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Original Paper

Phase I Pharmacological Study of Intra-arterially Infused Fotemustine for Colorectal Liver Metastases

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Fotemustine was investigated in 17 patients with progressive hepatic metastases from colorectal carcinoma to define the maximally tolerated dose for a daily hepatic intra-arterial infusion (HAI) schedule. Haematotoxicity was delayed, dose-dependent and related to pretreatment, with thrombo- and leucocytopenia being dose-limiting. Local side-effects at the liver were mild. Infection (WHO grade III) occurred in 1 patient due to neutropenia. Other side-effects, particularly renal, pulmonal, neurological or cardiac toxicity, mucositis and diarrhoea, hair loss or allergic reactions did not occur. Pharmacokinetic analysis indicated a short plasma half-life ($t_{1/2}$ = 25.8 ± 11.5 min) and a high body clearance (C_L = 2193 ± 870 ml/min) with large inter- and intra-individual variations. Of 15 evaluable patients, one complete and three partial responses were observed (ORR = 27%; $CI_{95\%}$ [4.5–49.5%]). All tumour remissions appeared at higher dose levels in previously untreated patients. Considering the absence of mucosal side-effects, such as mucositis/diarrhoea and of hepatic toxicity, this agent was well tolerated. The recommended intra-arterial dose for consecutive phase II trials is 125 mg/m^2/day$_{1–3}$.

Key words: nitrosourea derivate, fotemustine, colorectal carcinoma, hepatic intra-arterial infusion, pharmacokinetics
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INTRODUCTION

HEPATIC FAILURE is the most frequent cause of death for patients with liver metastases from colorectal carcinoma. Liver involvement is found in 50–70% of patients with advanced disease [1]. Hepatic intra-arterial infusion (HAI) offers interesting perspectives for the treatment of isolated liver metastases from colorectal carcinoma or other primaries. However, treatment will only be advantageous if effective agents are available. Therefore, we have investigated the nitrosourea derivate fotemustine in a clinical–pharmacological phase I trial. Fotemustine is a new alkylating agent containing an alpha aminophosphonic acid which is thought to facilitate passage across the cell membrane. Its pharmacokinetic properties with a short half-life (approximately 20–30 min) as well as the high liver extraction rate, make it potentially useful for HAI [2]. An intra-arterial (i.a.) phase II study of fotemustine has confirmed that myelosuppression is almost the only notable side-effect, with an objective response rate of 20% (n = 7/35) in metastatic colorectal carcinoma using a weekly infusion schedule of 100 mg fotemustine/m^2 for three or four consecutive weeks. This schedule was the same as the intravenous (i.v.) route except for the duration of infusion (4 h) in order to prolong the drug–tumour contact time [3]. The aim of the present monocentric phase I study was to determine the maximally tolerated dose (MTD) and toxicity of fotemustine investigated in a more practical application regime, which allows the treatment of patients without an implantable pump system directly after operation via Arteria femoralis-catheter. In addition, the pharmacokinetic properties of fotemustine were evaluated.

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Table 1. *Patients' characteristics*

No. pts enrolled	18
No. pts evaluable	
for toxicity	17
for response	15
Median age (range)	57 years (32–69)
Sex (male/female)	12/5
Median ECOG index (range)	1 (0–2)
Prior chemotherapy	8 (47%)
i.a.	4
i.v.	1
i.a. + i.v.	3

i.a., intra-arterial; i.v., intravenous.

PATIENTS AND METHODS

Patients and selection criteria

17 patients with metastatic colorectal cancer were treated with a 4-h infusion via a surgically placed hepatic artery catheter. Inclusion criteria were histologically confirmed colorectal cancer; age between 18 and 75 years; resection of the primary tumour, no previous radiation or chemotherapy with nitrosoureas; ECOG ≥ 2; life expectancy ≥ 3 months; measurable hepatic lesion with evidence of progression; WBC count $\geq 4000/mm^3$, platelet count $\geq 100\,000/mm^3$; liver and renal status (parameters ≤ 1.25 of normal values) and informed consent. Clinical response was judged on the basis of computed tomography (CT) scan examinations every fifth week and response was verified according to WHO criteria.

Treatment and study design

Fotemustine was infused intra-arterially over a 240-min period on days 1, 2 and 3. Treatment was repeated on day 36 unless severe toxicity was observed. After two cycles, patients with stable disease or tumour response received maintenance therapy with one infusion given every 3 weeks. The starting dose level was 75 mg/m^2/day. Doses were escalated according to a modified Fibonacci scheme up to 150 mg/m^2/day in 25 mg/m^2 steps.

Pharmacokinetics

Drug assay and the pharmacokinetic analysis followed the original procedure established by Gordon and associates [4].

RESULTS

17 eligible patients (1 enrolled patient was lost to follow-up during the first induction cycle and was therefore not assessable for toxicity or response) received HAT during this phase I trial. 8 patients were pretreated with 5-fluorouracil based regimes. The patients' characteristics are summarised in Table 1. 4 patients were treated at dose level 1, 5 patients at dose level 2, 4 at levels 3 and 4. A total of 28 induction and 31 maintenance cycles were given (first induction cycle: 17 patients; second induction cycle: 11 patients; maintenance cycles: 10 patients (median 3, range 1–8).

