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ORIGINAL ARTICLE

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

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Abstract

Purpose Ifosfamide is extensively used to treat several malignant conditions. Administration of ifosfamide can cause encephalopathy and other neurotoxic effects. The aim of this study was to obtain novel information on the onset profiles of ifosfamide-induced encephalopathy (IIE) considering other associated clinical factors using the US Food and Drug Administration Adverse Event Reporting System (FAERS) and the Japanese Adverse Drug Event Report (JADER) databases.

Methods We analyzed the reports of encephalopathy between 2004 and 2018 from the FAERS and JADER databases. To define IIE, we used the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and standardized queries. The reporting odds ratios (ROR) at 95% confidence interval (CI) was used to detect the signal for IIE and adjusted for covariates using a multivariate logistic regression technique. We evaluated the time-to-onset profile of IIE and used the association rule mining technique to discover undetected associations, such as potential risk factors.

Results In the FAERS database, the ROR (CI) for encephalopathy (preferred term, PT) and encephalopathy (standardized MedDRA queries, SMQ) was 56.58 (51.69–61.93) and 1.57 (1.48–1.67), respectively. In the JADER database, the ROR (95% CI) for encephalopathy (PT) and encephalopathy (SMQ) was 13.54 (9.91–18.50) and 1.24 (1.01–1.53), respectively. The multivariate logistic regression analysis showed a significant contribution in IIE signal in the ≥ 60 year group ($p = 0.00094$; vs. < 60 year group) and ≥ 2000 mg/m^2 dosage group ($p = 0.00045$; vs. < 2000 mg/m^2 dosage group). The association rules of {ifosfamide, aprepitant} → {encephalopathy (SMQ)} demonstrated high lift values. The average dose of ifosfamide in patients with encephalopathy (PT) and without encephalopathy (PT) was 2022.8 ± 592.8 (mean ± standard deviation) and 1568.5 ± 703.2 mg/m^2, respectively ($p < 0.05$). Encephalopathy within the first 7 days of ifosfamide administration was 94.1% for encephalopathy (PT) and 87.7% for encephalopathy (SMQ), respectively.

Conclusions The present analysis demonstrated that the incidence of encephalopathy with ifosfamide should be closely monitored for a short onset (within 7 days). The patients who are administered a high dose of ifosfamide or co-administrated aprepitant should be carefully monitored for the development of encephalopathy.

Keywords Ifosfamide · Encephalopathy · FDA Adverse Event Reporting System · Japanese Adverse Drug Event Report · FAERS · JADER

Introduction

Ifosfamide is extensively used to treat several malignancies [1]. Administration of ifosfamide can cause encephalopathy and other neurotoxic effects [2]. It has been proposed that chloroacetaldehyde produced from ifosfamide may cause encephalopathy, although its mechanism has not been

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elucidated [3]. The known risk factors of ifosfamide-induced encephalopathy (IIE) are as follows: poor performance status (PS), serum creatinine level, albumin level, hemoglobin level, 4 or 5 successive days of ifosfamide administration, and leptomeningeal metastasis [4–7]. It has been reported that ifosfamide-induced neurotoxicity occurs within a few hours to few days after the first administration of ifosfamide, and in most cases, it resolves within 48–72 h of discontinuation of the drug. However, it may persist for a longer period [8]. The detailed time-to-onset profiles of IIE are not clear in clinical settings.

The US Food and Drug Administration (FDA) has developed the FDA adverse event reporting system (FAERS) that is the best-known spontaneous reporting system (SRS) in the world. The Pharmaceuticals and Medical Devices Agency (PMDA), a regulatory authority in Japan, has released the Japanese Adverse Drug Event Report (JADER) database.

The aim of this study was to assess IIE by analyzing data from the SRS databases. In pharmacovigilance analysis, data mining algorithms have been developed to identify drug-associated adverse events (AEs) as signals using reporting odds ratio (ROR). We evaluated the possible relationship among reporting year, sex, age, and dosage of ifosfamide for IIE using adjusted RORs and a multivariate logistic regression technique. We obtained novel information on the time-to-onset profiles of IIE in the JADER database. Furthermore, association rule mining has been proposed as a new analytical method to identify undetected relationships such as possible risk factors between variables in the SRS databases [9, 10]. We applied the association rule mining technique to detect association rules between IIE and several clinical factors.

