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Phase I/II Pharmacokinetic Study of Mitoxantrone by Continuous Venous Infusion in Patients with Solid Tumours and Lymphoproliferative Diseases

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Phase I and pharmacokinetic studies were performed in order to evaluate the maximum tolerated dose and the efficiency of 120 h continuous venous infusion (CVI) of mitoxantrone. 25 patients suffering from either metastatic solid tumour or refractory lymphoproliferative disease were included in the study. The starting dose was 2 mg/m² per day and was increased by a 0.2 mg/m² per day step dose. The main toxicity observed was leukopenia which became limiting in more than 50% of the patients receiving 2.4 mg/m² per day (12 mg/m² over a 120 h period); this dose was defined as the maximal tolerated dose in these pretreated patients. One partial response and three stable diseases were observed. A plasma plateau concentration of mitoxantrone (2.13 [S.D. 0.54] μg/l at 2 mg/m² per day, 2.56 [1.32] μg/l at 2.2 mg/m² per day and 3.46 [1.32] μg/l at 2.4 mg/m² per day) was reached within 24–48 h. It was linearly related to the administered dose. The mean plasma clearance of mitoxantrone was 27.8 [14.2] l/h/m² and the volume of distribution of the β phase averaged 2327 [2125] l/m². An inverse relationship was established between the mitoxantrone clearance and the degree of hematologic toxicity. This 120 h CVI mitoxantrone schedule was safe and could be repeated every 3 weeks in an outpatient setting. The relationship between mitoxantrone clearance and the drug related haematotoxicity could be used for an individual dose adjustment.
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INTRODUCTION

MITOXANTRONE is a subsituted anthraquinone with an antitumour activity against various experimental tumours and is as effective as doxorubicin for the treatment of human tumours, but with a reduced cardiotoxicity [1–3]. The standard schedule for mitoxantrone is intermittent dose bolus therapy for 1, 3 or 5 consecutive days, repeated at 3-week intervals. At 12–14 mg/m², myelosuppression is found to be the dose-limiting toxicity [2, 3] associated with mucositis at higher dosages [4]. Antineoplastic activity has been demonstrated in clinical trials for breast cancer, acute leukaemia and non-Hodgkin lymphoma (NHL) [2, 3].

Although its mechanism of action is not specifically phase dependent, mitoxantrone induces a block in the G2 phase of the cell cycle and cells in S phase are most sensitive [5]. Additionally, mitoxantrone cytotoxicity in human colon adenocarcinoma cell lines *in vitro* is enhanced by lengthening the time of exposure to the drug [6]. According to initial pharmacokinetic reports [7–12] and reports on long-term continuous venous infusion (CVI) of mitoxantrone [13, 14], the steady state concentration should be reached 24–48 h after the beginning of infusion. So, mitoxantrone has been recognised as a suitable drug for a CVI device, according to Vogelzang's criteria [15].

A phase I/II study of 120 h CVI mitoxantrone (length of infusion usually used in clinical oncology) was initiated in patients with solid tumours or lymphoproliferative diseases. The aim of the trial was to evaluate whether this modality of administration achieves a higher maximum tolerated dose and/or different spectrum of toxicities in comparison with primary intravenous bolus studies [16]. Finally, a pharmacokinetic study was performed to determine the main parameters and eventual correlations between pharmacokinetic data and clinical results.

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PATIENTS AND METHODS

Inclusion criteria

Adult pretreated patients (18–75 years) with histologically proven and refractory malignant disease were entered in this study. Remaining requirements included: life expectancy greater than 3 months, WHO performance status level 2 or better, adequate haematologic, hepatic and renal status (leucocyte and platelet counts > 4000/μl and 100 000/μl, respectively, serum creatinine < 130 μmol/l, serum bilirubin < 35 μmol/l), no cardiomyopathy or rhythmic dysfunction supported by clinical, ECG, chest X-ray and radionuclide left ventricular ejection fraction (LVEF) assessment. Previous treatment with a regimen including anthracycline was a criteria of ineligibility if the total anthracycline dose was > 500 mg/m² (referring to doxorubicin cumulative dose).

The study had received the approval of the Regional Ethical Committee and written consent was required for all patients.

