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Ifosfamide Encephalopathy: a Reappraisal

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Abstract—*Eighteen consecutive cases of encephalopathy occurring after ifosfamide/mesna chemotherapy were prospectively assessed. No relationship was found with tumour type or chemotherapy response. Onset was from* 12 *to* 146 (*mean* 46) h *after the start of the infusion and median duration was* 3 *days* (*range* 1–12). *In two patients recovery was incomplete. A confusional state and agitation were the major clinical features. Plasma potassium fell from a mean of* 4.12 mmol/l *before chemotherapy to* 2.94 mmol/l *at the onset of encephalopathy* ($P < 0.001$) *with plasma potassium* < 3.0 mmol/l *in* 10 *patients. Duration of hypokalaemia was not related to duration of encephalopathy. Median survival following encephalopathy was* 25 *days. The incidence of encephalopathy in* 82 *patients treated on two protocols was* 11% *and the sensitivity of a published nomogram was* 18%. *It is concluded that ifosfamide/mesna encephalopathy is a serious complication which may be irreversible and remains difficult to predict.*

INTRODUCTION

IFOSFAMIDE is a structural isomer of cyclophosphamide and has activity against a range of tumours including sarcomas, lung cancer and ovarian cancer. The metabolic transformations following administration are similar, but the different clinical pharmacokinetics for the two isomers may explain the differing toxicity and therapeutic efficacy of the two drugs [1].

Dose-limiting urothelial toxicity prevented widespread use following the introduction of ifosfamide until the development of mesna (sodium 2 mercapto-ethane sulphonate), which detoxifies the urotoxic oxazophorine metabolite acrolein, and permitted the use of higher doses of ifosfamide [2]. In addition to the myelosuppressive effects there have been recent reports to suggest that there is a significant incidence of central nervous system effects associated with the use of ifosfamide/mesna [3, 4]. Early studies [5–7] identified the association of cerebral toxicity with ifosfamide/mesna therapy and this was recently characterized in more detail by Meanwell *et al.* [3] who suggested that serious cerebral toxicity could be prevented using a nomogram to identify 'at risk' patients although this method has not entered routine practice as a means of preventing the complication.

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There are inadequate data regarding the temporal relationship of clinically apparent encephalopathy to the ifosfamide infusion. The duration of the encephalopathy is not well characterized and it is not clear from the literature whether recovery is always complete, although Heim *et al.* [7] have found a persistent organic brain syndrome for up to 10 weeks in 50% of patients.

Over a 2-year period at the Mersey Regional Centre for Radiotherapy and Oncology (MRCRO) every case of suspected ifosfamide/mesna-associated encephalopathy has been assessed prospectively with the aim of defining in more detail the clinical characteristics and examining the usefulness of the nomogram described by Meanwell *et al.* [4].

METHODS

All cases of suspected ifosfamide/mesna encephalopathy occurring between October 1986 and October 1988 at MRCRO were reported to the authors and evaluated by two of them. Patients were included in the study when there was clinical evidence of cerebral toxicity in the absence of other possible causative factors such as cerebral metastases, pyrexia and heavy sedation.

Patients received ifosfamide as a single agent or in a variety of combination regimes (see Table 1). Ifosfamide was given as a 24 h infusion at a dose of 5 g/m^2 in 3 litres of normal saline. Mesna was given as a bolus before ifosfamide at a dose of 1 g/m^2 over 1 h in 500 ml normal saline. A further dose of

Table 1. Clinical details of patients with encephalopathy

Patient No.	Sex	Age	Diagnosis	Performance status	Regime
01	M	56	SCLC	0	IFOS
02	M	61	SCLC	3	IFOS
03	F	63	SCLC	0	IFOS/VP-16
04	F	56	SCLC	1	IFOS/VP-16
05	M	63	SCLC	2	IFOS/VP-16
06	F	69	SCLC	3	IFOS/VP-16
07	F	57	NSCLC	2	IFOS/DX/VDS/CDDP
08	F	67	Ovarian carcinoma	0	IFOS/JM-8
09	F	57	Ovarian carcinoma	1	IFOS/JM-8
10	F	38	Ovarian carcinoma	1	IFOS/JM-8
11	F	67	Ovarian carcinoma	2	IFOS/JM-8
12	F	39	Ovarian carcinoma	3	IFOS/JM-8
13	F	60	Ovarian carcinoma	3	IFOS/DX
14	F	42	Uterine leiomyosarcoma	2	IFOS/DX
15	F	64	Rhabdomyosarcoma	2	IFOS/DX
16	M	58	Mesothelioma	3	IFOS/DX/VDS/CDDP
17	F	26	NHL	3	IFOS/VP-16/DHAD/DEX
18	M	55	Unknown primary	0	IFOS