Materials and methods

The SRS such as FAERS and the JADER are publicly available and can be downloaded from the FDA website (www.fda.gov) and the PMDA website (www.pmda.go.jp), respectively. All data from the SRS database were fully anonymized by the regulatory authorities before use in the present analysis. We assessed the incidence of "encephalopathy" in the FAERS database from January 2004 to September 2018 and the JADER database from April 2004 to June 2018. We followed the FDA recommendations for excluding duplicate reports of patients and used the most recent case numbers to identify and exclude such records from the analyses [11].

The AEs in this study relied on the definition provided in the Medical Dictionary for Regulatory Activities (MedDRA)/Japanese (MedDRA/J, www.pmrj.jp/jmo/php/indexj.php) version 19.0. The standardized MedDRA Queries (SMQs) index consists of groupings of MedDRA terms ordinarily at the preferred term (PT) level that relates to a defined medical condition or area of interest. To evaluate the effects of ifosfamide on encephalopathy, we used encephalopathy (PT) (defined by PT code: 10014625) and SMQ for noninfectious encephalopathy/delirium (defined by SMQ code: 20000133, including 350 PTs).

We investigated the dose-dependency of ifosfamide using the JADER database. We estimated the daily ifosfamide dosage per square meter (mg/m^2) according to the amount of drug administered daily, body weight, and height against each case in the JADER database. Receiver-operating characteristic (ROC) curves are used in medicine to determine cutoff values for a clinical test. We applied the ROC curves to determine the cutoff of dosage of ifosfamide for encephalopathy (PT) and encephalopathy (SMQ). The area under an ROC curve (AUC) is a common measure of accuracy of a diagnostic test; however, it does not specify the "optimal" cutoff value directly. Youden index is often used to determine the optimal cutoff value (optimal decision threshold). The formula for Youden index is as follows: Youden index = sensitivity + specificity − 1. Higher values of Youden index are better than lower values [12]. Furthermore, we compared the dosage of ifosfamide between patients with and without encephalopathy using Student *t* test.

To detect the AE signal, we calculated the ROR, which is established for pharmacovigilance using a disproportionality analysis [13]. Signals are considered significant when the ROR estimates and the lower limits of the corresponding 95% confidence interval (CI) are > 1.

Using the ROR allowed adjustments using a multivariate logistic regression analysis and offered the advantage of controlling covariates [14]. To calculate the adjusted ROR, only reports with complete information of reporting year, sex, age, and ifosfamide dosage were extracted from the JADER database. To construct the multivariate logistic model, the following formula was used for analysis:

$$\text{Log (odds)} = \beta_0 + \beta_1 Y + \beta_2 S + \beta_3 A + \beta_4 D,$$

where, Y is the reporting year (2004–2008, 2009–2013, and 2014–2018), S is the sex, A is the age-stratified group (< 60 and ≥ 60 years), and D is the dosage-stratified group (< 2000 and ≥ 2000 mg/m^2). To comparatively evaluate the effect of variables, we selected explanatory variables using a stepwise method [15, 16] at a significance level of 0.05 (forward and backward). The contribution of selected variables in the final model was evaluated. The ROR was adjusted using the multivariate logistic regression model. A likelihood ratio test was used to evaluate the effects of explanatory variables.

Association rule mining is focused on finding frequent co-occurring associations among a collection of items. Given a set of transactions T (each transaction is a set of items), an association rule can be expressed as X [lhs: left-hand-side, the antecedent of the rule] → Y [rhs:

right-hand-side, the consequent of the rule]; where, X and Y are mutually exclusive sets of items [17]. Support, confidence, and lift were used as indicators to evaluate the association rule. The support of the rule is defined as the percentage of transactions in T that contains both X and Y [18]. The support was measured using the following formula:

$$\text{Support} = P(X \cap Y) = \{X \cap Y\}/\{D\},$$

where, D is the total number of transactions in the database. The confidence of the association rule is the ratio of the support of the itemset $X \cap Y$ to the support of the itemset X, which roughly corresponds to the conditional probability $P(Y|X)$ [18]. Because the confidence is an indicator of accuracy of related rules, an association rule with high confidence is critical. The formula for calculating confidence is as follows:

$$\text{Confidence} = P(X \cap Y)/P(X).$$

Lift is the ratio between the confidence of the rule and support of the itemset in the consequent of the rule. It is calculated as follows:

$$\text{Lift} = P(X \cap Y)/P(X)\,P(Y).$$

The lift evaluates the independence of X and Y, suggesting that the greater the lift value, the stronger the relationship. If X and Y are independent, the lift is 1. If X and Y are positively or negatively correlated, the lift is > 1 or < 1, respectively.

The association rule mining was performed using the apriori function of the arules library in the arules package of R software (version 3.3.3). The parameter of maxlen (maximum length of itemset/rule: a parameter in the arules package) is the maximum size of mined frequent itemsets. To extract association rules efficiently, the thresholds of the optimized support, confidence, and maxlen are defined depending on factors such as the size of data, number of items, and purpose of research. In this study, we defined the minimum support and confidence thresholds as 0.00001 and 0.001, respectively, and maxlen was restricted to 3.

Time-to-onset from the JADER database was calculated from the beginning of the time of a subject's first prescription to the occurrence of AEs. We excluded reports that did not have complete information on AE occurrence and prescription initiation time. It was necessary to consider the right truncation when evaluating the time of onset of AEs. We selected an analysis period of 180 days after the initiation of drug administration. The median, quartiles, and Weibull shape parameter (WSP) were utilized while evaluating the time-to-onset data [19, 20]. The shape parameter β of Weibull distribution indicated that the hazard was without a reference population. When β was equal to 1, the hazard was estimated to be constant over time and if β was > 1 and the 95% CI of β excluded the value 1, the hazard was considered to increase over time [19, 20].

Results

The FAERS database contained 11,527,468 reports. After excluding the duplicates according to the FDA recommendation, 9,702,166 reports were analyzed, of which 6.3% (523/8344 cases) and 14.7% (1226/8344 cases) AE cases related to ifosfamide corresponded to encephalopathy (PT) and encephalopathy (SMQ), respectively (Table 1). The ROR (95% CI) for encephalopathy (PT) and encephalopathy (SMQ) was 56.58 (51.69–61.93) and 1.57 (1.48–1.67), respectively. The JADER database contained 534,688 reports. The number of AE reports corresponding to encephalopathy (PT) and encephalopathy (SMQ) was 3.5% (42/1198 cases) and 7.9% (95/1198 cases) (Table 1). The ROR (95% CI) for encephalopathy (PT) and encephalopathy (SMQ) was 13.54 (9.91–18.50) and 1.24 (1.01–1.53), respectively.

The AUC from ROC curve for encephalopathy (PT) and encephalopathy (SMQ) was 0.675 and 0.602, respectively. The cutoff value for encephalopathy (PT) and encephalopathy (SMQ) was 2000 (Youden index = 0.307) and 2000 mg/m^2 (Youden index = 0.197), respectively.

Using a stepwise logistic regression model, we examined and selected significant variables related to IIE among the background factors (sex, age-stratified group), reporting year, and dosage-stratified group. The result in the final model indicated a significant contribution of the ≥ 60 year group ($p = 0.00094$) and ≥ 2000 mg/m^2 dosage group ($p = 0.00045$) to encephalopathy (SMQ). The contribution of sex and reporting year to encephalopathy (SMQ) was not significant (data not shown). The adjusted ROR of the ≥ 60 year group was 2.14 (1.37–3.34) compared with that of the control < 60 year group that was used as a reference. The adjusted ROR of the ≥ 2000 mg/m^2 dosage group was 2.15 (1.43–3.25) compared with that of the reference < 2000 mg/m^2 dosage group. However, the contribution of all the examined variables (sex, age, reporting year, and dosage) to encephalopathy (PT) was not significant (data not shown).

