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Prediction of Ifosfamide/Mesna Associated Encephalopathy

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Abstract—*Ifosfamide and mesna were administered to 77 patients with advanced malignancies. Seven (9%) experienced a severe but reversible encephalopathy. In 56% of patients in whom EEG data was available, characteristic changes were seen with or without mild clinical toxicity. Discriminant analysis identified low serum albumin concentration, high serum creatinine concentration and the presence of pelvic disease as variables which predispose patients to the development of severe encephalopathy. A nomogram has been constructed which can be used to determine the probability that an individual patient may be given ifosfamide and mesna safely. This has important implications for the clinical use of a highly active chemotherapy regimen.*

INTRODUCTION

IFOSFAMIDE (IFX) is an oxazaphosphorine cytotoxic agent which is usually administered intravenously together with sodium 2-mercaptoethane sulphonate (mesna). Mesna combines with 4-hydroxyisophosphamide and acrolein [1] in the efferent urinary tract preventing haemorrhagic cystitis [2,3]. Ifosfamide [4,5] and mesna (Uromitexan Data Sheet) both have central nervous system (CNS) effects. When given together, these agents cause transient confusional states in approximately 5% of patients [6,7].

Recent observations indicate that a characteristic, severe but reversible encephalopathy may be observed in some patient groups [8–10]. Since IFX is active in a variety of malignancies [11], characterisation and predictive indices of associated CNS toxicity are urgently required.

The aims of this study were (1) to determine the incidence and features of electroencephalographic changes associated with IFX/mesna therapy in a range of patients with advanced solid tumours, (2) to correlate EEG changes with clinical manifestations of CNS toxicity, (3) to identify pretreatment patient characteristics predisposing to the development of clinically significant encephalopathy and (4) to devise a simple and reliable predictive index of the risk of encephalopathy for individual patients.

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PATIENTS AND METHODS

The characteristics of 77 patients with progressive locally advanced or metastatic cancer, entered into Phase II trials of single agent or combined IFX/mesna chemotherapy, are summarised in Table 1.

All patients were given a bolus dose of mesna [1.5g/m^2 body surface area (m^2)], followed by IFX (5g/m^2) and mesna (5g/m^2) infusion in 3 l. dextrose saline (4% dextrose with 30 mmol/l sodium chloride) over 24 hr. Further mesna (3.0–3.2g/m^2) was then administered by 4-hourly injection or continuous infusion in 1 l. dextrose saline over 12 hr. A number of patients were treated with combination chemotherapy: 4/7 with sarcoma were given IFX/mesna and Adriamycin (60mg/m^2 bolus); 4/32 with cervical carcinoma received IFX/mesna, Bleomycin (30 mg over 24 hr) and *Cis* Platinum (50 mg/m^2 bolus); all lung cancer patients were treated with IFX/mesna and Mitomycin-C (6 mg/m^2 bolus). Treatment was repeated every 3–4 weeks.

Eight or sixteen channel EEGs were recorded in a standard manner using stick-on electrodes in the international 10–20 electrode placement system. In 30 patients pretreatment EEG records were followed by at least daily recordings for 3 days after the start of treatment. In four further patients EEG

Table 1. Patient characteristics

	Total	(With EEG Data)
Number (N)	77	(34)
Median age	58	(51)
Karnofsky status		
Mean	78	(81)
Range	40–100	(60–100)
Sex		
Female	56	(31)
Male	21	(3)
Disease at presentation		
Cervical cancer	32	(15)
Endometrial cancer	11	(6)
Soft tissue carcoma	7	(7)
Non-small cell lung cancer	27	(6)
Main disease site		
Thorax	40	(10)
Abdomen	11	(8)
Pelvis	38	(19)
Distant lymph nodes	22	(4)
Disease associated weight loss	42	(17)
Smallest lesion > 5 cm dia.	44	(27)
Objective response (WHO Ref)	28	(14)
IFX/mesna chemotherapy only	42	(20)
Other drugs		
Narcotic analgesia	21/56	(10/34)
Phenothiazine	10/56	(7/34)
Benzodiazepine	26/56	(10/34)
Metaclopramide	26/56	(9/34)

monitoring was commenced when grade 3 clinical toxicity was observed.

