal grading terminology. Second, records, descriptions of symptoms, and terminologies may have differed among physicians, which may have contributed to inconsistent information on neurologic symptoms and wide confidence intervals of relative risk. However, the significant risk factors identified in our study were generally consistent with previous reports,[5,7–9] which indicated the potentially important roles of these factors. Further prospective studies with predefined criteria are necessary to precisely quantify the association of ifosfamide-related encephalopathy with individual risk factors. Third, baseline data may not have been obtained immediately before treatment and may have been influenced by the previous cycle of chemotherapy, leading to erroneous assessment of organ functions.

In addition to the risk factors reported here, other factors should be assessed in future studies. Metabolism of

Table 3 Logistic regression of risk factors of encephalopathy.

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)
ECOG PS group		
0/1	Ref	Ref
2–4	5.97 (2.94–12.10)	5.15 (2.35–11.28)
S_{Cr} (1 mg/dL increase)	11.31 (3.67–34.88)	15.42 (4.36–54.59)
Albumin (1 g/dL increase)	0.31 (0.18–0.54)	0.33 (0.17–0.65)
AST (1 U/L increase)	1.01 (1.00–1.02)	1.00 (0.99–1.02)
WBC count (×1000 cells/mm^3 increase)	1.04 (1.01–1.07)	1.02 (0.98–1.06)
Total bilirubin		
≤3 mg/dL	Ref	Ref
>3 mg/dL	8.68 (2.08–36.28)	3.82 (0.5–29.17)

AST = aspartate aminotransferase; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; OR = odds ratio; PS = performance status; Ref = reference; S_{Cr} = serum creatinine; WBC = white blood cell.

Table 4 Characteristics of patients with encephalopathy.

Case	Age (y)	Sex	Diagnosis	Concurrent chemotherapy	Brain metastasis	Baseline ECOG PS	ECOG PS at onset	Daily dose (g/m^2)	Cumulative dose (g/m^2)	Symptoms	Number of episodes
1	80	F	Soft-tissue sarcoma	Doxorubicin	N	0	1	2.5	30.0	Delirium	1
2	75	M	Head & neck cancer	Etoposide	N	2	3	2	28.0	Restlessness	1
3	72	F	Head & neck cancer	Etoposide	N	0	0	2	4.0	Seizure	1
4	70	M	Renal cell carcinoma	Etoposide	N	3	3	2	4.0	Change in consciousness	1
5	66	F	Lung cancer	Etoposide	N	2	2	3	18.0	Change in consciousness	1
6	65	F	Uterine sarcoma	Epirubicin	N	1	1	5	5.0	Poor response	1
7	64	M	Lung cancer	Etoposide	N	2	2	3	6.0	Delirium	1
8	64	M	Head & neck cancer	Etoposide	N	2	2	2	32.0	Involuntary movement, dizziness	3
9	63	F	Ovarian cancer	Paclitaxel	Y	2	2	1.5	4.5	Change in consciousness	1
10	61	M	Head & neck cancer	Etoposide	N	1	2	3	12.0	Disorientation	1
11	60	F	Breast cancer	Etoposide	N	1	1	3	12.0	Hallucination	1
12	58	M	Head & neck cancer	Etoposide	N	1	1	2	4.0	Disorientation	1
13	58	M	Pancreatic cancer	Etoposide	N	1	1	2	6.0	Delirium	1
14	57	F	Uterine sarcoma	Etoposide	N	2	2	3	51.0	Delirium	1
15	57	M	Head & neck cancer	Etoposide	N	1	1	1.9	3.8	Change in consciousness	1
16	55	F	Endometrial cancer	Etoposide	Y	2	2	2	4.0	Change in consciousness	1
17	54	F	Head & neck cancer	Etoposide	N	2	2	2	4.0	Disorientation	1
18	54	M	Gastric cancer	Etoposide	N	3	3	3	6.0	Delirium	1
19	52	F	Unknown primary	Etoposide	N	1	1	2	4.0	Change in consciousness	1
20	51	F	Unknown primary	Epirubicin	N	2	2	1.65	5.0	Seizure	1
21	51	F	Head & neck cancer	Etoposide	N	2	2	2	14.0	Confusion	2
22	50	M	Lymphoma	Etoposide	Y	4	4	1.5	4.5	Change in consciousness	1
23	48	M	Head & neck cancer	Etoposide	N	0	2	3	18.0	Disorientation	1
24	48	M	Head & neck cancer	Etoposide	N	2	2	3	9.0	Hallucination	1
25	48	F	Head & neck cancer	Etoposide	N	1	1	2	24.0	Somnolence	1
26	47	F	Uterine cervical cancer	Etoposide	N	2	2	1.65	8.9	Disorientation	1
27	46	M	Head & neck cancer	Etoposide	N	0	0	3	16.0	Agitation	1
28	46	F	Breast cancer	Etoposide	N	3	3	2	6.0	Poor response	1
29	45	M	Head & neck cancer	Etoposide	N	2	2	2	4.0	Change in consciousness	1
30	45	M	Adrenal cancer	Doxorubicin	N	1	1	2	18.0	Hallucination, involuntary movement	1