We classified the reports according to the daily dose as follows: < 2000 (337 reports) and ≥ 2000 mg/m^2 (139 reports). The reporting ratio of encephalopathy (PT) in the < 2000 and ≥ 2000 mg/m^2 groups was 3.9% (13 reports) and 15.8% (22 reports), respectively. For encephalopathy (SMQ), the reporting ratio of encephalopathy in the < 2000 and ≥ 2000 mg/m^2 groups was 8.0% (27 reports) and 19.4% (27 reports), respectively. The average dose of ifosfamide for cases with encephalopathy (PT) and without encephalopathy

Table 1 Reported cases and reporting odds ratio (ROR) of encephalopathy

			Total	Encephalopathy (PT)[a]				Encephalopathy (SMQ)[b]			
				Case	Non-case	Ratio (%)	ROR[c] (95% CI[d])	Case	Non-case	Ratio (%)	ROR[c] (95% CI)[d]
FAERS			9,702,166	11,967	9,690,199	0.1		957,421	8,744,745	9.9	
Ifosfamide	Total		8344	523	7821	6.3	56.58 (51.69–61.93)	1226	7118	14.7	1.57 (1.48–1.67)
	Male		3151	228	2923	7.2	64.37 (56.19–73.75)	530	2621	16.8	1.85 (1.68–2.03)
	Female		2420	244	2176	10.1	84.15 (73.26–96.67)	535	1885	22.1	2.59 (2.36–2.85)
	0–59 y.o.	Total	3898	227	3671	5.8	51.02 (44.57–58.41)	624	3274	16.0	1.74 (1.60–1.90)
		Male	2167	102	2065	4.7	40.33 (33.03–49.24)	320	1847	14.8	1.58 (1.41–1.78)
		Female	1535	124	1411	8.1	71.90 (59.78–86.46)	293	1242	19.1	2.16 (1.90–2.45)
	≥60 y.o.	Total	963	122	841	12.7	118.67 (98.06–143.60)	270	693	28.0	3.56 (3.09–4.10)
		Male	480	66	414	13.8	129.80 (100.04–168.41)	119	361	24.8	3.01 (2.45–3.70)
		Female	458	56	402	12.2	113.33 (85.64–149.97)	149	309	32.5	4.40 (3.62–5.36)
	Reporting year	2004–2008	1040	59	981	5.7	48.94 (37.61–63.68)	208	832	20.0	2.28 (1.96–2.66)
		2009–2013	2401	135	2266	5.6	48.78 (40.97–58.09)	348	2053	14.5	1.55 (1.38–1.73)
		2014–2018	4903	329	4574	6.7	59.86 (53.45–67.05)	670	4233	13.7	1.45 (1.33–1.57)
JADER			534,688	1470	533,218	0.3		34,713	499,975	6.5	
Ifosfamide	Total		1198	42	1156	3.5	13.54 (9.91–18.50)	95	1103	7.9	1.24 (1.01–1.53)
	Male		683	26	657	3.8	14.60 (9.83–21.67)	57	626	8.3	1.31 (1.00–1.72)
	Female		451	16	435	3.5	13.48 (8.16–22.26)	38	413	8.4	1.33 (0.95–1.85)
	0–59 y.o.	Total	669	26	643	3.9	14.91 (10.04–22.15)	48	621	7.2	1.11 (0.83–1.49)
		Male	394	18	376	4.6	17.57 (10.92–28.27)	31	363	7.9	1.23 (0.85–1.78)
		Female	229	8	221	3.5	13.20 (6.51–26.77)	17	212	7.4	1.16 (0.70–1.89)
	≥60 y.o.	Total	242	5	237	2.1	7.68 (3.16–18.64)	22	220	9.1	1.44 (0.93–2.23)
		Male	130	3	127	2.3	8.58 (2.73–27.00)	15	115	11.5	1.88 (1.10–3.22)
		Female	109	2	107	1.8	6.79 (1.67–27.52)	7	102	6.4	0.99 (0.46–2.13)
	Reporting year	2004–2008	399	23	376	5.8	22.53 (14.74–34.43)	28	371	7.0	1.09 (0.74–1.60)
		2009–2013	278	4	274	1.4	5.31 (1.98–14.26)	25	253	9.0	1.42 (0.94–2.15)
		2014–2018	521	15	506	2.9	10.85 (6.48–18.18)	42	479	8.1	1.26 (0.92–1.73)