Pretreatment EEGs were designated as normal (all had well formed alpha activity) or abnormal (presence of small amounts of paroxysmal bilateral fronterotemporal theta activity). Treatment associated EEG recordings and clinical observations of CNS toxicity were graded 0–4 according to the criteria in Table 2. Visual EEG assessments and clinical observations were made independently. The worst EEG or clinical toxicity recorded for each patient was used in all analyses. No further IFX/mesna was given to patients with grade 3 or 4 clinical CNS toxicity.

Analysis of risk factors

Eighteen variables (Table 3) were used in a discriminant function analysis to determine the best weighted combination of pretreatment parameters for classifying patients into one of two groups: those developing minor or no clinical CNS toxicity (grades 0–2 — Group 1), and those developing severe encephalopathy (grades 3–4 — Group 2) requiring careful monitoring. The computer package of Biomedical Programs (BMDP) was used for these analyses [12].

Pretreatment EEGs, creatinine clearance values and data on concomitant drugs were not available for all patients. In preliminary analyses of subgroups for whom they were available, these variables did not contribute to the classification of the patients into the two groups. In 77 patients, sex and the presence of pelvic disease were highly correlated and their predictive value was very similar. In order to provide a classification index with general clinical application, sex was omitted. Eleven variables were used in the final analysis.

Tests of the robustness of the classification function

The performance of the classification index was tested 50 times by classifying random samples of 20% of the patients to either group 1 or 2 using an index derived from data on the remaining 80%. Patient classifications were then compared with observed clinical CNS toxicity.

RESULTS

Electroencephalographic and clinical observations of 34 patients are summarised in Table 4. These observations were highly correlated.

There was no significant association between

Table 2. Clinical and EEG CNS toxicity grading

Grade	EEG recording	Clinical observation
0	Normal	Alert
1	A drop in alpha frequency compared with pretreatment EEG with or without small amounts of paroxysmal theta activity	Transient lethargy
2	Predominant theta activity with or without intermittent delta activity.	Somnolence < 50% of the time and/or mild/moderate disorientation
3	Predominant delta activity with or without sharp (complex wave forms).	Somnolence > 50% of the time and/or severe disorientation, echolalia, perseveration of writing, pallilalia, logorrhoea, hallucinations or delusions
4	Continuous delta activity, complex wave forms and triphasic waves.	Coma

Table 3. Variables used in discriminant function analysis

	Summary of the continuous variables				
		Means			
	No.	All patients	CNS 0–2	Toxicity 3–4	*P*-value (*T*-test)
Creatinine	77	79.2	77.8	91.3	0.28
Urea	77	4.3	4.4	3.9	0.35
Albumin	77	35.0	35.8	28.0	0.00
Haemoglobin	77	12.4	12.5	11.3	0.07
Age	77	53.0	53.3	50.5	0.53
Karnofsky stat	77	77.9	78.6	72.5	0.20
Creat clearance	55	69.4	72.0	54.1	0.06

	Summary of other variables				
		No. patients			
	Total No.	Whole Group	CNS-Toxicity 0–2	3–4	*P*-value (Chi 1DF)
Sex (females)	77	56	48	8	0.16
Weight loss	77	42	37	5	0.92
Response	77	28	24	4	0.65
Pelvic disease	77	38	31	7	0.06
Bulky disease	77	44	37	7	0.15
IFX alone	77	42	37	5	0.92
Narcotics	56	21	17	4	0.69
Phenothiazine	56	10	8	2	0.94
Benzodiazepine	56	26	22	4	1.00
Metaclopramide	56	26	22	4	1.00
Baseline EEG (Abnormal)	30	10	9	1	1.00

Table 4. Observed frequency table of EEG and clinical observations

Clinical toxicity	Treatment EEG grading					
	0	1	2	3	4	Total
Grade 0	8	7	6	1	0	22
Grade 1	0	0	1	2	0	3
Grade 2	0	0	0	0	2	2
Grade 3	0	0	0	0	3	3
Grade 4	0	0	0	0	4	4
Total	8	7	7	3	9	34

Correlation (Goodman and Kruskal's gamma [14,15]) = 0.993.