(*continued on next page*)

Table 4 (*continued*)

Case	Age (y)	Sex	Diagnosis	Concurrent chemotherapy	Brain metastasis	Baseline ECOG PS	ECOG PS at onset	Daily dose (g/m^2)	Cumulative dose (g/m^2)	Symptoms	Number of episodes
31	43	M	Head & neck cancer	Etoposide	N	1	1	2	4.0	Change in consciousness	1
32	42	F	Head & neck cancer	Etoposide	N	3	3	3	6.0	Delirium	1
33	42	M	Osteosarcoma	Etoposide	N	1	2	3	204.0	Poor response, dizziness	2
34	38	M	Soft-tissue sarcoma	Dacarbazine, docetaxel	N	3	3	1.5	10.3	Behavior change	1
35	32	M	Germ cell tumor	Etoposide, cisplatin	Y	4	4	1	20.0	Hallucination	1
36	31	M	Lymphoma	Gemcitabine, vinorelbine	N	1	1	2	32.0	Change in consciousness	2
37	30	M	Head & neck cancer	Etoposide	N	2	2	3	72.0	Hallucination	1
38	23	M	Soft-tissue sarcoma	Etoposide	N	4	4	3	9.0	Dizziness	1

ECOG = Eastern Cooperative Oncology Group; F = female; M = male; N = no; PS = performance status; Y = yes.

ifosfamide mainly involves CYP3A enzymes and possibly CYP2B enzymes; therefore, clinically significant drug interactions may be possible. Although the importance of potential drug interactions was not assessed in this study, concomitant use of enzyme inducers, substrates, or inhibitors may be clinically relevant. The contribution of CYP 2B6 inhibitors to the risk of ifosfamide-related encephalopathy has already been reported.[10] There have been recent reports of ifosfamide-related central nervous toxicity linked to the use of aprepitant, a widely used antiemetic and CYP3A4 inhibitor.[17–20] An earlier analysis concluded that concomitant use of aprepitant increased the risk of ifosfamide-related encephalopathy, although the increase was not statistically significant.[21] This does not rule out the possibility of other enzyme inhibitors precipitating ifosfamide-related toxicity, which warrants further studies.

In summary, the incidence of ifosfamide-related encephalopathy in our medical center was 11%. Poor PS (ECOG PS of 2–4) and increase in S_{Cr} level are significant risk factors contributing to this condition, whereas higher albumin level significantly decreases the risk.