[a]Encephalopathy defined by the preferred term (PT) of encephalopathy (PT code: 10014625)

[b]Encephalopathy defined by the standardized MedDRA Queries (SMQ) of noninfectious encephalopathy/delirium (SMQ code: 20000133)

[c]*ROR* reporting odds ratiol

[d]*CI* confidence interva

(PT) was 2022.8 ± 592.8 (mean ± standard deviation) and 1568.5 ± 703.2 mg/m^2, respectively ($p < 0.05$). The average dose of ifosfamide for encephalopathy (SMQ) and without encephalopathy (SMQ) was 1836.4 ± 726.6 and 1573.1 ± 699.3 mg/m^2, respectively ($p < 0.05$).

We evaluated the possible associations between IIE and demographic data. The result of the mining algorithm was a set of 12 and 20 rules for encephalopathy (PT) and encephalopathy (SMQ) (Table 2). The association rules of {ifosfamide, osteosarcoma} → {encephalopathy (PT)} and {ifosfamide, aprepitant} → {encephalopathy (SMQ)} demonstrated high lift values (Table 2).

For the time-to-onset analysis, we extracted combinations that had complete information for the date of treatment initiation and the date of onset of AE. The median duration (interquartile range) for encephalopathy caused by ifosfamide in patients with encephalopathy (PT) and encephalopathy (SMQ) was 3.0 (2.0–5.0) and 3.0 (1.0–5.0) days, respectively (Fig. 1). Encephalopathy within the first 7 days of administration of ifosfamide was 94.1% for encephalopathy (PT) and 87.7% for encephalopathy (SMQ).

Discussion

In this study, we evaluated the relationship between ifosfamide and encephalopathy using data from the SRS databases. As the lower limit of 95% CI of RORs for encephalopathy

Table 2 Association rule mining for encephalopathy (PT) and encephalopathy (SMQ) (sort by lift)

ID	Lhs [left-hand side (antecedents)]		Rhs [right-hand side (consequent)]	Support	Confidence	Lift
rhs [encephalopathy (PT)]						
[1]	{Ifosfamide, osteosarcoma}	=>	{Encephalopathy (PT)}	0.000024	0.14	51.78
[2]	{Ifosfamide, age (20–29)}	=>	{Encephalopathy (PT)}	0.000011	0.06	22.67
[3]	{Ifosfamide, mesna}	=>	{Encephalopathy (PT)}	0.000021	0.06	22.52
[4]	{Ifosfamide, age (40–49)}	=>	{Encephalopathy (PT)}	0.000011	0.06	20.55
[5]	{Ifosfamide, age (30–39)}	=>	{Encephalopathy (PT)}	0.000011	0.05	19.63
[6]	{Ifosfamide, age (50–59)}	=>	{Encephalopathy (PT)}	0.000013	0.05	19.29
[7]	{Ifosfamide, age (10–19)}	=>	{Encephalopathy (PT)}	0.000021	0.05	18.08
[8]	{Ifosfamide, sex (male)}	=>	{Encephalopathy (PT)}	0.000049	0.04	14.37
[9]	{Ifosfamide, sex (female)}	=>	{Encephalopathy (PT)}	0.000030	0.04	13.42
[10]	{Ifosfamide}	=>	{Encephalopathy (PT)}	0.000079	0.04	13.22
[11]	{Ifosfamide, etoposide}	=>	{Encephalopathy (PT)}	0.000037	0.03	9.17
[12]	{Ifosfamide, doxorubicin}	=>	{Encephalopathy (PT)}	0.000015	0.02	7.27
rhs [encephalopathy (SMQ)]						
[1]	{Ifosfamide, aprepitant}	=>	{Encephalopathy (SMQ)}	0.000013	0.29	4.52
[2]	{Ifosfamide, granisetron}	=>	{Encephalopathy (SMQ)}	0.000039	0.24	3.78
[3]	{Ifosfamide, osteosarcoma}	=>	{Encephalopathy (SMQ)}	0.000037	0.22	3.37
[4]	{Ifosfamide, lymphoma}	=>	{Encephalopathy (SMQ)}	0.000015	0.21	3.18
[5]	{Ifosfamide, mesna}	=>	{Encephalopathy (SMQ)}	0.000056	0.17	2.59
[6]	{Ifosfamide, calcium folinate}	=>	{Encephalopathy (SMQ)}	0.000011	0.15	2.38
[7]	{Ifosfamide, dexamethasone}	=>	{Encephalopathy (SMQ)}	0.000032	0.12	1.91
[8]	{Ifosfamide, age (60–69)}	=>	{Encephalopathy (SMQ)}	0.000030	0.11	1.67
[9]	{Ifosfamide, age (20–29)}	=>	{Encephalopathy (SMQ)}	0.000019	0.10	1.60
[10]	{Ifosfamide, age (10–19)}	=>	{Encephalopathy (SMQ)}	0.000039	0.09	1.46
[11]	{Ifosfamide, rituximab}	=>	{Encephalopathy (SMQ)}	0.000019	0.09	1.41
[12]	{Ifosfamide, age (50–59)}	=>	{Encephalopathy (SMQ)}	0.000022	0.09	1.40
[13]	{Ifosfamide, lung metastases}	=>	{Encephalopathy (SMQ)}	0.000013	0.09	1.35
[14]	{Ifosfamide, sex (female)}	=>	{Encephalopathy (SMQ)}	0.000071	0.09	1.35
[15]	{Ifosfamide, sex (male)}	=>	{Encephalopathy (SMQ)}	0.000107	0.09	1.33
[16]	{Ifosfamide}	=>	{Encephalopathy (SMQ)}	0.000178	0.08	1.26
[17]	{Ifosfamide, age (30–39)}	=>	{Encephalopathy (SMQ)}	0.000017	0.08	1.24
[18]	{Ifosfamide, cytarabine}	=>	{Encephalopathy (SMQ)}	0.000024	0.08	1.17
[19]	{Ifosfamide, age (40–49)}	=>	{Encephalopathy (SMQ)}	0.000015	0.07	1.16
[20]	{Ifosfamide, etoposide}	=>	{Encephalopathy (SMQ)}	0.000101	0.07	1.05