EEGs recorded before and during treatment. Features of grade 3–4 EEG toxicity developed 12–24 hr before grade 3–4 clinical CNS toxicity. Electroencephalographic improvement preceded clinical improvement by 24–48 hr in all recovering cases. Seven of the 77 patients (9.09%) developed grade 3–4 clinical CNS toxicity with clinical features which were consistent with previous descriptions [8,9].

Stepwise discriminant analysis

There was no evidence that pre-treatment EEG observations predict the development of clinical encephalopathy either from their correlation or from the discriminant analysis. There was no evidence that concomitant medication is related to the development of encephalopathy.

Before any variable was entered into the discriminant function, the 'F-to-enter' was calculated for each variable. At this stage ('step 0'), the F-to-enter for a variable corresponds to the F statistic computed from a one-way analysis of variance of the variable for groups 1 and 2. The variable with the highest F-to-enter value, therefore, represents the single most predictive pretreatment parameter for classification of patients into group 1 or 2. Using data from all 77 patients, the variable with the highest F-to-enter at 'step 0' was serum albumin concentration [F-to-enter (1,75) = 15.9]. This variable was entered into the classification function equation at 'step 1'. Subsequent steps computed the F-to-enter for each remaining variable in combination with serum albumin concentration and entered serum creatinine concentration [F-to-enter (1,74) = 5.9] at step 2 and the presence of pelvic disease [F-to-enter (1,73) = 4.5] at step 3. At the end of step 3 none of the remaining variables could significantly improve discrimination between groups 1 and 2.

Weights for serum albumin concentration, serum creatinine concentration, the presence of pelvic disease and constants derived from the analysis were used to determine 'classification scores' (S1 and S2) for each patient:

$$S1 = (\text{score for patient classification into group 1 [0–2 clin. toxicity)} = -31.3381 + 1.1650 \times [\text{albumin}] + 0.1527 \times [\text{creatinine}] + 5.2841 \times (\text{pelvic value})$$

and

$$S2 = (\text{score for patient classification into group 2 [3–4 clin. toxicity]} = -28.5367 + 0.8398 \times [\text{albumin}] + 0.2055 \times [\text{creatinine}] + 7.1589 \times (\text{pelvic value}),$$

where the pelvic value for a patient without a pelvic lesion is 1 and with a pelvic lesion is 2. Albumin measured in g/l, creatinine measured in μmol/l.

Each of the patients was classified into the group for which they had the highest score (Table 5).

Results of random testing of the robustness of the classification function

In 35 of the 50 20% random samples, the function correctly classified all patients with observed grade 0–2 clinical toxicity to group 1. In 11/50 samples 90%, and in 6/50 samples 50–80%

Table 5. Patient classifications using classification scores S1 and S2

Clinical observation	Classification Group 1 (grade 3–4 clin. toxicity)	Group 2 (grade 0–2 clin. toxicity)
Grade 3–4	6	2
Observed grade 0–2	10	59
Predictive value of test	37.5%	96.7%

of patients with observed grade 0–2 toxicity were correctly classified. The sensitivity of classification into group 2 was 100% in 36/50 samples, 50–99% in 8 samples and less than 50% in the remainder.

Calculation of probability

Using classification scores, the probability of an individual patient developing grade 0–2 rather than grade 3–4 clinical CNS toxicity may be calculated:

$$\text{Probability of grade 0–2 toxicity} = \frac{e^{S1}}{e^{S1} + e^{S2}}.$$

In the clinical setting, this function may be performed using the nomogram shown in Fig. 1.

DISCUSSION

Severe clinical CNS toxicity is observed in 9% of patients treated with 36 hr IFX/mesna infusion as described. Electroencephalographic abnormalities with or without mild clinical CNS toxicity develop in a further 56% of patients treated with IFX/mesna. These observations have not previously been made and they define a spectrum of CNS toxicity ranging from pre-clinical characteristic EEG changes to florid clinical symptoms. This indicates that the drug reaction is not idiosyncratic.