Abbreviations: SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; NHL, non-Hodgkin's lymphoma.
Chemotherapy: IFOS, ifosfamide/mesna; VP-16, etoposide; DX, doxorubicin; VDX, vindesine. CDDP, cisplatin; JM-8, carboplatin; DEX, dexamethasone; DHAD, mitozantrone.

mesna at 5 g/m^2 was given simultaneously with the ifosfamide and this was followed by an 8 h infusion of mesna at 40% of the ifosfamide dose. The total dose of mesna was therefore 160% of the dose of ifosfamide. Potassium supplementation was not routinely given with the infusion.

The anti-emetic regime used was a continuous infusion of metoclopramide at a dose of 300 mg per 24 h in 500 ml of 5% dextrose, continued for up to 48 h. Patients received occasional other anti-emetic or anxiolytic agents as required.

At each admission haematological and biochemical profiles were checked routinely and these were repeated if indicated during treatment. Routine weekly interim haematological profiles were also performed. Plasma electrolytes were measured by standard autoanalyser methods.

All protocols defined exclusion criteria for patients with impaired renal and hepatic function. In most cases this required a 24 h creatinine clearance to be greater than 70 ml/min on entering the trial and for patients to have biochemical tests of hepatic function (serum transaminase and alkaline phosphatase) which did not exceed twice the upper limit of normal. The nomogram [4] was not employed prospectively.

Encephalopathy was graded according to Meanwell *et al.* [4] (Table 2). The nomogram devised by Meanwell *et al.* predicts the probability of not developing Grade 3–4 encephalopathy based on the serum albumin, serum creatinine and on the presence or absence of disease below the level of the renal pedicles [4]. They subsequently suggested that ifosfamide/mesna therapy should not be given to patients with less than 0.20 probability of remaining free from severe CNS toxicity [8]. The patient data in the present series was applied to the nomogram retrospectively to determine the sensitivity of the test.

Table 2. Clinical CNS toxicity grading

Grade	Clinical observation
0	Alert
1	Transient lethargy
2	Somnolence <50% of the time and/or mild to moderate disorientation
3	Somnolence >50% of the time and/or severe disorientation, echolalia, perseveration of writing, palilalia, logorrhoea, hallucinations or delusions
4	Coma

To determine the incidence of ifosfamide encephalopathy, and to define the operational characteristics of the nomogram all cycles of ifosfamide chemotherapy given to 82 patients treated in two protocols (ifosfamide/carboplatin for ovarian carcinoma and ifosfamide/etoposide for small cell lung cancer) were also examined.

Survival was calculated using the Kaplan–Meier method.

RESULTS

Eighteen cases of serious encephalopathy were recorded: 13 female and five male patients aged 26–69 years (median 58 years). Clinical details are shown in Table 1. Four patients had received other chemotherapy regimes on previous occasions (patients 01, 02, 13 and 17) which in two cases (13 and 17) had included ifosfamide/mesna with no history of encephalopathy. In 11/18 the encephalopathy occurred during the first cycle of ifosfamide/mesna. Of the remaining seven, two had received one cycle previously without any adverse event, four patients developed encephalopathy at cycle number 3 and one patient on cycle 6.

Clinical features

The predominant feature in all cases was confusion (by definition of the syndrome—see Table 2). Encephalopathy was grade 2 in two cases, 3 in 14 and 4 in two. Ten patients developed features of agitation, with sedation (benzodiazepines or major tranquillizers) being required in seven. Two patients developed delusional states. Auditory and visual hallucinations were recorded in one patient and visual hallucinations alone in a further patient. Twelve patients became incontinent of urine and/or faeces. On full neurological examination, no evidence of any focal defects were found. One patient developed generalized muscular twitching, but seizures did not occur. Five patients underwent computerized tomographic scans of the brain during or shortly after the episode of encelophalopathy, and no focal lesions were found.

