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A clinical and pharmacological study of high-dose mitozolomide given in conjunction with autologous bone marrow rescue

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Summary. In conjunction with autologous bone marrow rescue, high-dose mitozolomide was given i.v. to 16 patients with refractory malignancies at doses ranging from 100 to 400 mg/m^2 over 1 h. Neutropaenia occurred consistently at 300 mg/m^2, and three trivial infective episodes were recorded. Thrombocytopaenia occurred consistently at 150 mg/m^2, and three patients experienced episodes of minor bleeding. The death of one subject was attributable to pulmonary thromboembolism during the bone marrow reinfusion. Transient emesis and mild alopecia were the only other toxicities. Three of six evaluable patients receiving $\geq$300 mg/m^2 exhibited measurable reductions in tumour dimensions, although these failed to fulfil the criteria for a partial response. Mitozolomide was undetectable in plasma at 12 h after drug administration. The plasma pharmacokinetic data fitted mono- or biexponential models in all patients. Model-independent pharmacokinetic parameters were: peak plasma drug concentration, 3.4–46 mg/l; AUC, 8–82 mg h l^{-1}; clearance, 7.6–45 l/h; steady-state volume of distribution, 11–85 l; and plasma elimination half-life, 1.4–2.8 h. Dose-dependent pharmacokinetics were not observed, and only a small percentage of the delivered dose was eliminated unchanged in the urine. The maximally tolerated dose of mitozolomide given with autologous bone marrow rescue was >400 mg/m^2. At this dose myelosuppression was the only major toxicity, and the plasma drug levels and AUC values were comparable to those obtained after therapeutic doses in experimental models.

Introduction

The measurement of therapeutic effect is usually a secondary consideration in phase I clinical studies of antitumour cytotoxics in which the main aim is to establish the maximally tolerated dose (MTD). Notwithstanding definite endpoints set out in study protocols, the MTD depends on the amount of toxicity the patients and physician are willing and able to tolerate [2], which is strongly influenced by the expected outcome of the treatment. Patients and physicians may accept potentially lethal toxicity when there is a real prospect of cure and considerable morbidity if prolonged survival is a possible outcome. The responses achieved in phase I studies are rarely sufficient to prolong survival, and physicians are thus properly reluctant to inflict severe morbidity on their patients simply to define the MTD; therefore, the MTDs upon which phase II studies of clinical efficacy are based tend to represent conservative estimates. Since most phase II studies are conducted on tumours that are relatively insensitive to chemotherapy and the drug may be given at suboptimal doses, some potentially useful anticancer agents may be consigned to oblivion without being subjected to adequate testing.

Cytotoxics in clinical use are often given at doses higher than the MTDs of their phase II studies. For some agents such as cisplatin and methotrexate, this is due to the discovery of techniques that ameliorate their dose-limiting toxicities, i.e. intravenous hydration and folinic acid rescue. Myelosuppression is a common dose-limiting toxicity, and the use of autologous bone marrow rescue has enabled the doses of myelosuppressive drugs such as carmustine and melphalan to be escalated many-fold before the next dose-limiting toxicity is encountered.

The novel antitumour imidazotetrazine, 8-carbamoyl-3-(2-chloroethyl)imidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one (mitozolomide) was first synthesised by Stevens et al. in 1984 [21]. Its curative activity in murine tumour models [11] and its activity against human tumour xenografts [3] appears to occur by virtue of a decomposition product, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MCTIC), which forms DNA cross-links [5, 6]. Phase I clinical trials [12, 16] have identified delayed thrombocytopaenia as the dose-limiting toxicity. There were no other major toxicities. The dose recommended for phase II stud-

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ies was 90 mg/m^2 (for previously treated patients) and 100 mg/m^2 (for previously untreated subjects) given intravenously every 21 days. The results of phase II clinical studies carried out in malignant melanoma [9, 20], ovarian adenocarcinoma [10] and renal carcinoma [23] at these dose levels have been disappointing because of poor antitumour activity and severe unpredictable thrombocytopaenia. Delayed myelosuppression, the absence of major non-haematological toxicity, and a short elimination half-life are highly suitable features for drug administration in conjunction with autologous bone marrow rescue. This report describes a clinical and pharmacological study in which the dose of mitozolomide was escalated using concomitant autologous bone marrow rescue to reduce the effects of myelosuppression, the intention being to define the toxicities, pharmacokinetics and antitumour activity of high-dose mitozolomide.

