Pharmacokinetic advantage of intra-arterial hepatic oxaliplatin administration: comparative results with cisplatin using a rabbit VX2 tumor model

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The aim of this study was to compare intra-arterial hepatic administration (IAH) versus i.v. administration of oxaliplatin and cisplatin in a VX2 tumor model in rabbits. VX2 tumors were implanted in the livers of White New Zealand female rabbits and 2 weeks later they received either cisplatin (4 mg/kg) or oxaliplatin (6 mg/kg) administered by IAH or i.v. Platinum pharmacokinetic parameters were measured by atomic absorption spectrometry at baseline, 2, 5 10, 20, 40 and 60 min, and then at 2, 4, 6 and 24 h after drug administration. Animals were sacrificed 24 h after drug administration to measure platinum concentrations in various tissues. After IAH oxaliplatin administration, we observed a significant decrease for total and filterable platinum in the C_{max} compared with i.v. administration (12.4 versus 18.2 μg/l; $p = 0.02$ and 11.2 versus 17.3 μg/l; $p = 0.02$, respectively). Significant differences in various tissue concentrations were reported when comparing IAH and i.v. administration of oxaliplatin with IAH administration offering an advantage over i.v. administration. No differences in pharmacokinetic parameters or platinum tissue accumulation were apparent between the IAH and i.v. administration with cisplatin. We conclude that there is a significant pharmacokinetic advantage to using oxaliplatin for locoregional IAH chemotherapy compared with i.v. administration. *Anti-Cancer Drugs* 15:647–650 © 2004 Lippincott Williams & Wilkins.

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Introduction

The treatment of metastatic colorectal carcinomas remains a difficult challenge. Along with the development of new drugs for this disease, delivery of cytotoxic chemotherapy to the liver via intra-arterial hepatic administration (IAH) is an important tool in the therapy of unresectable metastases.

IAH chemotherapy allows minimization of drug dilution, drug metabolism and elimination before reaching the liver, increased local drug concentration enhanced by the preferential tumor blood flow, and decreased systemic concentrations due to hepatic clearance [1]. As liver metastases are mainly vascularized by the arterial system, they are ideal targets for anti-tumor drugs administered via the IAH route [2,3]. Several drugs, including fluorodeoxyuridine (FUDR), 5-fluorouracil (5-FU), bi-chloro-ethylnitrosourea (BCNU), mitomycin C and cisplatin [4], have demonstrated increased exposure after IAH compared to peripheral i.v. infusion. However, despite reported improved response rates after IAH chemotherapy compared to i.v. administration, the real benefit to survival remains controversial. Several randomized studies comparing FUDR to 5-FU i.v. or to best supportive care have failed to demonstrate an improvement in overall survival [5–12]. On the other hand, one French multicentric study [8] showed an impact on survival (15 versus 11 months), which was confirmed in two studies [13,14] and a recent meta-analysis [15].

Oxaliplatin is a diaminocyclohexane (DACH) platinum compound with a wide spectrum of activity and is clinically active in cisplatin-resistant tumors [16]. The observation that oxaliplatin is highly cytotoxic in the NCI panel colon cancer lines, notably in comparison to cisplatin, supports these clinical reports. This is of particular interest for patients with colon cancer, in whom cisplatin is not active [17].

Pharmacokinetic and pharmacodynamic advantages of pirarubicin over doxorubicin after IAH administration have been shown using the VX2 tumor model [18,19]. The activity of this anthracycline administered by IAH in colorectal cancer was later proven, confirming the

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preclinical insight [20]. This model is useful for the study of regional cancer therapy because cell suspensions are relatively easy to inject into the liver and tumor kinetics can be followed from the stage of endoluminal thrombi to that of macroscopic multiple nodules with secondary metastases in the lungs. It also allows easy measurement of intratumoral and hepatic drug concentrations. In the current study, the pharmacokinetics of both oxaliplatin and cisplatin are compared with respect to i.v. and IAH administration using the VX2 tumor model.

Materials and methods

VX2 tumor implantation and surgical procedure

The VX2 tumor (originating from spontaneously transformed Shope papilloma) was provided by Dr G. Orth (Institut Pasteur, Paris, France) and was maintained by serial passage in carrier rabbits. Liver samples were collected from one single animal and a fragment (20–25 mg) of a well-vascularized metastasis without central necrosis was dissected out and immediately implanted in the left median lobe of the liver of a female White New Zealand rabbit weighing 2.5–3.0 kg. Hepatic implantation was performed under general anesthesia using ketamine hydrochloride (50 mg/kg, Ketamine; Parke Davis, Courbevoie, France) and xylazine 2% (0.1 ml/kg, Rompun; Bayer, Puleaux, France). Twelve days later, the VX2 metastasis was 13–18 mm in diameter without major central necrosis, satellite metastases or distant metastases. At the time of drug injection 2 weeks after tumor implantation, a tumor could be visualized at the liver surface. At day 21, the percentage of metastases was greater than 80%.

