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Hepatic intra-arterial infusion of fotemustine: pharmacokinetics

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Summary. Fotemustine is a new nitrosourea derivative that contains an alpha-aminophosphonic acid and has a short half-life and a high plasma clearance. As myelosuppression occurs as the dose-limiting toxicity, local drug delivery has been investigated in the treatment of liver metastases arising from colorectal cancer. A pharmacokinetic study was undertaken in patients who received either i.v. or hepatic intra-arterial (HIA) infusion of 100 mg/m^2 fotemustine so as to estimate the advantage of local chemotherapy, considering the pharmacokinetic differences between the two routes together with the resultant toxicities (when available). Our findings substantiated the hypothesis that a 4-h HIA infusion of fotemustine would result in a lower exposure of healthy tissues to the drug, since the AUC measured in systemic plasma was reduced by approximately 50% following such treatment as compared with i.v. infusion. This reduction in AUC should indicate a manyfold increase in exposure of the liver tumour to the alkylating properties of the drug, since it represents the proportion of the dose that has degraded within the liver. The first-pass liver-extraction ratio of fotemustine given as a 4-h HIA infusion, which ranged from 0.4 to 0.9 as estimated in patients receiving i.v. and HIA infusions in a cross-over study, argues for further investigation of HIA fotemustine infusion for the treatment of liver metastases so as to increase the response rate and decrease the occurrence of major toxic side effects in such patients.

Introduction

Hepatic metastases of colorectal cancer are found in 18%–20% of patients at the time of diagnosis and in 60% of patients with advanced disease. In these patients the extent of liver involvement is directly related to the duration of their survival [3]. As the liver is the only site of metastatic disease in 50% of patients with colorectal cancer [13], hepatic intra-arterial (HIA) chemotherapy has been widely used in attempts to improve the response rate and the survival of such patients.

The rationale for HIA chemotherapy in the treatment of liver metastases of colorectal adenocarcinoma is based on anatomical observations of these tumours and on the pharmacological properties of chemotherapeutic agents. The extent of vascularisation of liver tumours is 80%–90% dependent on the hepatic artery, whereas the cells of the normal parenchyma are mainly supplied by the portal system; thus, the arterial route appears to be more effective than the portal one in the exposure of tumour cells to drug [1]. Therefore, increasing the dose and/or concentration of the drug may improve the response, as experimental data obtained both in vitro and in vivo indicate that most antitumour agents produce a steep dose-response curve [7].

Fotemustine is a new nitrosourea derivative containing an alpha-aminophosphonic acid that is thought to facilitate its passage across the cell membrane. This alkylating agent has a short half-life (≈20 min) and a high plasma clearance that approximates the hepatic blood flow [10, 19]. Phase II studies have confirmed that myelosuppression is the dose-limiting toxicity. Thus, the selective advantage of HIA versus i.v. administration of fotemustine in the treatment of liver metastases would rest in the relative exposure of the tumour target and the bone marrow to the drug, which might result in an increase in its efficacy relative to its toxicity.

The aim of the present study was to compare the systemic exposure achieved by HIA versus i.v. infusions using the same dose of fotemustine. Thus, the pharmacokinetics of fotemustine were determined in patients with metastatic colorectal cancer who received either i.v. or HIA infusions. The first-pass extraction ratio of the drug given as a 4-h HIA infusion was estimated in patients who received alternatively i.v. and HIA infusions in a cross-over study. The results of the pharmacokinetic study presented herein together with the haematotoxicity data, when available, are discussed in terms of the relative advantage

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of HIA versus i. v. infusion of fotemustine in the treatment of liver metastases.