Patients and methods

Patients. To be eligible for this study, patients of either sex were required to have an age of 21–65 years, pathologically confirmed malignancy that was refractory to conventional modes of treatment, a modified Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, a life expectancy of >3 months, assessable disease, no previous chemotherapy or radiotherapy, no bone marrow involvement, no significant intercurrent illness, a peripheral-blood WBC of $\geq 3.5 \times 10^9$/l, a peripheral-blood platelet count of $\geq 100 \times 10^9$/l, plasma creatinine levels of ≤ 100 μmol/l and creatinine clearance values of ≥ 90 ml/min.

Treatment. Mitozolomide was supplied by Rhone Pouleuc New Zealand Ltd. as a powder in glass vials containing 200 mg. It was dissolved in dimethylsulphoxide (6 ml), diluted to 1000 ml with sterile 0.9% sodium chloride (w/v), and given by continuous intravenous infusion over 1 h immediately after the completion of a bone marrow harvest. Patients were prehydrated and forced diuresis was maintained until the autologous bone marrow rescue had been given. Prior to mitozolomide administration, approximately 2×10^8 nucleated bone marrow cells/kg body weight were extracted from the iliac crests through multiple puncture sites with the patients under general anaesthesia. Blood taken with the marrow was replaced with packed cells during the procedure. The marrow was stored until 18 h after drug administration, at which time it was reinfused via a peripheral vein. Each patient received a single treatment with mitozolomide. The starting dose was that recommended for phase II studies (100 mg/m^2), and it was raised in 50-mg/m^2 steps. Three subjects were treated at each incremental step.

Toxicity and response. Toxicity was graded according to WHO criteria [15]. Tumour responses were defined as follows: complete response, the complete disappearance of all detectable disease; partial response, a decrease of at least 50% in the sum of the products of perpendicular diameters of all measurable lesions; and improvement, an objective measurable decrease in the size of lesions that falls short of the criteria for a partial response. These responses were scored on the basis of at least two measurements made at least 4 weeks apart. Progressive disease was defined as a measurable enlargement of existing lesions or the appearance of new lesions.

Sample collection. For drug analysis, peripheral venous blood samples were drawn from an indwelling intravenous catheter at 0, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12 and 24 h after drug administration. They were collected in glass tubes containing 0.5 ml 3.14% sodium tricitrate (w/v) and centrifuged at 3000 rpm for 5 min. The plasma was removed and acidified with 50 μl 6 M HCl/ml. Urine was collected for 24 h following drug administration, acidified [20 ml 50% HCl (v/v)] and maintained at 4° C during the collection period. Urine and plasma samples were stored at −20° C until analysis.

Table 1. Patients' characteristics

Patients entered	16
Evaluable patients	15
Median age	47 (range, 30–65) years
Sex:	M 12 F 4
Median performance status	1 (range, 0–2)
Tumours:	
Adenocarcinoma of the large bowel	5
Carcinoma of the bronchus:	
Large-cell undifferentiated	2
Squamous-cell	2
Squamous-cell carcinoma of the urethra	1
Transitional-cell carcinoma of the urethra	1
Renal-cell carcinoma	1
Malignant melanoma	1
Leiomyosarcoma of the stomach	1
Malignant fibrous histiocytoma	1
Carcinoma of unknown primary origin (cerebral metastases)	1

Drug analysis. The method applied for the extraction and quantitation of mitozolomide in plasma was essentially that of Slack and Goddard [19], except that no internal standard was used and only 0.5 ml plasma was taken. Calibration was accomplished using duplicate recoveries of drug in plasma at 2 and 5 mg/l and applying the recovery factors of the experimental data. A standard curve was run, with each batch of plasma being analysed to confirm the linearity of response and the data being analysed by least-squares regression ($r > 0.9995$). Because of the known instability of mitozolomide in aqueous media, the frozen samples were thawed and vortex-mixed to homogeneity and a 0.5-ml aliquot was dispensed and prepared for chromatographic analysis within 2 h. A 100×5 mm Waters RCM cartridge (10-μm particle size, C_{18}) was used with a Waters C_{18} precolumn. The mobile phase was 5% acetic acid in water (v/v) and methanol (3 : 7) pumped at 1 ml/min. Injection was either manual (Waters U6K injector) or automated (Waters 715 Ultrawisp), and detection was carried out at 325 nm using a Waters 490 UV detector. The injection volume was 50 μl, as this enabled duplicate samples. Recoveries averaged 85.5% (SD, 8.3%) and the results of duplicate analyses varied by ±2%.