Drug administration

Cisplatin (4 mg/kg; Lilly Laboratories, Suresnes, France) or oxaliplatin (6 mg/kg; Debiopharm, Lausanne, Switzerland) were administered by either i.v. or by IAH. Drugs were infused in 50–70 ml of 5% glucose with a pump over 10 min via either an intra-arterial catheter for IAH administration or the right auricular vein for i.v. administration.

For the IAH infusion, the rabbit was put under general anesthesia (see above) and a 24-gauge catheter was inserted into the gastrointestinal artery with its distal extremity at confluence with the hepatic artery. The collateral duodeno-pancreatic arteries were ligated. Fluorescein was injected through the catheter to monitor the extent of perfusion. Experimental drug injection was carried out 24 h after catheter positioning.

Blood sample collection

Heparinized systemic blood samples (2.5 ml) were collected prior to injection 2, 5, 10, 20, 40 and 60 min, then 2, 4, 6 and 24 h thereafter, and kept on ice. Blood samples were centrifuged (3500 *g*, 10 min) to obtain 1.5 ml of plasma which was centrifuged (3800 r.p.m., 30 min) in Centrifree tubes (Amicon, Fantenay-Sous-Bois, France) to obtain plasma ultrafiltrates. Samples were frozen at –20°C until spectrophotometric analysis.

Plasma platinum concentration determination

Samples were analyzed in a Perkin-Elmer Model 3030 Atomic Absorption Spectrophotometer with Zeeman background correction. Platinum standards were prepared by serial aqueous dilution of SPEX Aqueous Standard Dilution cisplatin (1000 g/ml).

Tissue platinum concentration determination

Animals were sacrificed 24 h after drug administration. Tissue samples (tumor and normal tissues such as liver, lung and kidney) were collected and immediately frozen at –20°C. One gram of tissue was digested with concentrated nitric acid and incubated overnight at room temperature. The samples were then boiled for 5 min, cooled to room temperature, 0.5 ml of 30% H_2O_2 was added, the solution boiled again, cooled to 5°C and then stored at room temperature. Tissue platinum concentrations were determined in the same way as for plasma samples (see above).

Pharmacokinetic analysis

Total AUC was determined using the trapezoidal method. Other pharmacokinetic parameters were calculated according to standard methods. Data are presented as the mean value ± SD. The Wilcoxon test was used to assess differences between means.

Results

A total of 29 rabbits were randomly assigned to receive treatment via either IAH or i.v. and within each of these two groups, rabbits received either oxaliplatin or cisplatin, giving a total of four treatment groups. Plasma and tissue platinum concentrations (total and ultrafiltrate) were determined as a measure of drug uptake after IAH and i.v. oxaliplatin and cisplatin administration.

Plasma platinum concentrations

Plasma platinum concentrations following i.v. and IAH administration of either cisplatin or oxaliplatin are shown in Tables 1 and 2. After IAH cisplatin administration, we did not observe any significant variations for either total or filterable platinum in the peak platinum plasma concentrations (C_{max}) or of the AUC when compared with i.v. administration. In contrast, IAH oxaliplatin infusion led to a small but significant decrease compared with i.v. administration of total platinum for mean C_{max} (12.4 versus 18.2 μg/l, respectively; $p = 0.02$). When considering the ultrafiltrable platinum, mean C_{max} was also significantly lower when oxaliplatin was given via IAH versus i.v. administration (11.2 versus 17.3 μg/l; $p = 0.02$). No significant differences were observed for

Table 1 Pharmacokinetic parameters for total plasma platinum after administration of 4 mg/ml cisplatin or 6 mg/ml oxaliplatin

	Treatment (route)			
	i.v. cisplatin ($N=8$)	IAH cisplatin ($N=5$)	i.v. oxaliplatin ($N=8$)	IAH oxaliplatin ($N=8$)
Maximum concentration (μg/l)	16.5 ± 2.2	15.2 ± 1.3	18.2 ± 4.3[a]	12.4 ± 1.7[a]
Area under the curve (μg/l/h)	74.5 ± 35.3	62.9 ± 26.8	54.4 ± 28.8	51.2 ± 13.9
$T_{1/2}$ (h)	37.3 ± 6.3	35.5 ± 15.6	19.4 ± 2.8	22.6 ± 6.9
Volume (l)	9.1 ± 1.1	8.2 ± 1.3	9.8 ± 1.3	10.6 ± 2.0
Plasma clearance (l/h)	0.19 ± 0.04	0.20 ± 0.07	0.38 ± 0.04	0.37 ± 0.1

[a]p value = 0.02.

