Eur J Cancer, Vol. 27, No. 9, pp. 1188–1189, 1991.
Printed in Great Britain
0277–5379/91 $3.00 + 0.00

Ifosfamide-related Acute Encephalopathy: Clinical and Radiological Aspects

Ofer Merimsky, Moshe Inbar, Irith Reider-Groswasser, Moshe Scharf and Samario Chaitchik

IFOSFAMIDE and the uroprotector mesna have been used in the treatment of various types of malignancies. Side-effects of ifosfamide include nausea and vomiting, myelosuppression, renal tubular acidosis and renal failure, interstitial pneumonitis, congestive heart failure and central nervous system (CNS) toxicity [1]. In our small group of patients CNS toxicity was observed in 5/18 (28%), 2–7 days following the first day of ifosfamide/mesna administration. The frequency of CNS toxicity ranges from 0% [2] to over 30% [1]. There was a wide spectrum of neurological manifestations in our patients (Table 1).

All the patients had evidence of disease progression before ifosfamide/mesna was given. None had any symptom of brain metastases or any neurological, mental or cognitive dysfunction, nor did they have any biochemical disturbance before treatment. The two drugs were administered together in 2000 ml NaCl 0.9% per day, by continuous intravenous drip. Metoclopramide (60–120 mg/day), furosemide (40–80 mg/day) and KCl supplement were also given.

Since only ifosfamide administration was common to all our patients, and the clinical presentation of CNS toxicity in every case was similar to previous reports, we related the neurological symptomatology to ifosfamide and not to any other drugs.

Table 1. Patients' data

No. (sex/age)	Primary tumour stage	Previous treatments; results	KPS (%)	Treatment daily (g/m²) × no. of days	CNS toxicity: Time to toxicity (day); effects	Metabolic alterations*	Outcome
1 (F/50)	Ovary IV	9 × CAP; PR 14 × melphalan; PR Abdominopelvic irradiation; PD 3 × LHRH agonists; PD	80	IFO 5 × 1 day M 5 × 1 day	2; personality changes, pathological reflexes, papilloedema, coma, normal brain CT	BUN=46 creat=3.4 alb=23 Ca^{2+}=4.9 Mg^{2+}=0.55	Fatal within 7 days
2 (F/49)	Ovary IIIc	2 × CP; PD	80	IFO 5 x 1 day M 5 × 1 day	5; personality changes, hemisyndrome, coma, grand-mal seizures, hyperreflexia, pathological reflexes, normal brain CT	BUN=84 creat=7.4 alb=18 Ca^{2+}=7.5 HCO^{-}_{3}=15.7 pH=7.36	Fatal within 7 days
3 (F/73)	Endometrial stromal sarcoma IV	None	80	IFO 2 × 4 day M 2 × 4 day VP16	7; personality changes, incontinence, brain CT: mass	creat=1.4 alb=21 Ca^{2+}=12.5 HCO^{-}_{3}=17.3 K^{+}=2.1 pH=7.32	Recovered
4 (F/64)	Leiomyo-sarcoma of colon IV	None	90	IFO 1.8 × 4 days M 1.8 × 4 days VP16	4; personality changes, incontinence, logorrhoea, normal brain CT	alb=26 K^{+}=2.9 Ca^{2+}=11.5 HCO^{-}_{3}=18.1 pH=7.33	Recovered
5 (M/56)	NHL in abdomen IV	6 × COPBLAM; PR	90	IFO 1 × 5 days M 1 × 5 days MTX	7; headache, behavioural changes, coma, normal brain CT	alb=32 K^{+}=2.3 creat=1.2 BUN=24 Ca^{2+}=8.5	Fatal within 12 days

CAP= cyclophosphamide/doxorubicin/cisplatin; CP= cyclophosphamide and cisplatin; COPBLAM= cyclophosphamide/oncovin/prednisone/bleomycin/doxorubicin/procarbazine, every 21 days; IFO= ifosfamide, M= mesna, VP16= etoposide 100 mg/m²/day on days 1,3, 5, MTX= methotrexate 20 mg/m²/day on day 3 and NOV= novantrone 10 mg/m²/day on day 8. NHL= non-Hodgkin lymphoma (diffuse mixed, small and large), KPS= Karnofsky performance status, PR= partial response and PD= progressive disease. BUN= blood urea nitrogen (normal 5–25 mg/dl), creat= creatinine (0.7–1.4 mg/dl), alb= albumin (35–50 g/l), K^{+} (3.5–5.3 mmol/l), Ca^{2+} (8.5–10.5 mg/dl); Mg^{2+} (1.7–2.4 mg/dl) and HCO^{-}_{3} (22–28 mEq/l).

* Major metabolic abnormalities: patient 1, on 4th day from diagnosis of encephalopathy; 2, on 5th day; 3, on 4th day; 4 on 2nd day and 5 on 9th day.

The precise aetiology of ifosfamide-related CNS toxicity has not yet been determined. Theories include accumulation of ifosfamide degradation products (chloroacetaldehyde, a chloral-hydrate-like substance), electrolyte and pH abnormalities in brain tissue, concomitant use of psychotropic drugs, water intoxication due to overhydration, or action of antidiuretic-hormone-like substances [1]. Other suggestions are inappropriate arginine vasopressin secretion [3], disturbance of a central neurotransmitter system by mesna-aggravated albumin binding of copper or iron or effects of tumour lysis on brain tissue [4]. We found no relation between response to treatment and development of toxicity or encephalopathy. Thus, tumour lysis did not appear to be the reason for CNS toxicity.

