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ORIGINAL ARTICLE

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Pharmacokinetics and antitumor effects of mitoxantrone after intratumoral or intraarterial hepatic administration in rabbits

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Abstract The intratumoral (i.t.) delivery of anticancer drugs aims at controlling tumor growth and thereby provides palliative treatment for liver neoplasms. Mitoxantrone is a good candidate for local or regional administration because (1) its metabolism is mainly hepatic, (2) it has a steep dose-response curve for multiple solid tumors, and (3) its fixation in tissues is sustained without vesicant effects after extravasation. We compared the tolerance, pharmacokinetics, and antitumor effects of mitoxantrone on hepatic VX2 tumors in rabbits treated with i.t. intraarterial hepatic (i.a.h.) or i.v. mitoxantrone, i.t. ethanol; or i.t. 0.9% NaCl and in control animals. Tumor growth rates (TGRs) were evaluated at 9 days after treatment. Myelosuppression was the limiting toxicity of i.v. mitoxantrone at 1.5 mg/kg (maximal tolerated dose, MTD), but neither i.t. nor i.a.h. administration led to hematologic toxicity at the same dose. The mitoxantrone retained in tumors after i.t. administration was seen as blue-stained areas of complete necrosis according to histologic analysis. Pharmacokinetic parameters showed a significantly decreased systemic exposure to the drug after both regional treatments, although the i.a.h. route appeared to have an edge over the i.t. route. TGRs were significantly reduced after i.t. mitoxantrone ($81 \pm 62\%$), i.a.h. mitoxantrone ($337 \pm 110\%$), and i.t. ethanol treatments ($287 \pm 117\%$) as compared with control values ($886 \pm 223\%$; $p < 0.01$). Treatment with i.v. mitoxantrone ($816 \pm 132\%$) had no antitumor effect, nor did NaCl injections ($868 \pm 116\%$). Mitoxantrone given i.t. induced the highest antitumor effects, resulting in a 3.5-fold reduction in TGRs as compared with i.a.h. mitoxantrone and i.t. ethanol treatments ($p < 0.02$). Treatment with i.t. mitoxantrone provided efficient antitumor therapy without producing major side effects. This method should be considered as palliative treatment for nonresectable liver tumors and other localized malignancies.

Key words Mitoxantrone · Intratumoral injections · Experimental liver tumors · Pharmacokinetics

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Introduction

The liver is a common site of neoplastic involvement either by primary or metastatic malignancies. As for most solid tumors, surgical resection offers the best chances of cure. Systemic chemotherapy can be palliative for advanced stages but provides little or no gain in terms of survival [20, 22]. Regional chemotherapy has obtained better responses in liver tumors than have i.v. infusions [11, 13, 24], probably by increasing drug availability to tumor cells and decreasing systemic exposure. Intraarterial hepatic (i.a.h.) perfusions, the most employed form of regional therapy, have given rise to severe local toxicities [7] and clinical trials, mostly with fluoropyrimidines, have failed to yield a survival benefit.

Intratumoral (i.t.) delivery of anticancer drugs can also potentially control tumor growth and, thereby, provide effective palliative treatment with limited systemic toxicity. This therapy is less cumbersome than i.a.h. administration and should produce maximal tumor exposure to cytotoxics along with minimal toxicity to the normal liver. Percutaneous ethanol

administration is currently the most widely used form of i.t. therapy [14, 26]. Although good palliation is obtained in small liver tumors [29], treatment of larger nodules by ethanol is limited because of its scanty diffusion in tissues and due to the excessive volume of ethanol necessary for complete eradication of these lesions.

Few anticancer agents fulfill the criteria for regional and local administration. To our knowledge, limited data are available on the i.t. delivery of cytotoxic drugs, and none of them concerns the administration of mitoxantrone in liver tumors. This compound is an anthracenedione derivative with a suitable profile for local or regional administration. Since hepatic metabolism is its main excretion pathway [23[, considerable first-pass hepatic extraction may attenuate systemic exposure to the drug [25]. Mitoxantrone has a steep dose-response curve in vitro in multiple solid tumors [30, 31], but exponential killing is obtained only at concentrations exceeding those attainable after i.v. therapy [1]. It has also been shown that mitoxantrone remains fixed in tissues for long periods [27] due to stable binding to proteins and DNA compared with a gradual release of the drug over a protracted period [5]. Finally, after s.c. extravasation, mitoxantrone, unlike anthracyclines, is devoid of vesicant effects [8], indicating that its administration by extravascular routes could be beneficial.