Patients and methods

Patients. A total of 15 patients with metastatic colorectal adenocarcinoma (11 men and 4 women) aged a median of 61 (range, 43–76) years received a 1-h i. v. infusion of fotemustine in five centres selected for a phase II study. Following 17 i. v. infusions, blood samples were taken and analysed. In all, 10 patients with evolutive liver metastases arising from a primary colorectal carcinoma (7 men and 3 women) aged a median of 59 (range, 43–70) years received a 4-h HIA infusion of fotemustine. Following 12 HIA infusions, blood samples were obtained and analysed in the Centre René Gauducheau, Nantes. In a cross-over study, 4 patients with hepatic and extrahepatic metastases of a colorectal carcinoma or a carcinoid tumour (1 patient) received HIA and i. v. infusions of fotemustine. The pharmacokinetic analysis of these treatments enabled the estimation of the first-pass extraction ratio of fotemustine given as a 4-h HIA infusion.

The pretreatment evaluation included a complete history and physical examination, a computerised tomographic (CT) scan of the liver and abdomen, a chest radiograph, an electrocardiogram, blood and differential counts as well as serum liver (GOT, GGT, APL, bilirubin) and renal (urea, creatinine) test series. Patients had to fulfill the following criteria for inclusion in the study: recovery from prior surgery, radiation therapy and chemotherapy; an anticipated survival of over 8 weeks; the absence of significant heart disease; a WBC of greater than 3,000/mm^3, and a platelet count of greater than 150,000/mm^3.

Hepatic arteriographs were required for preoperative evaluation of HIA patients; they showed 100% Ia-type hepatic arterial distribution as determined according to Daly et al. [5]. After the catheter placement, the quality of the hepatic perfusion and the hepatic arteriovenous shunt were evaluated by hepatic arterioscintigraphy performed according to the three-radiolabel method using colloidal [^{99m}Tc]-O_4 and ^{99m}Tc-labeled macroaggregated albumin [12].

The clinical response to treatment was judged on the basis of CT-scan examination at the 8th week. Further maintenance therapy was then scheduled in cases of disease stabilisation or response.

Chemotherapy. The schedule for i. v. and HIA infusions of fotemustine was similar: 100 mg/m^2 per week for 3 consecutive weeks. After a 5-week rest period, patients received maintenance therapy consisting of 100 mg/m^2 fotemustine given every 3 weeks. Fotemustine was dissolved in 250 or 50 ml 5% dextrose in water for i. v. or HIA administration, respectively, with the infusion solution being protected from light. For HIA infusions, a constant infusion pump was used. The infusion period was 1 h for i. v. treatment and 4 h for HIA therapy [18].

The hepatic arterial catheters were inserted through the gastroduodenal artery up to the proper hepatic artery and were connected to a s. c. vascular access (Celsa Laboratories, Celsit intra-arterial) by a surgical technique. During the same surgical time, cholecystostomy was performed in all patients, and collateral arteries were ligated to prevent the gastroduodenitis, duodenal ulcers and chemical cholecystitis known to occur after HIA chemotherapy [14].

Blood-sampling procedure. Heparinised blood samples were collected from a peripheral vein prior to drug infusion (time zero, T0), and at 15, 60, 75, 90, 120, 150 and 180 min after the start of i. v. infusions or at T0 and at 60, 120, 180, 240, 250, 260, 270, 280, 300 and 330 min after the start of HIA infusions. Drug levels were determined in the plasma prepared from the heparinised blood samples by centrifugation within 3 min of sampling. The plasma samples were immediately transferred to sample tubes immersed in liquid nitrogen at –80° C to minimize the degradation of unchanged fotemustine in a plasma matrix; these frozen samples could then be stored at –20° C in a dark environment for up to 15 days before analysis.

Drug assay. A reverse-phase high-performance liquid chromatographic (HPLC) technique was used to determine fotemustine levels in plasma. After frozen samples had been thawed to room temperature by immersion in a water bath (50° C), citric acid and internal standard S10338 (Laboratoires Servier, Gidy, France) were added. The assay involved a solid-phase extraction procedure carried out on a CBA Bond Elut Cartridge (Analytichem International, USA). The resultant methanolic extract was injected onto an HPLC C18 column (Spherisorb ODS, 7 µm) and the eluting peaks were monitored at 254 nm. The samples were kept at 4° C under protection from light throughout the assay. The validity of the assay procedure was checked versus the original procedure established by Gordon et al. [9]. Under these conditions, the lowest quantifiable amount was 50 ng/ml.