Toxicity

All patients were evaluable for toxicity. Delayed myelosuppression, particularly thrombocytopenia, was the dose-limiting side-effect, being cumulative. In pretreated patients, severe haematotoxicity occurred following administration of doses of 100 mg/m^2/day (dose level 2). Patients without prior chemotherapy were treated with fotemustine doses up to 150 mg/m^2 (dose level 4) (Table 2). At doses greater than 100 mg/m^2/day, WHO grade III/IV leucocytopenia occurred in 4 of the 8 patients and thrombocytopenia in 5/8 patients. Leucocytes started to decrease at day 19, the median nadir occurring on day 39 and recovery took place on day 78. For thrombocytes, the decrease started on day 19, the median nadir occurred on day 29 and recovery took place on day 79. Dose reductions or delay of treatment cycle occurred in 5 of 8 patients treated at the two upper dose levels 3 and 4. During the maintenance cycles with one infusion every 3 weeks, no severe myelosuppression (WHO grade III/IV) was observed.

Non-haematological toxicity was rare. 1 patient experienced WHO grade III abdominal pain after infusion of fotemustine probably related to treatment (0.6% of cycles). Nausea and vomiting starting 3 h after infusion were noted in 10% of cycles, but did not exceed WHO grade II. Nausea lasted for approximately 2–3 h under prophylactical antiemetic treatment with ondansetron. No significant liver toxicity—chemical hepatitis/sclerosing cholangitis—was seen, only transient liver enzyme elevations occurred but without a dose relationship. Infection and fever were observed in 3 patients ($1 \times$ grade III and $2 \times$ grade II) at the upper dose levels 3 and 4 due to neutropenia (2% of cycles). Other side-effects, particularly renal, pulmonal, neurological or cardiac toxicity, mucositis and diarrhoea, hair loss or allergic reactions did not occur. One patient experienced a catheter displacement without bleeding.

Tumour response

15 patients were evaluable for radiological response assessment. 2 patients were not evaluable for response because they had diffuse metastases in the whole liver at the initial

Table 2. *WHO grade III/IV toxicity per patient and per cycle during induction treatment*

	Dose level (dose in mg/m^2/day)							
	1 (75)		2 (100)		3 (125)		4 (150)	
	Pts	Cycles	Pts	Cycles	Pts	Cycles	Pts	Cycles
Total	4	8	5	8	4	7	4	5
Grade III/IV haematological toxicity								
Leucopenia	0	0	1	2	1	1	3	3
Neutropenia	0	0	1	1	1	1	2	2
Thrombopenia	0	0	1	2	2	2	3	3
Anaemia	0	0	1	1	1	1	1	1
Non-haematological toxicity								
Infection/fever	0	0	0	0	1	1	0	0
Frequency of platelet transfusions	0	0	0	0	1	1	2	2
Dose reductions/delay of next cycle	0	0	2	2	2	2	3	3

Table 3. Results of the pharmacokinetic analysis

	Pt 2				Pt 3		Pt 4		Pt 9	Pt 6		Pt 7			Pt 10		Mean ± S.D.
Cycle/Day of cycle	1/1	1/3	2/1	2/3	1/3	2/3	1/1	1/3	2/1	1/1	1/3	1/3	2/1	2/3	1/1	1/3	
Dose (mg/m^2)	75	75	75	75	75	75	75	75	75	100	100	100	100	100	125	125	
Dose (mg)	150	150	150	150	160	160	138	138	130	180	180	200	210	210	260	260	
Pharmacokinetic																	
$t_{1/2}$ (β) in min	28.7	39.9	28.8	40.4	8.2	16.3	14.6	41.0	17.5	11.6	17.2	25.3	25.1	46.8	25.6	26.1	25.8 ± 11.5
C_{max} (ng/ml)	286	541	547	450	319	254	262	602	271	353	360	248	361	477	983	1098	463.3 ± 25.3
AUC (ng/ml/min^{-1})	108 672	109 084	82 489	91 101	58 643	45 387	48 130	114 669	40 455	52 456	81 739	99 688	64 151	96 091	231 696	233 429	97 368 ± 58 091
V_{dss}(l)	58.2	71.0	98.4	88.0	27.0	63.7	55.3	66.8	81.4	24.7	50.6	23.8	114.4	61.5	41.5	41.9	60.5 ± 26.2
Clearance (ml/min)	1380	1375	1818	1646	2728	3525	2867	1203	3213	3431	2202	2006	3273	2185	1122	1113	2193 ± 870
AUC/Doses (10^{-2}/h/l^{-1})	1.21	1.21	0.91	1.01	0.63	0.48	0.58	1.38	0.51	0.48	0.76	0.83	0.51	0.80	1.50	1.50	
AUC (Tg 1)/AUC (Tg 2)		1.00		0.91				0.42			0.64			0.67		0.99	0.77 ± 0.23

Table 4. Mean values of pharmacokinetic data following i.v. and i.a. infusion of fotemustine in cancer patients (± S.D.)

