Incidence and severity of ifosfamide-induced encephalopathy

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This retrospective trial was performed to determine risk factors, incidence and severity of ifosfamide-induced encephalopathy in correlation with patient and treatment characteristics. Patients receiving ifosfamide were included consecutively with no restrictions concerning disease, prior chemotherapy or disease stage. Incidence and severity of encephalopathy were graduated according to common toxicity criteria. Between July 2001 and July 2002, 60 patients (32 male, 28 female, median age 47.5 years) were included; 26.6% of the patients ($n=16$) developed neurological symptoms [grade 1: 6.7% ($n=4$); grade 2: 3.3% ($n=2$); grade 3: 11.7% ($n=7$); grade 4: 5% ($n=3$)]. Encephalopathy occurred for the first time in 87.5% ($n=14$) in chemotherapy courses 1 and 2. In 56.25% ($n=9$) of these 16 patients only one episode was observed. There was no significant difference concerning age (38 versus 50 years, $p=0.08$) and dosage (median 2.9 versus 2.8 g, $p=0.74$) between patients with and without encephalopathy. No risk factors could be identified by this study, suggesting an individual predisposition in each patient. On the other hand, ifosfamide can be administered in older patients without increased risk of neurotoxicity. *Anti-Cancer Drugs* **15:347–350 © 2004 Lippincott Williams & Wilkins.**

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Introduction

The alkylant ifosfamide has proven efficacy in the treatment of a variety of malignancies, e.g. soft tissue sarcoma, malignant lymphoma, multiple myeloma, cancer of unknown primary, ovarian cancer and germ cell tumors. Ifosfamide is used as a single treatment or in combination with drugs like cisplatin, etoposide, etc. (Table 1).

Ifosfamide induced side-effects are sometimes treatment limiting. Most of these unintended effects are similar to the side-effects of other alkylating agents, e.g. cyclophosphamide, including hemorrhagic cystitis, nephropathy and cytopenia. Almost unique for ifosfamide is the appearance of neurotoxicity. These neurological complications can occur as a variety of symptoms, and range from slight depressive periods and dizziness to stupor or even coma.

The incidence of ifosfamide-induced encephalopathy has been estimated to be between 20 and 60%, thus being responsible for a high rate of treatment-related morbidity. In the past, this side-effect has been regarded to be dose related and mainly being caused by metabolites of ifosfamide. Ifosfamide is hepatically processed into several metabolites: among them chloroethylamine and SCMC are the substances supposed to be the ones causing ifosfamide-derived encephalopathy [1,2].

Predisposing factors for the development of encephalopathy in an individual patient have not yet been revealed exactly. It is believed that pre-existing renal or hepatic failure, low serum albumin and poor performance status increase the rates of neurotoxicity [4]. Moreover, the infusion time seems to be of importance in the development of the neurological symptoms. Oral application and rapid i.v. infusion have been reported to cause higher rates of encephalopathy than long-term or continuous (24 h) application of ifosfamide [5,6]. If the patient shows symptoms of neurological disorder during treatment with ifosfamide, the application of methylene blue as an antidote of chloroethylamine [2,3,7] has sometimes been successful, yet recommendations of the methylene dose and the way of application (i.v. or orally) differ. Most authors propose 50 mg of methylene blue 4–6 times daily as rapid infusion for at least 2 days. Yet ifosfamide-induced neurotoxicity is reported to be reversible in 48 h without any treatment at all [4]. Hence, there is no agreement of the use of methylene blue in ifosfamide encephalopathy [1,2,7]. In most studies, authors recommend the prophylactic use of methylene blue in cases where further use of ifosfamide is necessary and where patients have already suffered from neurotoxic side-effects.

There are some reports and small series about patients developing 'ifosfamide encephalopathy', yet to our knowledge no studies with larger patient numbers have evaluated the origin and incidence of this severe clinical problem. Parameters that might predict the individual

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risk of a patient developing neurotoxicity have not exactly been defined.

The objective of this retrospective study was to determine risk factors, incidence and severity of ifosfamide-induced encephalopathy in a large patient cohort in correlation with patient and treatment characteristics.

Patients and methods

Patient eligibility

Patients receiving ifosfamide-based chemotherapy either as single agent or in combination were eligible for this retrospective study. Patients included into this study were required to be older than 18 years, to be in adequate clinical conditions (Karnofsky index > 70%) and should not display any severe organ dysfunction. No restrictions were made concerning chemotherapy and disease stage. Patients were included consecutively.

Patient evaluation

All consecutive patients receiving ifosfamide during an 11-month period were investigated.

All patients were evaluated at each course of ifosfamide treatment. Performance status and laboratory data were registered at the beginning of the first ifosfamide treatment.