Data analysis. The chromatograms were recorded on a strip-chart recorder or an HP 3393 integrator from which the detection-signal peak heights were measured. The average peak height of duplicate samples was calculated and sample mitozolomide concentrations were read off the standard curve. The pharmacokinetic parameters were estimated by a noncompartmental method based on statistical moment theory [7] using a pharmacokinetic modelling programme (MK-MODEL) capable of calculating pharmacokinetic parameters in the presence of zero-order drug-input kinetics (e. g. continuous intravenous infusion). The area under the concentration vs time curve (AUC) and the area under the first moment curve (AUMC) were calculated by the trapezoid rule when successive values were increasing and by the logarithmic trapezoid rule when successive values were decreasing, and were then extrapolated to infinity. The apparent volume of distribution at steady state was determined by dividing the product of the dose and the AUMC by the square of the AUC. The slope of the terminal phase of the semilogarithmic concentration-time curve was used to calculate the plasma elimination half-life ($t_{1/2} = \log_e 2/\text{slope}$), and the plasma clearance was calculated by dividing the dose by the AUC. Mono- and biexponential models were constructed for the observed pharmacokinetic data using MK-MODEL, which applies the extended least-squares method and calculates an index of fit that enables models to be compared. Correlations between the pharmacokinetic parameters and the dose were analysed by linear regression, and the significance of differences in pharmacokinetic parameters was assessed

Table 2. Haematological toxicity

Dose (mg/m^2)	Neutrophil count of $<2 \times 10^9/l$			Platelet count of $<100 \times 10^9/l$		
	Number/number treated	Nadir	Duration (days)	Number/number treated	Nadir	Duration (days)
100	0/3	–	–	1/3	–	–
150	0/3	–	–	2/3	75 (175–68)	5 (0–15)
200	1/3	–	–	3/3	18 (34–17)	13 (9–14)
300	1/2	1.3 (2–0.6)	6 (0–13)	2/2	16 (16–16)	5 (2– 9)
350	3/3	0.9 (1–0.3)	25 (7–28)	3/3	28 (18–50)	15 (13–19)
400	1/1	0.8	22	1/1	17	16

Ranges are shown in parentheses

using Student's *t*-test [22]. This study was approved by the Wellington Hospital Ethical Committee.

Results

Patients

Each of 16 patients received one course of treatment; their characteristics are shown in Table 1. In all, 15 subjects were evaluable for response and toxicity and 1 patient was unevaluable because of early death, which occurred under the following circumstances. A 58-year-old man underwent an uneventful bone marrow harvest followed by administration of 400 mg/m^2 mitozolomide. As the bone marrow was being reinfused, he complained of tightness in the chest and underwent cardiac arrest. Echocardiography revealed massive dilatation of the right side of the heart consistent with pulmonary embolism. Resuscitation was started immediately after cardiac arrest, but the patient remained pulseless and deeply cyanosed for 45 min, after which there was an abrupt return of spontaneous heart beat and good skin perfusion. Repeat echocardiography showed a marked reduction in the right heart dilatation, suggesting that the pulmonary embolus had become dislodged. Prolonged hypoxia and hypotension led to brain damage and renal failure. At 11 days after treatment, the patient became neutropaenic and thrombocytopaenic. He died on day 17, exhibiting clinical evidence of bronchopneumonia. Subsequent necropsy revealed a blood clot in the peripheral pulmonary blood vessels.

Toxicity

The haematological toxicity encountered in the present study is shown in Table 2. Only one of nine patients receiving <300 mg/m^2 mitozolomide became transiently neutropaenic (neutrophil count, $<2 \times 10^9/l$). Neutropaenia was seen more consistently as the drug dose was increased to >300 mg/m^2. The recorded nadir counts did not correlate with the drug dose. There were three infectious episodes in evaluable patients: a small pustule at the site of insertion of an intravenous cannula, a transient episode of oral moniliasis and a urinary tract infection in a patient with an indwelling catheter. With a single exception, all subjects treated with ≥ 150 mg/m^2 became thrombocytopaenic, but this was not related in severity or duration to the dose of drug. Two patients displayed minor epistaxis that resolved spontaneously during periods of thrombocytopaenia. Another subject developed extensive bruising associated with platelet counts in the range of $20-30 \times 10^9/l$ but was in renal failure at that time, exhibiting a plasma creatinine value of 200 μmol/l (upper limit of normal, 120 μmol/l).