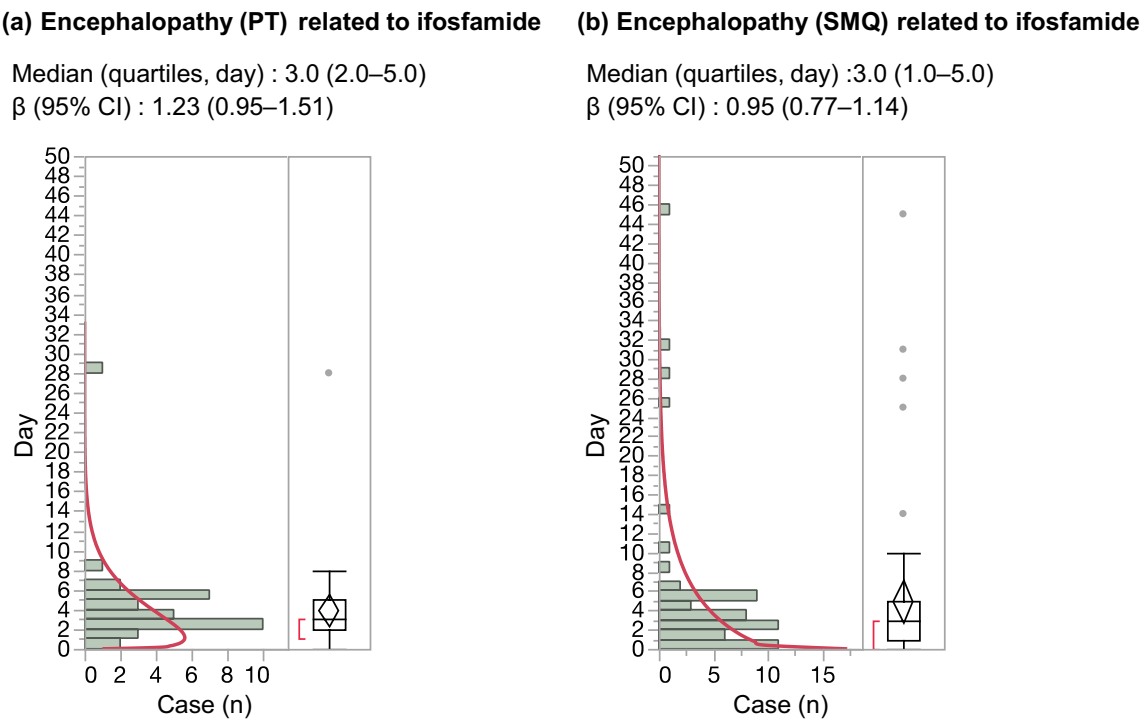

Fig. 1 Time-to-onset profiles of ifosfamide-induced encephalopathy in the JADER database. **a** Defined by preferred term (PT) of encephalopathy (PT code: 10014625). **b** Defined by the standardized MedDRA Queries (SMQ) of noninfectious encephalopathy/delirium (SMQ code: 20000133)

(PT and SMQ) was > 1 in both SRS databases, our results suggest that ifosfamide increases the incidence of encephalopathy. Central nervous system toxicity was observed in 10–30% of ifosfamide-treated patients [21]. These results also corresponded with those of previous reports.

The results of the multivariate logistic regression analysis indicated the risk of aging and higher dose of ifosfamide for encephalopathy (SMQ). It has been reported that the laboratory values of increased serum creatinine increase the IIE risk [5, 6]. Aging decreases renal drug elimination because of reduced glomerular filtration rate and tubular function [22]. We considered that the evaluation of IIEs related to aging and associated with renal disorders would be an extremely interesting subject. On the contrary, we could not observe the effects of aging and higher dose of ifosfamide for encephalopathy (PT). The reason might be the small number of reporting case for encephalopathy (PT) in our used data set of the JADER (Table 1).

Previously, the high cumulative dose has been proposed as a risk factor of encephalopathy [23]. On the contrary, some studies have reported that a high cumulative dose is not a risk factor [24]. From the results of the multivariate logistic regression analysis and from the comparison of the average dose of ifosfamide in patients with encephalopathy (PT) and without encephalopathy (PT), we have demonstrated the possibility of an increased risk of encephalopathy with a higher dose of ifosfamide. From the AUC and Youden index in the ROC curves, encephalopathy (PT) might be a more stringent criterion than encephalopathy (SMQ). Robust epidemiological studies are required to throw light on this risk factor.