For each treatment course, laboratory data, e.g. whole blood count, serum electrolytes, transaminases and serum creatinine, were assessed. During chemotherapy, all co-medication, i.e. other chemotherapeutic agents and supportive medication, were listed. If the patients showed any symptoms of ifosfamide neurotoxicity according to clinical observation, they were registered and graduated according to the NCI-CTC criteria in four levels: grade 1 represented daze or slightly depressive periods, grade 2 neurotoxicity was marked by extensive sleep or agitation, grade 3 toxicity was given in case of heavy depression, beginning hallucinations or stuporous condition and grade 4 encephalopathy was diagnosed in patients with manifest state of hallucinations or coma.

Treatment protocols

Different chemotherapy protocols, each comprising ifosfamide, were used during this study. A minimum of one chemotherapy course was required for inclusion with a maximum of six courses. Reasons for discontinuation of ifosfamide were disease progression, but not ifosfamide side-effects. Table 1 depicts the administered protocols.

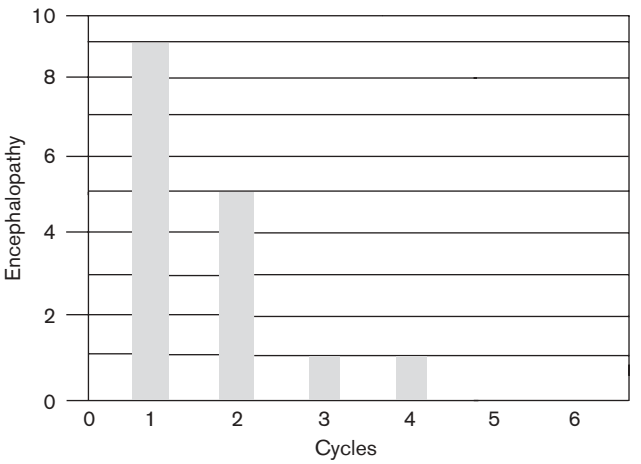
Table 1 Chemotherapy regimen

Chemotherapy regimen	*n*
Doxorubicin/ifosfamide	13
Ifosfamide/carboplatin/etoposide	9
Etoposide/ifosfamide/doxorubicin	11
Cisplatin/etoposide/ifosfamide	4
Ifosfamide/epirubicin/etoposide	11
Other	12

Table 2 Number of treated malignancies and incidence of encephalopathy

Diagnosis	*N*	Encephalopathy (%)
Germ cell tumors	6	4 (80)
Sarcoma	33	10 (30)
Non-Hodgkin's lymphoma	10	1 (10)
CUP	2	0 (0)
Multiple myeloma	6	0 (0)
Others	3	1 (33)

Fig. 1



Appearance of encephalopathy according to treatment cycle.

Results

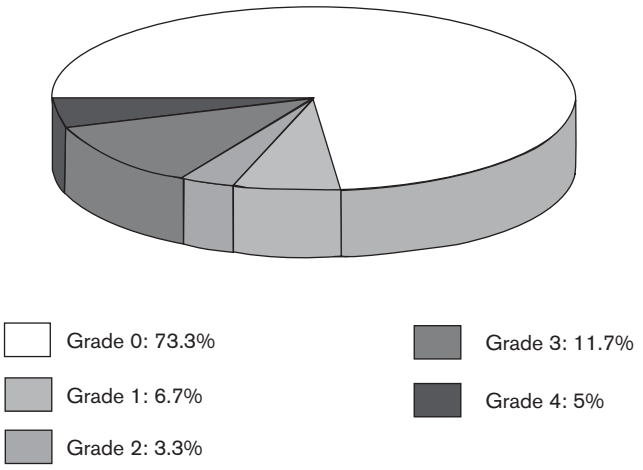
Patient characteristics

Between July 2001 and May 2002, a total number of 60 patients were evaluated. The study population consisted of 32 male and 28 female patients. Median age was 47.5 years (range 19–74). A median of 2 cycles of chemotherapy courses was administered (range 1–6) with a median ifosfamide dosage of 2.8 g (range 1.2–10.6). Thirty one Patients received high-dose ifosfamide (defined as higher dosage than the median of 2.8 g absolute). For detailed characteristics of treated entities, see Table 2.

Incidence and severity of neurotoxicity

Of the patients, 26.6% ($n = 16$) developed neurological symptoms during ifosfamide treatment. Encephalopathy occurred for the first time in 87.5% ($n = 14$) during the first two chemotherapy courses. In courses 3 and 4, only two patients newly developed neurotoxicity, one in each course. In the subsequent cycles, no patient experienced neurological symptoms for the first time (Fig. 1).

Fig. 2



Severity of encephalopathy.