Treatment plan

Mitoxantrone was administered as a 120 h CVI, every 3 weeks, through a central catheter connected to an external pump device. The first course of therapy was performed under hospital supervision for clinical and pharmacokinetic study. Clinical and

Table 1. Clinical characteristics of patients

	Group 1	Group 2
No. of patients	18	7
Mean age (years)	50	51
(range)	(23–70)	(39–65)
Sex		
Male	8	3
Female	10	4
Performance status (median)	1	1
Tumour type		
Digestive	6	
Sarcoma	4	
Ovary	3	
Kidney	2	
Other	3	
CLL		2
Non-Hodgkin lymphoma		5
Previous chemotherapy	15	7
Anthracycline-based regimen	6	6
Measurable disease	17	7

Table 2. Haematological toxicity (WHO scale)

	Dose (mg/m² per day)			
	2	2.2	2.4	2.6
First cycle of chemotherapy				
No. of evaluable patients	4	11	10	
Leukopenia (grade)				
1		1	2	
2	1	4	3	
3	1	4	5	
Thrombopenia (grade)				
2		1		
All courses of chemotherapy				
No. of evaluable courses	7	19	15	4
Leukopenia (grade)				
1		1	2	1
2	2	5	2	1
3	1	6	8	2
Thrombopenia (grade)				
1		1		
2		1		

laboratory controls were required at days 8, 15 and 21. ECG was repeated at day 21; chest X-ray and LVEF every 9 weeks. On the basis of primary reports [16, 17], the starting dose was 2 mg/m² per day over a 120 h CVI. At least 3 patients had to be investigated before deciding to increase the dosage. The increment for each dose step was 0.2 mg/m² per day up to limiting toxicity.

Criteria for clinical assessment

The maximum tolerated dose was defined as the dose inducing grade 3 or grade 4 toxicity using the WHO grading system, in at least 50% of patients explored at each dose level. Intrapatient dose escalation was allowed. To be evaluable for response, patients with measurable disease were followed for at least 12 weeks from the start of treatment. Tumour response was assessed according to standard WHO criteria.

Blood sampling

Blood samples were obtained during the first course of chemotherapy at the following times: before injection, then 6, 12, 24, 48, 72, 96 and 120 h after the initiation of administration and then 10 and 30 min, 1, 2, 4, 6, 12, 24 and 48 h after the end of infusion. The blood was collected in tubes containing EDTA with addition of an antioxidant (0.001% sodium bisulphite) and immediately centrifuged. Plasma was removed and frozen at −20°C until analysis.

Drug analysis

Mitoxantrone concentrations were determined by HPLC as described by Choi *et al.* [18] using electrochemical detection. Under these conditions, the retention times (S.D.) of mitoxantrone and bisanthrene were respectively 7.2 (0.6) and 10.4 (0.5) min. The limit of detection of the method was 0.2 ng/ml. The within and day-to-day coefficients of variation were 5.4 and 8.3%, respectively.

Data analysis

The plasma concentration versus time data was best fitted to a biexponential equation using a Siphar computer program on an IBM/PC computer. The main pharmacokinetic parameters were thus computed: half-lives for the distribution and elimination phases = $t_{\frac{1}{2}}\alpha$, $t_{\frac{1}{2}}\beta$, area under curve determined by trapezoidal rule and extrapolated to infinity.

RESULTS

Patients' characteristics

Patients' characteristics are summarised in Table 1. A total of 25 patients divided into 2 groups were treated with mitoxantrone 120 h CVI. Group 1 included 18 patients suffering from disseminated solid malignancies: digestive (6), sarcoma (4), ovary (3), other (3). Three of these patients were given mitoxantrone CVI as first line chemotherapy. 6 of the 15 pretreated patients had previously received an anthracycline-based regimen. A total of 39 courses have been performed in this group, with a median of 2 courses per patient (range 1–4). Group 2 included 7 patients with refractory lymphoproliferative diseases: CLL (2), NHL (5). 5 patients had received a doxorubicin-containing regimen (median dose: 396.5 mg/m²; range: 100–435 mg/m²), another had been treated by intravenous bolus mitoxantrone (cumulative dose: 48 mg/m²). A total of 16 courses were performed in that group.

All patients but 1 had measurable disease; 6/18 patients in group 1 showed liver metastasis without hepatic test disturbances greater than WHO grade 1; 3 of the 7 patients in group 2 showed bone marrow involvement. 3 patients who showed no sign of congestive heart failure were included in spite of LVEF < 50% (43%, 43%, 48%).