Pharmacokinetic analysis. Plasma profiles of fotemustine were best fitted to the one-exponential equation $C_t = A.e^{-\alpha t}$, where C_t is the drug level at time t, A is the intercept term at the origin and a represents the elimination rate constant. The parameters were estimated by a non-linear

Table 1. Pharmacokinetics of fotemustine given by i. v. infusion at 100 mg/m^2

Patient number	Course	C_{max} (µg/ml)	$t_{1/2}$ (h)	AUC (µg h ml^{-1})	Cl (l/h)	V_{dss} (l)	Toxicity grade	
							WBC	Platelets
1	1	2.76	0.25	2.70	61	24	IV	III
3	1	3.95	0.39	4.53	40	23	II	IV
4	1	2.10	0.37	2.04	93	48	0	0
5	1	7.9	0.19	7.64	21	6	II	0
6	1	3.2	0.42	3.58	53	32	III	III
7	1	4.6	0.50	3.86	44	31	0	0
8	1	2.4	0.37	3.35	52	28	III	II
9	1	1.65	0.26	1.97	84	24	IV	III
	2	2.11	0.31	2.61	63	24		
10	1	2.63	0.38	2.83	71	47	II	0
	2	1.86	0.40	2.31	87	48		
11	1	3.10	0.34	3.42	51	24	III	III
12	2	3.72	0.32	4.61	39	16	NE	NE
19	2	3.11	0.32	3.95	47	24	NE	NE
20	1	2.20	0.35	2.58	65	30	NE	NE
21	1	–	0.36	2.89	69	36	NE	NE
22	2	4.94	0.26	6.42	7	9	NE	NE

NE, Not evaluable

Table 2. Pharmacokinetics of fotemustine given by HIA infusion at 100 mg/m^2

Patient number	Course	C_{max} (μg/ml)	$t_{1/2}$ (h)	AUC (μg /h/ml^{-1})	Cl (l/h)	V_d (l)	Toxicity grade		Hepatic arteriovenous shunt[a]
							WBC	Platelets	
13	1	0.60	0.31	1.80	104	41	0	0	–
	2	0.48	0.28	2.12	88	36			–
14	1	0.67	0.50	2.54	73	48	I	I	–
15	1	0.58	0.53	1.78	89	62	0	0	30%
16	1	0.69	0.27	2.29	72	27	II	II	–
19	1	0.48	0.35	1.93	96	46	NE	NE	–
20	2	0.35	0.26	0.84	200	60	NE	NE	–
21	2	0.83	0.28	0.40	497	17	NE	NE	–
22	1	1.20	0.28	4.08	12	16	NE	NE	–
17	1	0.77	0.36	2.55	65	33	III	I	++
	2	1.13	0.26	4.30	39	14			++
18	1	0.84	0.26	2.90	66	24	III	II	++

[a] –, shunt <30%; ++, shunt >30%
NE, Not evaluable

Table 3. Mean pharmacokinetic parameters following i. v. and HIA infusion of fotemustine in patients with metastatic colorectal cancer

Number of courses	Dose (mg/m^2)	C_{max} (μg h ml^{-1})	$t_{1/2}$ (h)	AUC (μg h ml^{-1})	Cl (l/h)	V_{dss} (l)
i. v. ($n = 17$)	100	3.26 ± 1.56	0.34 ± 0.07	3.60 ± 1.52	56 ± 22	28 ± 12
HIA ($n = 9$)	100	0.65 ± 0.25	0.34 ± 0.10	1.98 ± 1.04	137 ± 144	39 ± 17

least-squares fitting program (Siphar software, SIMED SA, Créteil) installed on a digital computer [8].