The time to onset of the encephalopathy was measured from the start of the infusion to the time when encephalopathy became apparent, but only one patient developed encephalopathy during the 24 h ifosfamide infusion. The mean duration of the ifosfamide infusion was 26 h (range 23–29 h). The time to onset of encephalopathy, the duration of encephalopathy and the extent of recovery is shown in Table 3. The mean time to onset was 46 h from the start of the infusion (range 12–146 h). The duration of encephalopathy was the time from onset to the time of complete clinical recovery (16 patients) and the median duration was 3 days (range 1–12). Five patients took 1 week or more to recover and there was incomplete recovery in two patients, who died at days 22 and 29 with persistent clinical evidence of encephalopathy. Complete clinical recovery was defined as the time at which the patient's mental condition was considered to be normal.

Tumour response and survival

One patient was in complete remission after cycle 2 and then developed encephalopathy with cycle 3. Two patients achieved a partial response (>50% reduction) to treatment but in the remaining 15 patients there had either been no response to the previous cycles (six patients) or the patients developed encephalopathy on the first cycle before response could be evaluated (nine patients).

Seventeen patients have died between 5 days and 23 months following the cycle of treatment with encephalopathy with a median survival of 25 days. One patient is alive at 8 months. Death was due to progressive disease in 9/17 patients, neutropenic fever during a subsequent cycle of chemotherapy in three, a sudden cardiovascular event in two and to unknown causes in three. The survival curve for all 18 patients is shown in Fig. 1.

Table 3. Details of encephalopathy

Patient No.	Time to onset (h)	Recovery	Duration (days)	Grade of encephalopathy	Cycle number of encephalopathy
01	31	Full	7	2	1
02	111	Partial	22	3	1
03	25	Full	4	4	3
04	12	Full	2	2	2
05	101	Full	8	3	1
06	29	Full	3	3	1
07	36	Partial	29	3	3
08	23	Full	8	3	1
09	37	Full	3	3	3
10	33	Full	2.5	3	1
11	36	Full	12	3	1
12	26	Full	3.5	3	1
13	36	Full	12	4	1
14	32	Full	4	3	1
15	25	Full	2.5	3	3
16	146	Full	2	3	1
17	35	Full	1	3	2
18	62	Full	3	3	6

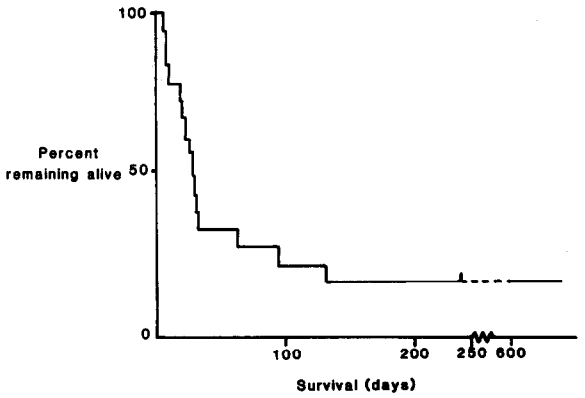

Fig. 1. Survival curve for 18 patients experiencing ifosfamide encephalopathy. Survival taken from first day of cycle with encephalopathy to date of death (17 patients) or date last known to be well (one patient).

Electrolytes

Plasma potassium concentrations before the start of chemotherapy, at the onset of encephalopathy and the nadir levels are shown in Fig. 2 for the 17 patients in whom these data are available. Plasma potassium concentration fell from an initial mean of 4.12 mmol/l before chemotherapy to 2.94 mmol/l at the onset of encephalopathy and 2.88 mmol/l at the nadir for plasma potassium (both $P < 0.001$ compared to initial value). Initial plasma potassium concentration was above 3.0 mmol/l in all patients, but fell to less than 3.0 mmol/l in 10 patients (the hypokalaemic group). In 14 patients the nadir in plasma potassium was at the time of onset of encephalopathy and in three the potassium fell subsequently. When hypokalaemia occurred, a potassium concentration $\geq$3.0 mmol/l was restored in 1–4 (median 2) days. In two patients (with nadir plasma potassium concentration, 2.1 and 2.6 mmol/l) hypokalaemia was attributable to prolonged vomiting, but no specific cause was present in the other cases. The duration of hypokalaemia (i.e. plasma potassium concentration $\leq$3.0 mmol/l) was shorter than that of the encephalopathy in 9/10 patients (by 1–26 days). No significant changes in plasma sodium of serum calcium concentrations were noted.