Route of administration (no. of courses)	C_{max} (μg/ml)	$t_{1/2}$ (h)	AUC (μg h ml^{-1})	C_L (ml/min)	[Ref.]
i.v. ($n = 17$)	3.26 ± 1.56	0.34 ± 0.07	3.60 ± 1.52	933 ± 367	[7]
i.a. ($n = 9$)	0.65 ± 0.25	0.34 ± 0.10	1.98 ± 1.04	2283 ± 2400	[7]
i.a. ($n = 16$)	0.46 ± 0.25	0.26 ± 0.12	1.62 ± 0.97	2193 ± 870	(current series)

C_L, body clearance; AUC, area under the curve; C_{max}, maximal concentration during infusion; $t_{1/2}$, half-life of fotemustine.

CT-scan so the hepatic lesions could not be measured accurately. They were therefore excluded from response evaluation, but were included in the assessment of toxicity. One complete response and three partial responses were achieved lasting a median of 8 months (range, 3–13 + months). Altogether 8 patients had stable disease (SD)/minor responses (MR) for a median duration of 8.5 weeks (4–23). 3 patients had disease progression (PD) after the first treatment cycle of fotemustine. At the third and the fourth dose level, 4 of 7 untreated patients had CR or PR (57%). No objective remissions could be observed at the lower dose levels 1 and 2 in pretreated patients.

Pharmacokinetic analysis

7 patients (16 courses) were included in the pharmacokinetic study. The plasma concentration profile was best described by a one-compartment model with first-order elimination of the drug. The results of the pharmacokinetic analysis showed a marked inter- and intra-individual variability in measured fotemustine levels, a short half-life of the intact compound ($t_{1/2} = 25.8 \pm 11.5$ min) and a large volume of distribution close to body weight ($V_{dss} = 60.5 \pm 26.2$ l). Plasma clearance was determined at 2193 ± 870 ml/min, C_{max} at 0.46 ± 0.25 μg/ml and 'area under the curve' (AUC) at 1.62 ± 0.97 μg h ml^{-1}. Mean AUC measured at the first day of infusion was lower compared to day 3 ($AUC_{Day\ 1/Day\ 3} = 0.77 \pm 0.23$). Individual data, including dosing details and pharmacokinetic parameters, are summarised in Table 3.

DISCUSSION

The concept of creating the S 10036 fotemustine compound was based on pharmacodynamic considerations. Fotemustine differs from the other chloroethylnitrosoureas only in the presence of a diethylphosphonate group. This non-polar part of the molecule enables rapid penetration of the drug through the cell membrane [2]. As compared with BCNU, fotemustine has been shown to be a poor inhibitor of glutathione reductase and this property might explain its lower level of side-effects [5].

The main goal of the current study was to establish the safety and maximally tolerable dose of fotemustine when administrated by HAI using a daily treatment regimen in patients with liver metastases from colorectal cancer. No life-threatening toxicity was observed. Considering the absence of mucosal side-effects such as mucositis/diarrhoea and major hepatic toxicity, fotemustine could be considered as well tolerated when given intra-arterially. Although hepatotoxicity was observed in a larger series using HAI of fotemustine, it was never dose limiting and was surprisingly lower compared with intravenous dosing [3, 6]. Delayed and cumulative myelosuppression, particularly thrombo- and leucocytopenia in pretreated patients, were the major side-effects in this trial. This has been reported before both for intravenous as well as for intra-arterial use of fotemustine. The degree of haematotoxicity was lower with i.a. application when comparative dose intensities were achieved. The median dose intensity per cycle reached in the current study was nearly twice as high as results from a previous i.a. trial without a higher rate of leucocytopenia but with more severe thrombocytopenia. Significant gastrointestinal or local hepatic toxicities did not limit dose escalation of fotemustine.

The results of the present pharmacokinetic study are in accordance with a previous trial using a weekly HAI schedule of fotemustine [7]. Plasma profiles were described by a one-compartment model, showing marked intra- and inter-individual variations and only minor differences in the measured pharmacokinetic parameters between the infusion of fotemustine at days 1 and 3. Both pharmacokinetic studies demonstrate that HAI leads to a low concentration of fotemustine in the systemic circulation and to an increased total body clearance due to the hepatic extraction (Table 4) [7, 8].

The possibility of achieving higher dose intensities during this phase I study with a daily schedule was partly transferred into an impact on response compared with the results from a phase II study of Khayat and associates with a weekly HAI of fotemustine reporting an objective response rate of 20% [6]. In the present trial, 4 of 7 untreated patients at higher dose levels (125/150 mg/m^2) responded favourably. In pretreated patients, dose escalation was stopped at 100 mg/m^2 (dose level 2) because of myelosuppression and no objective remission could be observed in those patients.

In summary, HAI of fotemustine demonstrates the advantage of locoregional drug application, since this agent has been found to exert only marginal activity against colorectal carcinoma following intravenous administration [9]. The recommended i.a. dose for consecutive phase II trials is 125 mg/m^2.

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