The other parameters were calculated according to the following equations:

Half-life ($t_{1/2}\alpha$, in hours) = log $2/\alpha$
Area under the concentration-time curve (AUC, in micrograms per millilitre per hour^{-1}) = $\zeta_0^\infty C_t dt$
Plasma clearance (Cl, in litres per hour) = F dose/AUC
Volume of distribution at steady state (V_{dss}, in litres) = CL/α

On the basis of the theoretical considerations described by Chen and Gross [4], the hepatic extraction ratio was defined as follows: $E_H = 1 - AUC_{HIA}/AUC_{i.v.}$, where $AUC_{i.v.}$ and AUC_{HIA} represent the AUC obtained following i. v. and HIA infusion, respectively, of the same dose in one patient. This parameter, which describes the first-pass liver-extraction ratio of fotemustine given on this schedule, was evaluated in patients who alternately received the two treatments.

Toxicity. Medullar, hepatic and renal effects were monitored weekly by analysis of blood samples, whereas digestive toxicity was assessed by nurses and physicians. The results were coded according to WHO gradation scales.

Statistical analysis. The non-parametric Mann-Whitney *U*-test was used to compare systemic drug exposure in patients who received the same dose of fotemustine by either i. v. or HIA infusion.

Results

Tables 1 and 2 present the pharmacokinetics of fotemustine following the administration of 100-mg/m^2 i. v. and HIA infusions, respectively, together with the observed toxic effects on white cells and platelets (when available). The mean values (± SD) obtained for the pharmacokinetic parameters are summarised in Table 3 for patients with a normal arteriovenous liver shunt. The systemic drug levels achieved by HIA or i. v. infusion in these patients were compared using the distribution-free Mann-Whitney statistical test.

A significant difference was found between the C_{max} values obtained after i. v. versus HIA infusion ($P < 0.0001$) and between $AUC_{i.v.}$ and AUC_{HIA} values ($P < 0.0001$), showing that systemic drug exposure was higher after i. v. treatment than after HIA administration of 100 mg/m^2 fotemustine (calculations of AUC values using the trapezoidal rule also revealed significant difference). The elimination half-life of the drug remained constant, but the plasma clearance of fotemustine given as a 4-h infusion seemed higher than that resulting from a 1-h infusion. This apparent dose-route difference in fotemustine clearance seems paradoxical. However, it is artefactual; since the equation used to calculate plasma clearance following HIA infusion includes a bioavailability term, F, the resultant values do not reflect drug clearance or volume of distribution but instead represent the respective parameters divided by F. When the drug is given i. v., F = 1 since all of the compound enters the systemic circulation. Following 4 h HIA infusion, a large proportion of the dose is degraded in the liver before it reaches the systemic circulation and F is therefore <1. The use of the bioavailability term thus provides an alternative method for determining the fotemustine first-pass extraction in the liver: $E_H = 1 - F$.

Table 4. Cross-over pharmacokinetic study of i.v. and HIA infusion of fotemustine: liver first-pass effect

Patient number	AUC_{HIA} ($\mu g\ h\ ml^{-1}$)	$AUC_{i.v.}$ ($\mu g\ h\ ml^{-1}$)	$E_H = 1 - \frac{AUC_{HIA}}{AUC_{i.v.}}$
19	1.93	3.95	0.51
20	0.84	2.58	0.67
21	0.40	2.89	0.86
22	4.08	6.42	0.36

The pharmacokinetic results were consistent with the haematological observations. After i.v. administration, grade III–IV leucopenia occurred in 5/10 (50%) patients and grade III–IV thrombocytopenia developed in 5/10 (50%) patients whereas no grade III–IV haematotoxicity was observed in HIA-treated patients who had not observed a hepatic arteriovenous shunt, although grade III leucopenia occurred after HIA administration in the two patients in whom a shunt had been observed. That the bioavailability term F after HIA infusion was lower in patients bearing such a shunt suggests that the liver plays a role in the degradation of the drug and substantiates our supposition that the decreased value determined for AUC_{HIA} as compared with $AUC_{i.v.}$ was not attributable to differences in infusion time or in population sampling between the two treatment groups.

Table 4 shows the results of the cross-over study of i.v. versus HIA infusion that was undertaken in four patients. These include the estimated first-pass liver-extraction ratio for a 4-h HIA infusion of fotemustine, which ranged from 0.36 to 0.86. In the patient who gained the least benefit from HIA (first-pass extraction ratio, 0.36), it is noteworthy that the AUC values were high. The major liver metastatic involvement at the time of inclusion together with the evident hepatic impairment (grade II ALP, grade II bilirubin) may have influenced the disposition of the drug in this patient.