Table 2 Pharmacokinetic parameters for ultrafiltrable plasma platinum after administration of 4 mg/ml cisplatin or 6 mg/ml oxaliplatin

	Treatment (route)			
	i.v. cisplatin ($N=8$)	IAH cisplatin ($N=5$)	i.v. oxaliplatin ($N=8$)	IAH oxaliplatin ($N=8$)
Maximum concentration (μg/l)	15.6 ± 2.4	14.2 ± 2.2	17.3 ± 4.4[a]	11.2 ± 1.3[a]
Area under the curve (μg/l/h)	6.8 ± 0.9	6.9 ± 0.9	5.1 ± 1.3	4.4 ± 0.2
$T_{1/2}$ (h)	0.47 ± 0.1	0.50 ± 0.1	0.84 ± 0.8	2.48 ± 1.4
Volume (l)	1.00 ± 0.1	0.96 ± 0.2	1.95 ± 0.7	6.1 ± 2.6
Plasma clearance (l/h)	1.83 ± 0.3	1.7 ± 0.2	4.43 ± 1.4	4.23 ± 0.9

[a]p value = 0.02.

Table 3 Tissue platinum concentrations after administration of 4 mg/ml cisplatin or 6 mg/ml oxaliplatin

Platinum concentration (ng/mg)	Treatment (route)					
	i.v. cisplatin ($N=8$)	IAH cisplatin ($N=5$)	p	i.v. oxaliplatin ($N=8$)	IAH oxaliplatin ($N=8$)	p
Tumor	10.1 ± 4.6	15.3 ± 1.7	NS	7.3 ± 0.4	7.6 ± 5.2	NS
Liver	5.0 ± 2.8	3.7 ± 2.3	NS	3.5 ± 1.2	2.38 ± 1.4	NS
Lung	5.3 ± 1.7	6.5 ± 1.3	NS	6.4 ± 0.9	3.6 ± 1.5	0.003
Kidney	25.6 ± 11.4	19.1 ± 13.9	NS	17.9 ± 7.6	10.8 ± 4.9	0.07
Pancreas	1.4 ± 0.9	1.9 ± 1.9	NS	2.6 ± 1.7	1.0 ± 1.0	0.02
Spleen	4.8 ± 1.4	5.5 ± 1.6	NS	6.6 ± 2.2	6.7 ± 2.8	NS
Heart	3.2 ± 0.8	2.9 ± 1.5	NS	4.4 ± 1.4	3.1 ± 1.1	0.08

NS = not significant.

either total or filterable platinum in the mean platinum half-life, AUC and mean plasma clearance when oxaliplatin administration was given via IAH administration compared to i.v.

Tissue platinum levels

Platinum concentrations in tumor tissues and other tissues are presented in Table 3. After cisplatin administration, no significant differences in platinum accumulation either in normal or tumoral tissues were observed when comparing the two modes of administration. However, levels of platinum accumulation in normal tissues were lower after IAH oxaliplatin administration compared with i.v. oxaliplatin infusion. These differences were statistically significant for lung (3.6 versus 6.4 ng/mg; $p = 0.003$) and pancreas (1.0 versus 2.6 ng/mg; $p = 0.02$); however, they did not reach statistical significance for kidney (10.8 versus 17.9 ng/mg; $p = 0.07$) and heart levels (3.1 versus 4.4 ng/mg; $p = 0.08$). Tumoral and hepatic platinum levels were not different when oxaliplatin IAH and i.v. administration are compared.

Discussion

These results demonstrate the feasibility of oxaliplatin IAH administration in the rabbit and that oxaliplatin has a favorable profile for IAH chemotherapy in colorectal cancer patients with liver metastases. We observed a significant pharmacokinetic advantage when oxaliplatin was used as locoregional IAH chemotherapy, notably with decreased peak platinum plasma concentrations, compared to i.v. administration which may improve the therapeutic index. This is in contrast to the results observed with cisplatin where the route of administration resulted in no apparent change to these parameters. This may be due to different physicochemical properties of these two platinum derivatives. In addition, we observed a significantly lower accumulation of oxaliplatin in peripheral tissues when comparing i.v. and IAH administration. This difference did not reach statistical significance in the kidney or the heart, probably due to the variability of tissue platinum concentration and the small sample size.

This favorable pharmacokinetic profile of IAH infusion of oxaliplatin increasing local drug delivery could enhance the efficacy of treatment of liver metastases in colorectal cancer patients. The lower peripheral tissue exposure to oxaliplatin after IAH administration may provide the additional benefit of delivering low doses of chemotherapy systemically, which may in turn allow combination with active systemic chemotherapy, thus allowing control

of residual microscopic disease. This lower peripheral exposure may also reflect lower systemic toxicity, notably with respect to nausea and vomiting, and possibly lower neurotoxicity, and as such merits evaluation in clinical trials.

Overall, it appears that the pharmacokinetic advantage of IAH administration of oxaliplatin over cisplatin is of particular interest in the treatment of colorectal carcinoma patients with liver metastases. These pharmacokinetic results need to be extended in phase I/II studies in humans to examine the feasibility, the antitumor activity, and tolerance of oxaliplatin IAH administration alone and in combination with systemic chemotherapy. Preliminary clinical observations using IAH administration of oxaliplatin are encouraging [21–23], notably by the efficacy and the absence of hepatotoxicity. However, further evaluations and extensive analyses are essential and are warranted to confirm these data and to assess a differentiated contribution to colorectal cancer patient management.

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