Nine patients experienced nausea and vomiting. Mitozolomide infusion was started immediately after the bone marrow harvest; thus, patients were also recovering from general anaesthesia, which may have contributed to their emesis. One subject vomited intermittently for 3 days, but the other eight vomited only on the day of treatment and this was controlled by prochlorperazine and metoclopramide. Nausea persisted for 3 days in two patients, for 2 days in three cases and for 1 day in three subjects. Neither the severity nor the duration of nausea and vomiting was related to the dose of mitozolomide.

Two of the four assessable patients who were treated with ≥ 350 mg/m^2 noted thinning of the hair, although not to the extent that wigs were required. In the weeks after treatment, increasing levels of plasma alkaline phosphatase were found in five subjects, four of whom developed hyperbilirubinaemia, the deterioration commencing with progression of liver metastases. In two other patients, increasing alkaline phosphatasaemia coincided with deterioration of bone metastases. One patient became uraemic at 17 days after treatment, but this was attributable to obstructive uropathy.

Responses

No partial or complete responses were observed; however, three of six evaluable tumours treated with ≥ 300 mg/m^2

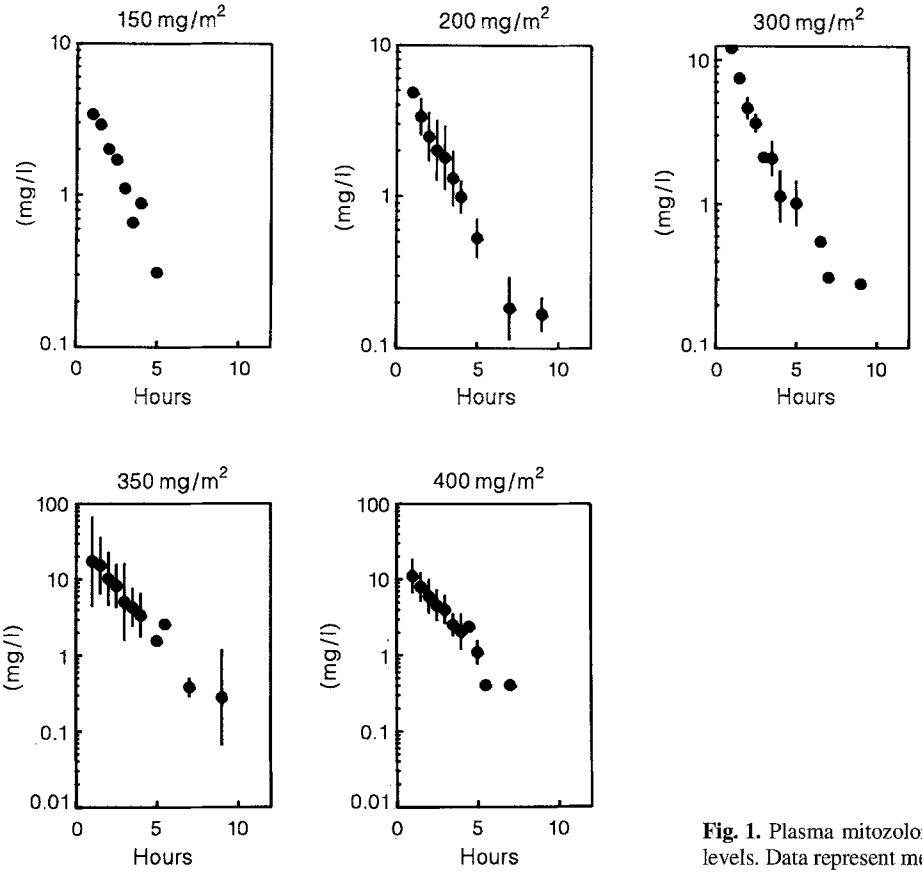

Fig. 1. Plasma mitozolomide concentration vs time curves at five dose levels. Data represent mean values ± SD

improved, but the measurable reductions in tumour dimensions fell short of the criteria for a partial remission. The responding tumours were squamous-cell and large-cell undifferentiated carcinomas of the bronchus and an adenocarcinoma of the colon.