To the best of our knowledge, there have been no previous reports on association rule mining analyses for IIE using SRS. The association rule mining revealed that the incidence of encephalopathy (SMQ) with primary disease-related items such as aprepitant was high because of the lift values of two combined items. An association between IIE and aprepitant is commonly accepted [25–27]. Therefore, we believe that aprepitant might be associated with the risk of IIE. Ifosfamide has been a part of various treatment protocols such as osteosarcoma (MAPIE protocol: cisplatin, doxorubicin, methotrexate, ifosfamide, and etoposide) and non-Hodgkin's lymphoma (MINE protocol: mesna, ifosfamide, mitoxantrone, and etoposide). Therefore, the lift value of combined item of ifosfamide and osteosarcoma, ifosfamide and other anticancer drug such as etoposide, doxorubicin, mesna, and etoposide might be apparently high. Further epidemiological studies might be required to confirm these results.

Methylene blue, thiamin, and dexmedetomidine are known to prevent and treat IIE [28–31]. In patients with encephalopathy (PT) and encephalopathy (SMQ), we

preliminary analyzed the number of cases in which ifosfamide and these drugs (methylene blue, dexmedetomidine, and thiamin) were used in combination. In the JADER database, no reports in which ifosfamide and concomitant drugs such as methylene blue, dexmedetomidine, and thiamin were used in combination for encephalopathy (PT) and encephalopathy (SMQ). In the FAERS database, there were no reports on the combination of ifosfamide and methylene blue or thiamin for encephalopathy (PT). The combination of ifosfamide and methylene blue was 0.2% (19/8344) for encephalopathy (SMQ). The combination of ifosfamide and thiamin was 0.2% (17/8344) for encephalopathy (SMQ). There were no reports on the combination of ifosfamide and dexmedetomidine for encephalopathy (PT) and encephalopathy (SMQ). The effect of the treatment with methylene blue, thiamin, and dexmedetomidine is clinically interesting. However, as the number of reports of the combination therapy was small, we did not examine further.

