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.

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

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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

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kidney, liver, bone and pelvis were treated with 10–75 mg mitomycin, resulting in a 70% response rate. Systemic toxicity was mild, consisting of transient myelosuppression in 30% of patients. Furthermore, Suguita *et al.* reported a 35% partial response rate in 32 patients with hepatocellular carcinoma [4].

However, these studies did not contain any patients with colorectal liver metastases. Our aim, therefore, was to evaluate the maximum tolerated dose of regionally administered, mitomycin-loaded ethylcellulose microcapsules in patients with biopsy-proven colorectal liver metastases.

At laparotomy, a gastroduodenal artery cannula (internal diameter 1.2 mm) was secured with its tip flush with the hepatic artery, thereby not compromising hepatic arterial flow. All hepatic arterial branches supplying extrahepatic organs were ligated and divided and the gallbladder was removed. The catheter was then flushed with methylene blue to ensure that substances delivered via the catheter were only distributed to the liver and that both lobes were perfused.

Mitomycin was encapsulated in ethylcellulose [5]. 20 mg mitomycin solution may be administered, via the hepatic artery, with minimal toxicity [5]. Microcapsules containing 20 mg mitomycin were used, therefore, as the starting dose for this phase I study.

15 patients entered the study (11 men, 4 women). Mean age was 56 years (range 39–73). Due to the size of the ethylcellulose microcapsules (250 μm), and their tendency to clump in saline despite vigorous shaking, considerable force was frequently required to deliver the microcapsules through the catheter. The first 6 patients were given 20 mg microencapsulated mitomycin. The next 6 patients received 30 mg and the final 3 received 40 mg.

Each patient underwent full clinical assessment and venous blood was sampled for full count, urea and electrolytes, serum amylase and liver function daily for the first week after treatment and weekly thereafter for the next 2 months. Other investigations were arranged when clinically indicated. Toxicity was graded according to WHO criteria.

Haematological and biochemical results are summarised for each dose level in Table 1. There was no evidence of myelosuppression, mucositis, renal failure or alopecia in any patient. The only patient with thrombocytopenia had suffered a major postoperative haemorrhage from severe oesophagitis. Liver enzymes rose on the first day following treatment and returned to normal within a month. This was not accompanied by clinical evidence of hepatic failure. 5 patients experienced local toxicity: pancreatitis ($n = 3$) and gastroduodenal ulceration ($n = 2$). All patients responded to conservative treatment.

Our previous pharmacokinetic studies have shown a favourable profile following regional administration of microencapsulated mitomycin compared with bolus arterial delivery of free drug [5]. These results were confirmed by the absence of systemic toxicity in the present study following doses of up to 40 mg of intrahepatic arterial microcapsulated mitomycin. We did not attempt to escalate the mitomycin dose further because of the local complication rate. We suspect that extrahepatic organs, in particular stomach and pancreas, were perfused with mitomycin microcapsules despite meticulous surgical technique and perfusion studies; this may have arisen from the force required to inject the particles resulting in their retrograde flow to the coeliac artery. However, the use of smaller microcapsules may overcome the problems associated with this preparation and also permit repeated doses postoperatively. We are investigating new formulations with a variety of encapsulating compounds in an attempt to improve the efficacy of this promising innovation.

Table 1. Blood test results before and after treatment

	Mitomycin (mg)		
	20 ($n = 6$)	30 ($n = 6$)	40 ($n = 3$)
WBC × 10^6/l			
Pre	7 (5–10)	9 (6–22)	12 (10–13)
Post*	7 (3–9)	7 (6–12)	9 (7–11)
Platelets × 10^9/l			
Pre	352 (174–376)	339 (281–632)	484 (478–489)
Post*	232 (147–270)	237 (180–302)	202 (59–345)
Creatinine μmol/l			
Pre	85 (80–110)	90 (60–100)	60 (50–70)
Post†	100 (100–200)	100 (85–110)	80 (70–85)
AST U/l			
Pre	48 (16–72)	21 (14–63)	67 (52–82)
Post†	233 (145–1540)	410 (232–610)	1295 (1150–1440)
ALT U/l			
Pre	26 (18–95)	16 (11–32)	33 (29–36)
Post†	101 (68–970)	270 (118–630)	465 (350–580)

Median (range).
* nadir; † peak.
WBC = white blood cells, AST = aspartate and ALT = alanine aminotransferase.

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Correction

Internalisation of the Bowman-Birk protease inhibitor by intestinal epithelial cells.—In this article by Dr P. C. Billings *et al.* (Vol. 27, 903–908), the photomicrographs in Fig. 4 should have appeared as Fig. 6, and vice versa. The figure legends are correct.