Predictability of encephalopathy

Table 4 shows the serum albumin and creatinine values, and whether or not the patient had disease below the renal pedicles. The probability of remaining free of grade III/IV encephalopathy is calculated from the Meanwell nomogram. Only 3/18 patients had a probability of remaining free of Grade 3–4 encephalopathy $\leq$0.20. The two patients who had Grade 2 encephalopathy had probabilities of 0.81 and 0.97. Thus, of the patients with Grade 3–4 encephalopathy only 3/16 might have been deemed ineligible for ifosfamide/mesna if the nomogram had been used. This gives a sensitivity of 18% (95% confidence limits, 0–36%).

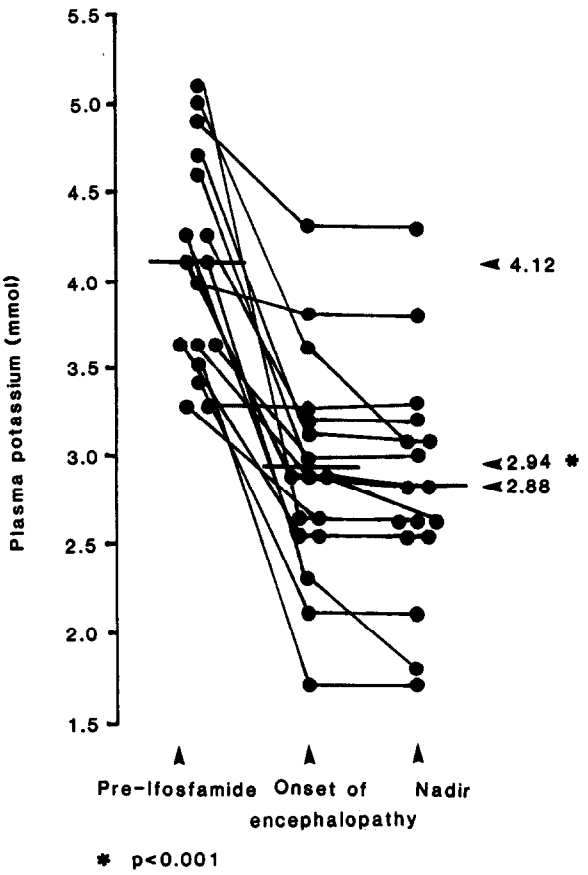

Fig. 2. Plasma potassium concentrations before and after ifosfamide encephalopathy. Mean values are indicated.

Eight patients had received ifosfamide/mesna previously either as part of an earlier regime (one patient) or in previous cycles with the same regime (seven patients). The probability of not developing Grade 3/4 cerebral toxicity was calculated for the previous occasion on which the patient received ifosfamide but did not have encephalopathy. These results are shown in Table 5. The probability of remaining free of encephalopathy fell from the previous to the incident cycle in six patients, but to $\leq$0.20 in only two patients.

Incidence of encephalopathy

Nine of the patients (50%) were entered onto larger chemotherapy trials and the incidence of encephalopathy in each of these trial groups has been calculated. Of the nine, there were four treated with ifosfamide and etoposide for small cell lung cancer (IE) and five with ifosfamide and carboplatin for ovarian cancer (ICAP). In all, there were 52 patients enrolled on IE and 30 on ICAP. This gives an incidence of encephalopathy of 8% (4/52) for the lung cancer patients and 16% (5/30) for the ovarian cancer patients. The overall incidence, therefore, in these two trials was 9/82 (11%).

Operating characteristics of the nomogram

All cycles of chemotherapy given to 82 patients on IE and ICAP, described above, were examined.

Table 4. Determination of probability of not developing grade 3/4 CNS toxicity

Patient No.	Grade of encephalopathy	Serum albumin (g/l)	Serum creatinine (micromol)	Pelvic disease (+/−)	Probability*
01	2	39	76	−	0.97
02	3	36	76	−	0.95
03	4	41	163	−	0.40
04	2	31	71	−	0.81
05	3	33	111	−	0.50
06	3	40	80	+	0.90
07	3	33	53	−	0.95
08	3	34	71	+	0.70
09	3	33	70	−	0.90
10	3	37	70	−	0.97
11	3	32	108	−	0.98
12	3	31	48	+	0.75
13	4	28	92	+	0.10
14	3	29	84	+	0.18
15	3	30	70	−	0.80
16	3	38	78	−	0.96
17	3	34	152	+	0.04
18	3	32	91	+	0.30

*The probability value is calculated by use of the nomogram [4].