In 56.25% ($n = 9$) of these 16 patients only one episode of neurological complications occurred. In 43.75% ($n = 7$), more than one episode was documented. Six patients (37.5%) had two episodes and one patient (6.25%) had six episodes.

Severity was evaluated as mentioned above. Grade 1 toxicity was documented in 6.7% ($n = 4$); 3.3% ($n = 2$) developed grade 2 toxicity and 11.7% ($n = 7$) grade 3. In 5% ($n = 3$), grade 4 toxicity was seen (Fig. 2).

Correlation of neurotoxicity with patient parameters

Patients who developed encephalopathy tended to be younger than patients without neurological symptoms (38 versus 50 years), but this difference did not reach statistical significance ($p = 0.08$). There was also no statistical difference concerning gender, as there was an equal distribution in the whole group and in the neurotoxicity group (eight female, eight male patients).

Patients who experienced encephalopathy received an absolute median dosage of 2.9 g, the patients without neurological complications 2.8 g ($p = 0.74$, not significant). A similar picture arises when looking at patients who received high (> 2.8 g)- or low (≤ 2.8 g)-dose ifosfamide. There was no statistical difference between young and old patients receiving different amounts of ifosfamide (Table 3).

Table 3 Correlation of age and dosage of ifosfamide

	Standard dose (≤ 2.8 g)		High dose (>2.8 g)	
	≤ 48 years	>48 years	≤ 48 years	>48 years
Without encephalopathy	11	12	9	12
With encephalopathy	5	3	5	3

Discussion

To our knowledge, this is the first large study to evaluate the incidence and severity of ifosfamide-induced encephalopathy in cancer patients. In our collective, the incidence of this side-effect was 26.6% and, thus, similar to that reported in earlier studies. In contrast, the clinical prejudice that a higher amount of administered ifosfamide or older age is correlated with a higher appearance of neurological symptoms cannot be supported. Patients who developed neurotoxicity tended to be younger, although this feature did not reach statistical significance. Also, appearance of encephalopathy was independent of sex, liver and renal parameters (ALT, AST, bilirubin and creatinine). Instead, neurotoxicity showed up independent of all these parameters and mainly during the first 2 cycles. These facts indicate that there seems to be a certain individual predisposition in patients to develop neurological symptoms, especially as every second patient shows more than one episode. Yet we, as others, were unable to identify these predispositions to date.

Otherwise, these data suggest that an adequate amount of ifosfamide can be administered in elderly patients with the same risk as in younger patients and that the fear of neurotoxicity is not a proper argument for withholding aggressive therapy in these patients. We were able to show that even old patients with a higher amount of infused ifosfamide were not at a higher risk of developing encephalopathy than young patients with standard-dose ifosfamide. As, in addition to age, the clinical status of the patient is believed to be a predisposing factor, the performance status of the patient most probably is of importance. However, no conclusion can be drawn out of this study, as only patients with an adequate performance status were included.

As every fourth patient develops signs of neurotoxicity and almost 60% of the patients experienced grade 3 or higher toxicity, this side-effect remains an important clinical problem, both for the treating physician, and also for the patient and his relatives. The scary events of strange behavior, hallucinations or even coma can sometimes lead to terminating treatment by wish of the patient, especially when not correctly informed. In a curative case, these neurological events might be taken into risk, such as nephrotoxicity or cytopenia are; in a purely palliative setting, however, things might look different, as patients sometimes suffer very much from these complications, especially when a higher degree of neurotoxicity appears. Therefore, laboratory or clinical parameters are needed to identify patients at risk and thus initiate proper protective measures. Having such a risk profile would be important as there are two options to

protect the patient from such an unintended effect. First, the use of methylene blue might be considered. Although the protective effect of methylene blue is equivocal, several cases and experimental data suggest a certain benefit [7]. Pelgrims *et al.* [8] reported on a collective of 52 patients with 12 cases of encephalopathy. Three of those patients received methylene blue prophylaxis in the subsequent courses. Two patients had milder neurotoxicity than during the first course and one patient experienced no further neurological side-effects at all. Our data suggest that even without prophylaxis with methylene blue the development of an episode of neurotoxicity is followed by a subsequent episode in only half of all cases. Still, the prophylactic use of methylene blue might be helpful in certain risk groups, but must be further evaluated in randomized trials. Second, it might be better to treat patients with a specific risk profile with an alternative chemotherapeutic agent than ifosfamide if the efficacy is similar.

As a certain risk profile has not been identified to date, the most important task remains to inform the patient and his relatives correctly about this complication. Although this measure cannot prevent neurotoxicity, it might prevent fear and insecurity, and helps to sustain confidence in the physician and the treatment.

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