Toxicity

Haematological toxicity is summarised in Table 2 which included first cycle and overall assessment. Leukopenia was confirmed as the only dose-related and dose-limiting toxicity providing grade 3 in 50% of patients at 2.4 mg/m² per day dose level. The mean leucocyte nadir count was 2.2 × 10^9/μl (range

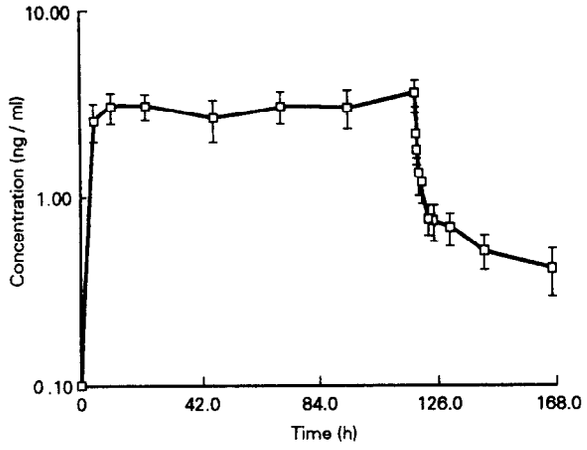

Fig. 1. Plasma concentrations of mitoxantrone as a function of time after 120 h continuous venous infusion of 2.2 mg/m² per day in 10 patients (mean, S.D.).

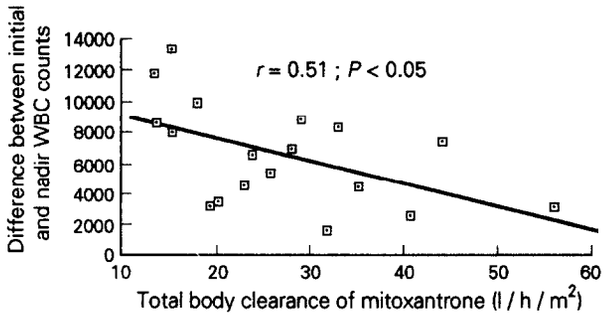

Fig. 2. Relationship between the total body clearance of mitoxantrone and the difference between the initial and the nadir WBC counts for the different patients during the first course of chemotherapy.

1.2–3.3 × 10^9/μl) and the mean time of leukopenia onset was day 15 (range: day 8–17). No leukopenia-related sepsis occurred. The toxicity profile did not significantly differ between pretreated and non-pretreated patients. Considering all the courses received, leukopenia has been thought to be dose dependent. In 6 patients with grade 1 or 2 toxicity at the first cycle, the mitoxantrone dose level was increased (2 patients at 2.4 mg/m² per day, 4 patients at 2.6 mg/m² per day), resulting in a more pronounced leukopenia in 4 cases. Associated thrombopenia was infrequent.

Non-haematological toxicities included mild digestive intolerance (4 patients), infrequent mucositis (3 patients), reversible increment in creatinine level (grade 1: 2 patients). No cases of mitoxantrone-related congestive heart failure occurred, particularly in patients with initial LVEF < 50%. However, in 2 patients, LVEF reassessment after therapy completion was significantly decreased (−19% and −11% after 4 and 2 cycles, respectively). No patient showed alopecia. With regard to central venous access supervision, 1 patient developed local infectious complications so that the implanted catheter had to be taken off after 3 courses.

Clinical response

24 patients were evaluable for response. 1 patient with non-Hodgkin lymphoma (group G according to the Working Formulation) showed a partial response. This patient had failed to respond to CHOP-bleomycin and MIME regimens. The response duration to CVI mitoxantrone regimen was 3 months. Three patients had stable disease (12–20 weeks) with metastatic colorectal carcinoma which failed to respond after previous 5-fluorouracil-containing chemotherapy. The remaining 20 patients had progressive disease within 2 months of therapy.

Table 3. Pharmacokinetic parameters [mean (S.D.)] of mitoxantrone after 120 h continuous venous infusion

Dose (mg/m² per day)	C ss (μg/l)	$t_{\frac{1}{2}}\alpha$ (h)	$t_{\frac{1}{2}}\beta$ (h)	AUC (μg/l × h)	Cl (l/h/m²)	$V_d\beta$ (l/m²)
2	2.13	2.56	75	78.1	25.6	3312
	(0.54)	(1.32)	(51)	(25.6)	(8.4)	(2000)
2.2	2.56	0.65	120	73.1	30.1	2540
	(1.32)	(0.48)	(144)	(45.9)	(18.9)	(2576)
2.4	3.46	1.14	32	93.4	25.7	1543
	(1.32)	(0.79)	(29)	(23.6)	(6.5)	(1072)
Mean		1.08	82.7		27.8	2327
(S.D.)		(1.37)	(107)		(14.2)	(2125)

$t_{\frac{1}{2}}\alpha$ = distribution half-life, $t_{\frac{1}{2}}\beta$ = elimination half-life, Cl = clearance, V_d = volume of distribution.