Table 5. Data on previous cycle of ifosfamide/mesna without encephalopathy. Probability (1) is previous cycle value and probability (2) value on cycle with encephalopathy

Patient No.	Grade of encephalopathy	Albumin (g/l)	Creatinine (micromol)	Pelvic disease (+/−)	Probability (1) Previous cycle	Probability (2) Cycle with encephalopathy
03	4	41	120	−	0.90	0.40
04	2	36	73	−	0.80	0.81
07	3	33	62	−	0.95	0.95
09	3	33	54	−	0.95	0.90
13	4	41	67	+	0.96	0.10
15	3	30	44	−	0.95	0.80
17	3	44	71	+	0.98	0.04
18	3	34	87	+	0.50	0.30

The values for serum albumin and creatinine concentrations were noted for each cycle and the probability of not developing serious encephalopathy calculated using the nomogram. There were complete data in 177 cycles of treatment in patients who never developed encephalopathy and for 14 cycles of chemotherapy given to the patients on these trials who showed evidence of encephalopathy.

A probability of ≤ 0.20 of remaining free of encephalopathy was found for one cycle, and encephalopathy did not occur during this cycle (positive predictive value 0%). A probability of >0.20 was found for 190 cycles, among which nine episodes of encephalopathy occurred (predictive value of a negative result = 95%). None of the cases of encephalopathy on the IE and ICAP protocols would have been prevented if a probability of ≤ 0.20 had been used as a cut-off. No alternative cut-off value would have distinguished those cycles in which encephalopathy occurred from those in which it did not.

DISCUSSION

Initial reports of CNS effects of ifosfamide/mesna suggested an incidence of 5% [9, 10] but these effects were poorly characterized. Morgan *et al.* [11] noted CNS toxicity in 13 out of 254 patients (5.1%) treated with ifosfamide without mesna for non-small cell lung cancer (doses 4 g/m^2/day 1 and 1.2 g/m^2 days 1–5) but no detailed description was given. Meanwell *et al.* [3] noted severe encephalopathy in five of 31 women treated for gynaecological malignancies with ifosfamide 5 g/m^2 and mesna 8 g/m^2. In one patient death was thought to be due to CNS side-effects. Cantwell and Harris [12] reported their experience with 119 patients treated with ifosfamide and mesna each given at a dose of 5 g/m^2 over 24 h. Seventy patients with small cell

lung cancer (SCLC) received ifosfamide/mesna monotherapy of whom one female had transient blunting of affect, fatigue and syncope after one course. Thirty-three other SCLC patients received ifosfamide/mesna in combination with other agents and one female developed confusion, postural hypotension, depression and long-lasting fatigue after the fourth course of treatment. One out of 16 sarcoma patients developed the characteristic encephalopathy described by Meanwell *et al.* [3]. The authors suggested that their incidence of serious CNS toxicity of less than 1% might in part be explained by the use of a lower dose of mesna.

Serious encephalopathy has been reported following rapid infusion over 6 h of ifosfamide [13] as well as the more usual 24 h and fractionated daily schedules which can be used without mesna. The syndrome has also been seen in children and may be fatal [14].

There are very little data regarding the temporal relationship of encephalopathy to the ifosfamide infusion, although Meanwell *et al.* suggest that onset is 20–50 h from the start of the infusion which would imply that onset is not later than 26 h from the end of a 24 h infusion. In the patients reported here onset was between 12 and 146 h from the start of the infusion with a mean delay of 46 h before encephalopathy was apparent. In three patients encephalopathy was not apparent for a much longer period: 101, 111 and 146 h from the start of the infusion. The complication may therefore go unrecognized as most patients are discharged after 48–72 h. It may also cause diagnostic confusion if a patient receiving ifosfamide in a major centre is readmitted to a local hospital with encephalopathy.