The reported, statistically significant risk factors for neurotoxic effects are poor performance status, creatinine higher than 1.5 mg/dl, pretreatment bicarbonate below 15 mEq/l [5] and female gender with bulky disease [6]. Other risk factors include previous treatment with cisplatin [7], low serum albumin [8] and rapid infusion rate of ifosfamide [4]. In our series, 4 patients were women with bulky disease confined to the lower abdomen and pelvis. The 2 patients who had previously had cisplatin were treated with a high dose of ifosfamide over a short period (5 g/m^2 over 24 h) and consequently had a fatal outcome.

Episodes of ifosfamide-related CNS toxicity are usually reversible [1, 7], especially when the drug is given in a fractionated regimen [9]. 2 of our 3 fatalities occurred when ifosfamide was given over 1 day.

Computed tomography (CT) of the scans was normal, except in 1 patient who also had a pre-existing solitary asymptomatic metastasis. Morphometric studies showed no correlation between the severity of the encephalopathy and the width of the ventricles and the sulci. The significance of this finding is that the clinical picture is related not to brain atrophy nor to structural changes, but rather to toxic or metabolic effects.

Additional findings in our series included pancytopenia in all the patients, appearing after the onset of encephalopathy and causing further deterioration. The 2 women who were given a 24 h infusion of ifosfamide developed hypocalcaemia, and those 2 women who received a fractionated schedule developed hypercalcaemia.

The management of CNS toxicity included interruption of treatment immediately neurological impairment was diagnosed, avoidance of CNS depressants including anti-emetics, tranquilisers, narcotics and antihistamines, correction of pH and electrolyte imbalance [9] and supportive treatment [1].

We suggest use of a fractionated schedule for ifosfamide, especially in women with abdominal mass and/or previous treatment with cisplatin to minimise the risk of encephalopathy. Immediate interruption of ifosfamide is warranted whenever neurological impairment is observed. Other causes for CNS symptoms should also be excluded.

Correspondence to O. Merimsky.
O. Merimsky, M. Inbar and S. Chaitchik are at the Department of Oncology, I. Reider-Groswasser is at the Section of Neuroradiology and M. Scharf is at the Department of Neurology, Ichilov Hospital, 6 Weizman Street, Tel-Aviv 64239, Israel.
Revised 2 May 1991; accepted 16 May 1991.

1. Elias AD, Eder P, Shea T, Begg CB, Frei E, Antman KH. High dose ifosfamide with mesna uroprotection: a phase I study. *J Clin Oncol* 1990, **8**, 170–178.
2. Shepherd FA, Goss PE, Latreille J, *et al.* A phase II study of ifosfamide, cisplatin, etoposide in patients with advanced non-small cell lung cancer: a preliminary report. *Semin Oncol* 1990, **17** (Suppl. 4), 19–23.
3. Cantwell BMJ, Idle M, Millward MJ, Hall G, Lind MJ. Encephalopathy with hyponatremia and inappropriate arginine vasopressin secretion following an intravenous ifosfamide infusion. *Ann Oncol* 1990, **1**, 232.
4. Osborne RJ, Slevin ML. Ifosfamide mesna and encephalopathy. *Lancet* 1985, **i**, 1398–1399.
5. Antman KH, Elias A, Ryan L. Ifosfamide and mesna: response and toxicity at standard and high dose schedules. *Semin Oncol* 1990, **17** (Suppl. 4), 68–73.
6. Meanwell CA, Blake AE, Blackledge G, *et al.* Encephalopathy associated with ifosphamide/mesna therapy. *Lancet* 1985, **i**, 406–407.
7. Pratt CB, Green AA, Horowitz M, *et al.* Central nervous system toxicity following treatment of pediatric subjects with ifosfamide/mesna. *J Clin Oncol* 1986, **4**, 1253–1261.
8. McCallum AK. Ifosfamide/mesna encephalopathy. *Lancet* 1987, **i**, 987.
9. Zalupski M, Baker LH. Ifosfamide. *J Natl Cancer Inst* 1988, **80**, 556–566.

Eur J Cancer, Vol. 27, No. 9, pp. 1189–1190, 1991.
Printed in Great Britain
0277-5379/91 $3.00 + 0.00

A Phase I Study of Regionally Administered Mitomycin Microcapsules for Patients with Colorectal Liver Metastases

John H. Anderson, Jacqueline A. Goldberg, John G. Eley, Tony L. Whateley, David J. Kerr, Timothy G. Cooke and Colin S. McArdle

INTRAHEPATIC ARTERIAL administration of mitomycin may be effective in patients with colorectal liver metastases [1]. However, although hepatic arterial infusion of mitomycin produces a 2.5–3.6 fold increase in liver mitomycin concentration compared with intravenous delivery, hepatic extraction is only 23% and peripheral venous mitomycin concentrations remain high and potentially toxic [2].

Kato *et al.*, therefore, incorporated the drug into ethylcellulose microcapsules [3]. Arterial administration of these particles (diameter 250 μm) causes infarction of tumour by embolising in small arterioles where mitomycin is released. Tumours of

Correspondence to J.H. Anderson.
J.H. Anderson, J.A. Goldberg, T.G. Cooke and C.S. McArdle are at the University Department of Surgery, The Royal Infirmary, 10 Alexandra Pde, Glasgow, G31 2ER; J.G. Eley and T.L. Whateley are at the Department of Pharmacy, Strathclyde University; and D.J. Kerr is at the CRC Department of Medical Oncology, Glasgow University, Glasgow, U.K.
Revised 24 Apr. 1991; accepted 25 Apr. 1991.