It has been reported that IIE occurs more frequently after oral administration rather than infusion. IIE might be affected by the administration route of drugs. For example, cyclophosphamide has two dosage forms, namely, oral and intravenous. However, ifosfamide is administered by intravenous form. In the JADER database, no case of oral administration was reported. In the FAERS, the input of oral administration was only 0.1% (11/8344).

We also applied time-to-onset analysis to validate the results, which provided novel insights into the time-to-onset of encephalopathy. That is, > 40% of the encephalopathy cases were observed within 3 days in the real-world data set, and > 80% of the reports on encephalopathy following the administration of ifosfamide were recorded within 7 days of treatment initiation. However, ifosfamide-induced encephalopathy occurring after day 7 of drug administration should not be overlooked.

In this study, we applied the time-to-onset analysis. After extraction of the combinations with complete information on the date of starting medication and the date of AE onset, time-to-onset duration was calculated from the beginning of a subject's first prescription to the occurrence of AEs. In the FAERS, matching between the date of AE onset and the date of starting treatment of each individual drug is difficult because the information date for each drug was not recorded in the FAERS. Therefore, we used the JADER database for the time-to-onset analysis in this study.

Our study has some limitations that are worth mentioning. First, the FAERS and JADER databases do not contain detailed background information on medical history (e.g., treatment regimen). It was difficult to obtain and evaluate the accurate dosage and duration of the drug from, and the duration of neurotoxicity and/or encephalopathy. For example, in the JADER and the FAERS, the percentage of items for which some dosage data has been entered was 55.3% (913/1650) and 41.7% (4099/9840), respectively. In the FAERS database, the description format of the field of "DOSE_VBM" that is verbatim text for dose, frequency, and route, as entered in reports was not unified and trouble in interpretation. On the contrary, the input of the dose and frequency of administration in the JADER database was relatively standardized. Furthermore, other information such as body weight was limited in the FAERS compared with that in the JADER. We have already reported the AE analysis with the daily dosage of Kampo preparation according to the amount administered daily in each case report using the JADER database [32]. Therefore, we evaluated using the JADER database and did not evaluate using the FAERS database. Second, the SRS is subject to over-reporting, under-reporting, missing data, exclusion of healthy individuals, lack of a denominator, and presence of confounding factors [33]. The "Weber effect" is a well-known limitation in the spontaneous reporting of AEs. The Weber effect is an epidemiological phenomenon describing AE-reporting peaks at the end of the second year after a regulatory authority approves a drug, which then plateaus and eventually declines [34, 35]. However, the Weber effect was not always observed [35]. Based on our results using the multivariate logistic regression analysis, the clear decline in the reporting ratio was not observed during 2004–2018.

The comparison study demonstrated distinct discrepancies in reported drugs, reported AEs, seriousness, and average number of reported events per case, between the JADER and FAERS [36]. As differences can arise as a result of discrepancies in reporting rules and customs in each country such as reporters and reported AE terms, which are associated in regulations, the two databases showed different features [36]. For example, the SRS databases mostly depend on the compliance of pharmaceutical companies to report according to regulatory requirements. Companies in the US need to submit case reports with non-serious AEs, but reporting of known non-serious AEs is not mandatory for Japanese companies [36]. Therefore, it is difficult to directly compare the RORs of the FAERS with those of the JADER. However, we could demonstrate the same trend among each database as follows: the crude RORs of encephalopathy were higher than 1 in both the databases. Information from both databases might be considered of complementary value.

Conclusions

This is the first study to evaluate the correlation between ifosfamide and encephalopathy using an SRS analysis strategy. Despite the limitations inherent to SRS, we showed the potential risk of encephalopathy with ifosfamide use in a real-life setting. The present analysis demonstrated that patients administered ifosfamide should be closely

monitored for the development of encephalopathy within a short duration (7 days). The patients who are administered with a high dose of ifosfamide or co-administrated aprepitant should also be carefully monitored for the development of encephalopathy.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest to declare.

Ethical approval Ethical approval was not sought for this study because the study was a database-related observational study without directly involving any research subjects.

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