Pharmacokinetics

21 treatment courses were evaluated for pharmacokinetics. Figure 1 shows the mean plasma versus time curve obtained at a dose level of 2.2 mg/m² per day. The time to reach the plateau concentrations was comprised between 24 and 48 h. A linear relationship between the mean (S.D.) plateau and the administered dose (r=0.979) was observed: 2.13 (0.54) μg/l at 2 mg/m² per day, 2.56 (1.32) μg/l at 2.2 mg/m² per day and 3.46 (1.32) μg/l at 2.4 mg/m² per day. Table 3 summarises the main pharmacokinetic parameters of mitoxantrone after 120 h CVI. In all of the cases studied, the plasma disappearance was biexponential: the mean distribution half-life was 1.08 h (range 0.09–2.6 h) and the mean elimination half-life was 82.7 h (range 3.8–112 h). The total body clearance showed also a large interindividual variability [27.8 (S.D. 14.2) l/h/m²] with a marked interpatient variation in the apparent volume of distribution of the β phase [2327 (2125)l/m²].

Correlation between pharmacokinetic and pharmacodynamic parameters was investigated. As shown in Fig. 2, the total body clearance was significantly correlated (r = 0.51, P < 0.05) with the haematological toxicity expressed by the difference between pretreatment and nadir WBC counts.

DISCUSSION

In this phase I/II of 120 h CVI mitoxantrone including a majority of heavily pretreated patients, the maximum tolerated dose (MTD) reached 2.4 mg/m² per day and was defined by leukopenia. It is worth noting that this MTD (12 mg/m²) was about the same as that obtained in initial reports investigating bolus injection schedules (12–14 mg/m²) [2, 3, 16] and provided very similar haematological profile i.e. frequent (more than 50% of patients), marked (grade 3) but promptly reversible leukopenia. Therefore, spreading the usual mitoxantrone dosage over 120 h did not offer any significant advantage in terms of dose intensity as for doxorubicin [19]. By contrast, in two recent studies [13, 14] investigating mitoxantrone long-term infusion (21 or 14 days), the MTD per day ranged from 1.1 to 1.5 mg/m², allowing a total dose deliverance per cycle (23.1–22 mg/m²) about two times higher than with standard schedules.

When focussing on non-haematological toxicity, 120 h CVI mitoxantrone is a safe treatment providing only mild gastrointestinal and mucosal side-effects. In contrast to 96 h CVI doxorubicin [19], mucositis was not a limiting toxicity. In addition, Greidanus *et al.* [13] did not report high mucosal toxicity in a 21-day CVI study. These results suggest that mitoxantrone-induced mucositis might be related to the peak concentration. Because of the short duration of therapy for each patient, the results obtained in our study did not allow us to conclude whether mitoxantrone-induced cardiotoxicity was reduced when administered by 120 h CVI as described for doxorubicin [20].

Our 120 h CVI schedule has provided only 3 stable diseases in patients with solid tumours and 1 partial response in the lymphoproliferative disease group. However, most of the patients of group 1 were suffering from tumours usually resistant to anthracyclines and previously characterised by expressing *de novo* MDR phenotype. Among patients treated for lymphoproliferative diseases, all but 1 had been pretreated with anthracyclines and had been considered as resistant to chemotherapy. That could explain the present low response rate which is similar to that obtained by Greidanus *et al.* [13].

Few kinetic studies have been performed during CVI of mitoxantrone [4, 13]. After intravenous bolus, the plasma concentration versus time curves were well described by an open three-compartment model with an elimination half-life ranging from 9 to 84 h [7–12]. In our study, the plasma concentrations were fitted by a biexponential decay with an elimination half-life of 83 h. The pharmacokinetics of mitoxantrone showed high interindividual variability which has been evaluated by a NONMEM method [11]: the coefficients of variation were 46%, 26% and 51% for total body clearance, elimination half-life and volume of distribution, respectively. Our study confirmed this interindividual variability in terms of pharmacokinetic parameters. We have observed, as in another report [13], that the plateau concentration of mitoxantrone was reached within 24–48 h. The plateau concentrations observed for each dose level correlated with those predicted based on the clearance of mitoxantrone when given as a 1 h infusion.