References

1. Lokiec F. Ifosfamide: pharmacokinetic properties for central nervous system metastasis prevention. *Ann Oncol* 2006; **17**(Suppl. 4):iv33–6.
2. Misiura K. Ifosfamide. Metabolic studies, new therapeutic approaches and new analogs. *Mini Rev Med Chem* 2006;**6**: 395–400.
3. Verstappen CCP, Heimans JJ, Hoekman K, Postma TJ. Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. *Drugs* 2003;**63**: 1549–63.
4. Savica R, Rabinstein AA, Josephs KA. Ifosfamide associated myoclonus–encephalopathy syndrome. *J Neurol* 2011;**258**: 1729–31.
5. Tajino T, Kikuchi S, Yamada H, Takeda A, Konno S. Ifosfamide encephalopathy associated with chemotherapy for musculoskeletal sarcomas: incidence, severity and risk factors. *J Orthop Sci* 2010;**15**:104–11.
6. Janeway KA, Grier HE. Sequelae of osteosarcoma medical therapy: a review of rare acute toxicities and late effects. *Lancet Oncol* 2010;**11**:670–8.
7. Sweiss KI, Beri R, Shord SS. Encephalopathy after high-dose ifosfamide: a retrospective cohort study and review of the literature. *Drug Saf* 2008;**31**:989–96.
8. Reiger C, Fiegl M, Tischer J, Ostermann H, Schiel X. Incidence and severity of ifosfamide-induced encephalopathy. *Anticancer Drugs* 2004;**15**:347–50.
9. David KA, Picus J. Evaluating risk factors for the development of ifosfamide encephalopathy. *Am J Clin Oncol* 2005;**28**: 277–80.
10. Szabatura AH, Cirrone F, Harris C, McDonnell AM, Feng Y, Voit D, et al. An assessment of risk factors associated with ifosfamide-induced encephalopathy in a large academic cancer center. *J Oncol Pharm Pract* 2015;**21**:188–93.
11. Richards A, Marshall H, McQuary A. Evaluation of methylene blue, thiamine, and/or albumin in the prevention of ifosfamide-related neurotoxicity. *J Oncol Pharm Pract* 2011; **17**:372–80.
12. Pelgrims J, De Vos F, Van den Brande J, Schrijvers D, Prové A, Vermorken JB. 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—4.
13. Lombardi G, Zustovich F, Nicoletto MO, Donach M, Pastorelli D. Important role of thiamine in preventing ifosfamide-induced encephalopathy. *J Oncol Pharm Pract* 2010;**16**:135—6.
14. Wait S, Chen DS. Towards the eradication of hepatitis B in Taiwan. *Kaohsiung J Med Sci* 2012;**28**:1—9.
15. Chen SM, Kung CM, Yang WJ, Wang HL. Efficacy of the nationwide hepatitis B infant vaccination program in Taiwan. *J Clin Virol* 2011;**52**:11—6.
16. Floyd J, Mirza I, Sachs B, Perry MC. Hepatotoxicity of chemotherapy. *Semin Oncol* 2006;**33**:50—67.
17. Durand JP, Gourmel B, Mir O, Goldwasser F. Antiemetic neurokinin-1 antagonist aprepitant and ifosfamide-induced encephalopathy. *Ann Oncol* 2007;**18**:808—9.
18. Jarkowsky A. Possible contribution of aprepitant to ifosfamide-induced neurotoxicity. *Am J Health Syst Pharm* 2008;**65**:2229—31.
19. Shin YJ, Kim JY, Moon JW, You RM, Park JY, Nam JH. Fatal ifosfamide-induced metabolic encephalopathy in patients with recurrent epithelial ovarian cancer: report of two cases. *Cancer Res Treat* 2011;**43**:260—3.
20. Shindorf ML, Manahan KJ, Geisler JP. The interaction of ifosfamide and aprepitant in gynecologic malignancies. *Gynecol Oncol Case Rep* 2013;**6**:34—5.
21. Howell JE, Szabatura AH, Hatfield Seung A, Nesbit SA. Characterization of the occurrence of ifosfamide-induced neurotoxicity with concomitant aprepitant. *J Oncol Pharm Pract* 2008;**14**:157—62.