Pharmacokinetics

Pharmacokinetics were studied in 11 patients. One showed a mildly elevated serum creatinine level (patient C), and three exhibited disturbed liver function tests (patients D, F and H) at the time of drug administration. All patients were receiving medication in addition to mitozolomide, mainly preoperative medication, anaesthetic agents or postoperative analgaesics and antiemetics. Plasma mitozolomide concentration vs time curves are shown in Fig. 1. At all five doses studied, the plasma mitozolomide levels were undetectable within 12 h of drug administration and plasma concentrations appeared to fall in a linear fashion on semilogarithmic plots. The plasma concentration vs time data fitted linear pharmacokinetic models for all patients. The data obtained on some subjects fitted best to monoexponential models, whereas those of others fitted best to biexponential models.

Model-independent pharmacokinetic parameters and urinary drug elimination are shown in Table 3. Mitozolomide showed a short plasma elimination half-life

Table 3. Pharmacokinetic parameters

Patient	SA (m^2)	Dose (mg/m^2)	c_{max} (mg/l)	AUC (mg h l^{-1})	C (l/h)	V_{ss} (l)	$t_{1/2}$ (h)	Urinary excretion (% dose)
A	1.7	150	3.4	8	30	55	1.4	2.9
B	1.9	200	4.7	11	33	50	1.6	3.6
C	1.9	200	4.8	14	25	53	2.1	3.6
D	1.6	200	5	10	30	27	2.8	8.1
E	1.5	300	12	21	20	21	2	3.6
F	1.8	300	12	25	21	25	2.1	5.3
G	1.9	350	5.7	16	40	85	2.2	3.7
H	1.6	350	31	63	9	12	2.1	–
I	1.8	350	46	82	7.6	11	1.4	21
J	2.1	400	7.7	18	45	84	2	0
K	1.8	400	16	33	21	37	1.5	–

SA, Surface area; c_{max}, peak plasma concentration; AUC, area under the plasma concentration vs time curve; C, clearance; V_{ss}, volume of distribution at steady state; $t_{1/2}$, plasma elimination half-life

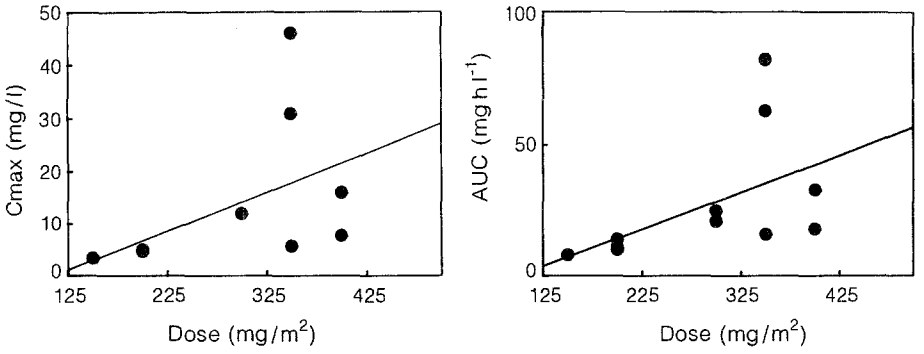

Fig. 2. Peak plasma concentration (c_{max}) and AUC vs the mitozolomide dose

(range, 1.4–2.8 h) that exhibited no dose-related changes. Only a small percentage of the delivered dose was eliminated in urine as unchanged parent drug (mean percentage of the total dose excreted unchanged in urine = 4.4%). Peak plasma concentration (c_{max}) and AUC correlated positively with dose, the correlation coefficients being 0.49 and 0.53, respectively (Fig. 2). The considerable interindividual variation in pharmacokinetic parameters at the 350- and 400-mg/m^2 dose levels was not consistently attributable to pretreatment renal or liver function or to other patient factors. There was no significant statistical difference in c_{max} or AUC values achieved in responding vs non-responding patients ($P > 0.05$). Similarly, no correlation was found between pharmacokinetic parameters and the severity of myelosuppression or alopecia.

Discussion

In conjunction with autologous bone marrow rescue, we gave our patients mitozolomide at doses of up to 4 times the previously defined maximally tolerable dose. This study was discontinued at the dose level of 400 mg/m^2 when our supply of the drug was exhausted. Had additional mitozolomide been available, several further dose escalations may have been possible, since only minor sequelae of myelosuppression but no other dose-limiting toxicities were encountered.