The duration of encephalopathy was also very variable (median 3 days, range 1–12 days) and in two patients there was considered to be incomplete recovery with persistent psychological disturbance for up to 1 month. The incidence of irreversibility of 11% (2/18) is less than that of 50% (5/10 patients) seen by Heim *et al.* [7], although we have not performed psychometric testing. Heim also noted the pronounced psychological components of the syndrome of ifosfamide encephalopathy, particularly restlessness and confusion with or without hallucinations and delusions. Common to all reported cases is the absence of focal neurological findings.

The spectrum of activity of ifosfamide is broad [15] but it is not clear whether ifosfamide/mesna encephalopathy is a disease-specific phenomenon. The range of tumours represented in both our study and those of other groups would simply appear to reflect those solid tumours against which ifosfamide has demonstrable activity, notably lung cancer, ovarian and testicular cancer, gastro-intestinal cancer and sarcomas.

We were unable to demonstrate any useful response to chemotherapy in 15/18 patients although 9/15 were receiving their first cycle of treatment and five died within 4 weeks. In five of these patients there was sudden, unexpected death but in the remainder of deaths disease progression was documented. It therefore seems unlikely that encephalopathy is associated with response to chemotherapy and cases of encephalopathy seem to occur in patients whose tumours are resistant to ifosfamide.

The median survival of 25 days was alarming, particularly in view of the good performance status of the patients, and in three cases it is likely that myelosuppression was contributory. The relative contribution of encephalopathy to these early deaths cannot be assessed from this study but a further three patients died inexplicably.

A second study by Meanwell *et al.* [4] identified low serum albumin, high serum creatinine and the presence of disease below the level of the renal pedicles as variables which were associated with the highest risk of developing severe encephalopathy. Seven out of 77 patients (9%) developed severe CNS toxicity. They suggested that a nomogram based on these three variables was a sensitive test to identify those patients at risk of encephalopathy and in a subsequent study [8] found that none of 38 patients with a computed probability of greater than 0.20 of remaining free from Grade 3–4 toxicity showed any evidence of this level of toxicity. We have evaluated the nomogram by applying it retrospectively to our data. We have shown that, using a cut off probability of 0.2, the test is not useful for predicting encephalopathy. Others [13] have suggested that if the nomogram is used the cut-off value may need to be altered from one study to another if serious encephalopathy is to be avoided. Our view is that no cut-off value would have been useful in the patients. Of the eight patients who had received ifosfamide on a previous occasion without encephalopathy (Table 5), six showed a lower probability on the cycle with encephalopathy, that is to say there was a higher probability of developing Grade 3–4 cerebral toxicity. Two of these fell to 0.04 and 0.10 and are the patients who would have been predicted by the nomogram had it been used. It does not seem to us a practical proposition for each centre to develop its own classification function if encephalopathy is to be successfully predicted and we doubt that the nomogram is truly transferable between centres.

We initially reported hypokalaemia in association with ifosfamide/mesna in four patients (three of whom are also reported here) [17] and the present results confirm this as a side-effect of ifosfamide/mesna chemotherapy. While the association may be spurious, in that electrolytes are likely to be

measured more frequently in a confused patient, 10 out of 11 patients we have reported with hypokalaemia also had encephalopathy. Hypokalaemia is unlikely to be associated with the pathogenesis of encephalopathy since there was no relationship between their duration. Plasma potassium concentration fell after ifosfamide in 16/17 patients, with a specific cause (vomiting) evident in only two. Ifosfamide is nephrotoxic, causing subclinical tubular damage in all patients in one study [18], despite use of mesna. Hypokalaemia might be a manifestation of tubular damage and could be exacerbated by the infusion of intravenous fluids not containing potassium. A further possibility is that the hypokalaemia is caused by the encephalopathy, and an example of stress hypokalaemia [19] which is thought to be an adrenergic effect [20]. Hypokalaemia has also been described in association with delirium tremens [21]. The pathogenesis of hypokalaemia in patients with ifosfamide encephalopathy may well be multifactorial. Hypokalaemia is potentially serious and one death due to cardiac arrest in association with hypokalaemia following ifosfamide/mesna chemotherapy has been reported [17]. It is unclear whether supplementation of intravenous fluids with potassium will prevent the hypokalaemia, which may represent a potential hazard if outpatient schedules for ifosfamide are widely adopted [22].

Encephalopathy is a serious, often prolonged and sometimes irreversible complication of ifosfamide/mesna chemotherapy. The syndrome may go unrecognized and attempts to predict its occurrence using a nomogram have been unsuccessful.

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