This pharmacokinetic variability could be correlated with the pharmacodynamic variability and particularly the haematological toxicity: according to the patients, the dose-limiting leukopenia ranged from 2.2 to 2.6 mg/m^2 per day. We have been able to establish an inverse relationship between the degree of haematological toxicity and the total body clearance of mitoxantrone. Knowledge of such a relationship could be used for a dose adjustment during the first or subsequent cycles of chemotherapy. Since the reviews of Powis [21] and Moore and Erlichman [22], reports about the relationships in man between toxic events and pharmacokinetic parameters of anticancer drugs have been published and the time concentration products (AUC) have been used to predict toxicity of doxorubicin [23], carboplatin [24], etoposide [25] and 5-fluorouracil [26]. Although different dependent variables are used in each of these models, in each case, a direct relationship to drug effect has been established. Therefore, if these relationships are validated on a larger population of subjects, each may allow prospective pharmacokinetic monitoring to achieve a desired pharmacodynamic effect. Santini *et al.* [26] have shown that such a dose adjustment may improve the therapeutic index of 5-fluorouracil in head and neck cancer. However, our study did not allow us to forecast the pharmacokinetic behaviour of mitoxantrone since we have been unable to establish a relationship between a pretreatment parameter and clearance or volume of distribution as elaborated by Calvert *et al.* [24] for carboplatin.

This phase I/II trial of 120 h CVI mitoxantrone has defined a maximum tolerated dose of 2.4 mg/m^2 per day (12 mg/m^2 over a 120 h period) in pretreated patients. Leukopenia is the only dose-limiting toxicity. This schedule was safe and could be repeated every 3 weeks in an outpatient setting. The knowledge of a pharmacokinetic–pharmacodynamic relationship could allow an individual dose adjustment in patients previously treated or not. Although 120 h CVI did not modify the therapeutic index (similar MTD and toxicities), the low response rate reported does not preclude that patients would not benefit from such a schedule when given as first line treatment in tumours usually sensitive to mitoxantrone.

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Bepridil in Combination with Anthracyclines to Reverse Anthracycline Resistance in Cancer Patients

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The use of calcium antagonists as multidrug resistance reversing agents is limited by acute cardiac toxicity which, for verapamil, becomes prohibitive when concentrations in plasma approach those required *in vitro* for its action. A new calcium antagonist, bepridil, is as active as verapamil in reversing drug resistance *in vitro*. In addition, bepridil has some more favourable pharmacological properties compared with verapamil and other calcium antagonists. 14 patients with progressive advanced cancer, resistant to doxorubicin or epirubicin, were treated with the same anthracycline in combination with bepridil. Bepridil was administered in a continuous 36 h infusion at 22 mg/kg/36 h, with a dose scheme which should result in a steady state plasma concentration of approximately 5 μmol/l, able to reverse anthracycline resistance *in vitro*. Pharmacokinetic studies demonstrated a median bepridil plasma concentration of 5.3 μmol/l (range 2.6–19.3 μmol/l), at the time of administration of the anthracycline. No acute cardiac toxicity was observed and apparently bepridil did not induce an increase or change in anthracycline toxicity. However, 2 patients developed overt chronic heart failure after treatment discontinuation, which caused 1 patient's death, and a significant reduction in left ventricular ejection fraction was seen in 4 patients. This chronic cardiac toxicity could be related to the total anthracycline dose received. 5 patients attained short lasting minor responses, 3 had stable disease and 6 progressed. Immunohistochemical studies in 7 tumours failed to reveal P-glycoprotein expression. Further trials with escalating doses of bepridil in combination with multiple drug resistance related anticancer agents are warranted.
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INTRODUCTION

THE OCCURRENCE of drug resistance is considered as a major cause of chemotherapy failure in solid tumours. Several mechanisms of drug resistance have been discovered in *in vitro* systems and in animal models, but their significance in human cancer awaits confirmation. Anthracyclines are among the most effective antineoplastic drugs in current use. *In vitro* studies have revealed that anthracyclines display crossresistance to a group of structurally and functionally unrelated cytotoxic agents. This phenomenon, called multidrug resistance (MDR), is related to a decreased intracellular drug accumulation and changes in intracellular distribution of drugs [1–3]. The overexpression of a 170–180 kD P-glycoprotein [4], is thought to be responsible for an energy dependent outward transport of xenobiotics and cytotoxic drugs derived from them [5, 6]. It has been shown that P-glycoprotein mediated resistance to anthracyclines can be reversed *in vitro* by several substances, including a number of calcium channel blockers [7]. The results of clinical studies in

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