Neutropaenia did not occur consistently until doses of ≥ 300 mg/m^2 had been given. Neutrophil counts of $< 2 \times 10^9$/l were observed for periods of 7–25 days, but severe neutropaenia (neutrophil count, $< 0.5 \times 10^9$/l) was encountered in only a single patient, and it lasted for <7 days. The recorded episodes of sepsis were trival. Thrombocytopaenia lasting from 9 to 21 days occurred at doses lower than those at which neutropaenia developed, but only four subjects exhibited platelet counts of $< 20 \times 10^9$/l, which persisted for up to 6 days. Two minor episodes of epistaxis were attributable to chemotherapy-induced thrombocytopaenia, and one thrombocytopaenic patient who was also uraemic developed extensive bruising.

Mitozolomide administration was immediately preceded by bone marrow harvest under general anaesthesia, which complicated the evaluation of nausea and vomiting due to the drug. Emesis was generally transient and easily controlled and was not related in intensity or duration to the dose of mitozolomide given. Alopecia insufficient to require a wig was the only other toxic effect that was definitely attributable to mitozolomide. None of the tumour responses, which were transient, fulfilled the criteria for a partial remission, but they occurred in tumours that are not particularly chemosensitive, especially to single agents, and resulted from single treatments that produced little in the way of side effects.

The 16th patient studied sustained a pulmonary embolus, probably promoted by reinfusion of autologous bone marrow, an unusual complication of this procedure [4]. This pulmonary embolus, which caused cardiac and respiratory arrest that resulted in hypoxic brain damage and renal failure, was a major factor leading to this patient's death at day 17 after the event. Neutropaenia probably contributed to terminal bronchopneumonia.

We studied the clinical pharmacokinetics of mitozolomide in 11 subjects. At high doses, this agent exhibits a short elimination half-life and produces plasma levels that decline in a mono- or biphasic fashion. These findings are similar to those previously obtained at conventional clinical doses [12, 16] and in experimental animals [1, 8]. Dose-dependent pharmacokinetics were not encountered, and in this respect mitozolomide is unlike many other cytotoxic drugs [17]. The previously described chemical decomposition of this agent in aqueous solutions at physiological pH [21] may explain our observation that only a small proportion of the delivered dose was eliminated unchanged in the urine. Interindividual variation of pharmacokinetic parameters was noted in this study. Interestingly, one patient exhibiting disturbed liver function tests displayed comparatively high plasma drug concentrations. The lack of correlation between pharmacokinetic parameters and toxicity concurs in part with the findings of Kerr et al. [13].

During phase II clinical evaluation at conventional doses, mitozolomide was found to be inactive against ovarian [10] and renal cell carcinoma [23] and showed poor activity against malignant melanoma [9, 20]. These disappointing results may be explained by the low plasma levels and AUC values achieved in cancer patients. At conventional doses in man, Kerr et al. [13] found peak plasma concentrations and AUC values ranging from 1.5–6.5 mg/l and 5.7–15.8 mg h l^{-1}, respectively, and similar clinical values have been reported by Newlands et al. [16]. In contrast, at therapeutic doses in mice, Goddard et al. [8] and Workman et al. [24] found peak plasma

concentrations ranging from 19 to 25.2 mg/l and AUC values of 22.4–31.3 mg h l^{-1}. Since four of seven patients receiving $\geqslant 300$ mg/m^2 exhibited peak plasma levels or AUC values that lay within the range reported by Goddard et al. [8] and Workman et al. [24], the present study demonstrates the feasibility of achieving therapeutic plasma drug levels in cancer patients by the administration of high-dose mitozolomide in conjunction with autologous bone marrow rescue.

After 48 h storage, the repopulating capacity of harvested human bone marrow falls by at least 50% [14]. Prolonged storage of bone marrow requires cryopreservation, but this is a relatively complicated and expensive procedure [18]. Since mitozolomide is eliminated rapidly and drug plasma levels are undetectable at 12 h following the administration of high doses, it would appear safe to reinfuse harvested marrow at this early time, which in turn may optimise marrow viability and make cryopreservation unnecessary.

In conclusion, the maximally tolerated dose (MTD) of mitozolomide given in conjunction with autologous bone marrow rescue is >400 mg/m^2, and at 4 times the previously identified MTD, myelosuppression remains the only major toxicity and plasma drug levels are similar to those associated with preclinical antitumour activity.

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