Discussion

The primary mechanism of action of the 2-chloroethylnitrosourea group of compounds is thought to involve the chemical degradation of an inherently unstable molecule to a chloroethyldiazohydroxide intermediate. This gives rise to a reactive carbonium ion which can subsequently alkylate macromolecules at or near its site of production [17]. Thus, any procedure capable of targeting these drugs to the site of the tumour, where they subsequently degrade and expose the tumour to high concentrations of the reactive carbonium ion, might enhance the therapeutic success. Moreover, if at the same time the exposure of normal, healthy tissues to the alkylating properties of the drug could be reduced, the undesirable side effects would be less severe, resulting in an additional benefit to the patient.

In the treatment of liver tumours, the drug can be given via the hepatic artery, thereby exposing the liver to high initial concentrations due to a lack of the prior dilution of drug into other tissues that is associated with i.v. administration. The overall advantage, Rd, of the increased exposure of the tumour and decreased exposure of the healthy tissues to alkylation has been expressed by Chen and Gross [4] by the following equation:

$$Rd = \frac{Cl}{Q\,(1-E)} + \frac{1}{1-E}\ ,$$

where Cl is the total body clearance obtained during i.v. infusion; Q is the rate of blood flow to the region, i.e. hepatic blood flow; and E is the fraction of the drug extracted during a single pass through the region, i.e. the hepatic extraction ratio of the drug.

In addition, exploitation of the dose-response curve of a drug via HIA infusion may be profitable only when the agent has previously been found to exert marginal activity against this particular tumour following its i.v. administration [6]. Although the data are limited, fotemustine has demonstrated some activity as a single agent in the i.v. treatment of these tumours, with 1 partial response and 1 minor response lasting for more than 7 months as well as 2 cases of disease stabilisation being observed in a phase II study involving 14 patients with colorectal cancer [2]. Therefore, increasing the exposure of the tumour, i.e. liver metastases, via the use of an HIA infusion could be of benefit.

The results of the present pharmacokinetic study substantiate the hypothesis that a 4-h HIA infusion of fotemustine would result in a lower exposure of healthy tissues to the drug, since the AUC measured in systemic plasma was reduced by approximately 50% following such treatment as compared with a 1-h i.v. infusion. The reduction in AUC represents the proportion of the dose that has degraded in the liver, indicating a manyfold increase in the exposure of the tumour to the alkylating properties of the drug. The anticipated overall advantage, Rd, of a fotemustine HIA infusion for the treatment of hepatic metastases would therefore be great, since the clearance of fotemustine approximates the hepatic blood flow and the first-pass extraction ratio, i.e. the degradation of the drug within the liver into an alkylating intermediate with a very short half-life (<1 s), ranges from 0.4 to 0.9.

It is noteworthy that although the haematotoxicity data reported in this study for the two groups of patients who received either i.v. or HIA infusions of 100 mg/m^2 fotemustine are incomplete, they are in accordance with the results of previous phase II clinical trials in melanoma patients. In the latter studies, grade III–IV neutropenia and thombocytopenia were noted in 30% and 15%, respectively, of the 30 patients receiving HIA infusions [16] and in 46% and 40%, respectively, of the 153 patients undergoing i.v. treatment [11]. Therefore, HIA infusion of fotemustine in patients with liver metastases would seem to offer some advantage, since our results support the theory that HIA administration should provide the dual advantage of enhancing the exposure of the hepatic tumour to the alkylating intermediate of fotemustine whilst simultaneously reducing the exposure of normal healthy tissues.

The main aim of the present study was not to correlate pharmacokinetic results with clinical results. However, 35 patients with liver metastases from colorectal cancer

received fotemustine according to the described HIA protocol. A response rate of 20% has been reported [15]. Hence, further investigations using fotemustine either in combination with other drugs or on a different schedule are warranted.

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