Clinical CNS toxicity is highly correlated with the development of EEG features of generalised cortical disturbance. These studies therefore suggest that IFX/mesna causes a type of metabolic encephalopathy and this provides clues regarding the mechanism of toxicity.

The pretreatment EEG does not predict the development of encephalopathy with IFX/mesna treatment. Other drugs with known CNS effects and commonly used in the treatment of cancer (narcotic analgaesia, benzodiazepines, phenothiazines and metaclopramide) appear to have no influence upon the development of CNS toxicity. Nevertheless, these drugs should be used cautiously in patients with established encephalopathy since the mechanism of toxicity remains unclear.

The discriminant function analysis has identified low serum albumin concentration, high serum creatinine concentration and the presence of pelvic tumour as pretreatment parameters which increase the risk of severe encephalopathy. The probability of not developing severe encephalopathy may be ascertained for individual patients using the nomogram (Fig. 1). This prediction gives a correct classification in at least 96% of cases (Table 5). This has important clinical implications since

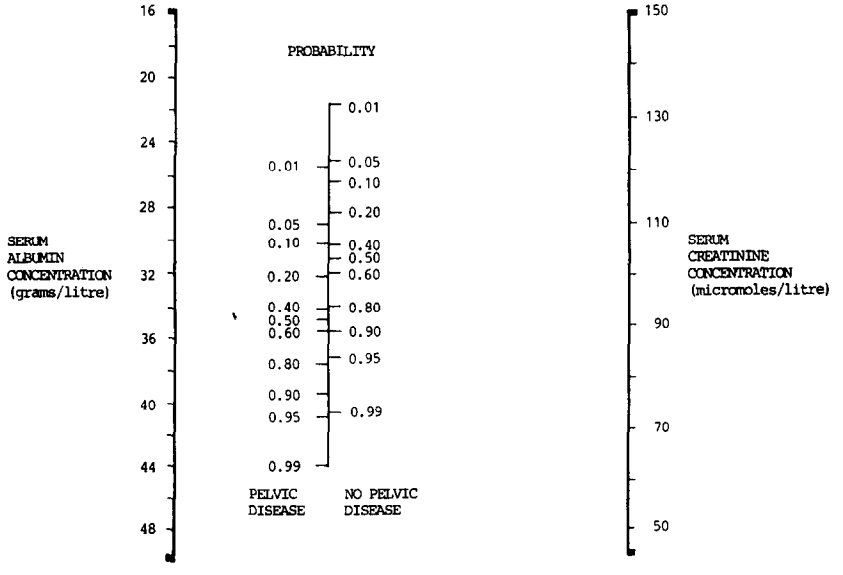

Fig. 1. Nomogram to determine probability of not developing grade 3–4 clinical CNS toxicity with ifosfamide/mesna 36 hr infusion. The probability that a patient will **NOT** *develop severe CNS toxicity falls on the intersection of a straight line joining their serum albumin and serum creatinine concentrations on the appropriate pelvic disease scale.*

IFX/mesna may be given confidently when grade 0–2 toxicity is predicted.

Low serum albumin concentrations may reflect a neoplasia associated catabolic state or hepatocellular insufficiency. Ifosfamide is metabolised in the liver [13] and hepatic impairment may cause qualitative or quantitative alterations in ifosfamide pharmacokinetics. The analysis indicates that impaired renal function predisposes to IFX/mesna encephalopathy and infers that the causative agent is metabolised by or excreted through the kidneys. The presence of pelvic cancer is often associated with minor degrees of obstructive nephropathy and in some cases, markedly low serum albumin concentrations may also contribute to renal impairment by reducing glomerular filtration rate.

This study permits a rational approach to the pretreatment assessment of risk for the development of an important IFX/mesna side effect. Accurate prediction of encephalopathy facilitates the management of patients with tumours amenable to IFX/mesna therapy and should permit these agents to be used in a wider range of malignancies, including gynaecological cancer.

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