The purpose of this study was to determine the feasibility of i.t. injection of mitoxantrone, to analyze the pharmacokinetics of i.t. and i.a.h. administration, and to assess the antitumor effects of these two routes as compared with local injection of ethanol. The rabbit VX2 tumor model was selected because of its reliability, its relevance to clinical regional chemotherapy [10, 18], and the similarity of its vascularization to that of human liver metastases and primary tumors [17].

Materials and methods

Animals, anesthesia, and VX2 tumor inoculation

White female New Zealand rabbits weighing 2.7–3.2 kg were used. All procedures were carried out using general i.v. anesthesia with ketamine hydrochloride (50 mg/kg; Ketamine, Parke Davis) and 2% xilazine (0.1 ml/kg; Rompun, Bayer) and were conducted in accordance with French and European legislation concerning animal welfare. The VX2 tumor was maintained by serial passage in the liver of carrier rabbits. Hepatic implantation of the VX2 carcinoma was accomplished through a small median subxyphoid incision. A sample of 10^7 VX2 cells in 100 µl volume was injected with a 30-gauge needle under the capsule of the left hepatic lobe. A solitary tumor was obtained 2 weeks later on the surface of the liver.

Drug administration and collection of biological samples

Mitoxantrone dihydrochloride was provided by Laboratoire Lederle (Rungis, France) and used for i.v., i.t. , and i.a.h. therapy. Other i.t. treatments consisted of injections of sterile solution of 95% ethanol (Meram, Melun, France) and of 0.9% NaCl for i.t. controls. At 14 days after tumor inoculation, a laparotomy was performed to verify the presence of a tumor. The animals were randomly assigned to six groups of six rabbits each as follows: group 1, i.t. mitoxantrone, group 2, i.a.h. mitoxantrone, group 3, i.v. mitoxantrone, group 4, i.t. ethanol group 5, i.t. 0.9% NaCl and group 6, controls (no treatment). All i.t. treatments were performed with a 30-gauge needle. Mitoxantrone, ethanol, or 0.9% NaCl was delivered by repeated injections given under direct visual control over 4 min into the center and the boundaries of the liver tumors so as to treat the whole tumor volume. For i.a.h. treatment a catheter was inserted into the gastroduodenal artery with its distal tip located at the confluence with the hepatic artery. After ligation of collateral gastric and duodenal arteries, fluorescein was injected to ensure adequate homogeneous perfusion of the liver. All i.v. perfusions of mitoxantrone were performed through the auricular vein. All i.v. and i.a.h. mitoxantrone perfusions were given as a 4-min infusion controlled by an electric pump.

For pharmacokinetics studies, heparinized blood samples (2 ml) from animals treated with mitoxantrone were drawn from the left ear artery prior to injection and at 2, 5, 8, 10, 15, 30, 45, and 60 min as well as 2, 4, 6, and 24 h thereafter. Samples were centrifuged (2000 *g*, 10 min) and frozen at -20° C until analysis by high-performance liquid chromatography (HPLC) with 0.001% sodium bisulfite serving as an antioxidant. The hematologic toxicity (white blood cell counts) as well as the clinical tolerance of i.t. and i.v. mitoxantrone were evaluated at 5, 7, and 14 days after treatment and the data were compared with pretreatment baseline values for groups of six rabbits treated at five dose levels (1, 1.5, 2, 2.5, and 3 mg/kg).

Determination of mitoxantrone plasma concentrations

Plasma concentrations were determined using reversed-phase HPLC according to previously published methods [2]. All solvents used for extraction and HPLC analyses were of HPLC grade. A 0.5-ml volume of plasma was extracted on 100 mg octadecyl (C18) columns (1 ml Bakerbond spe, Baker, Phillipsburg, N.J.) preconditioned with 3 ml methanol followed by 3 ml water. After a washing step with 1 ml 0.01 *N* HCl, the elution was accomplished with 800 µl 0.5 *N* HCl-methanol. The volume was then reduced to dryness under a nitrogen stream and reconstituted with 200 µl mobile phase before HPLC injection. The rate of drug recovery for this procedure was 80%. The HPLC system consisted of a C18 column (Nucleosil C, 10 µm, 3.9 × 300 mm; SFCC, Neuilly-sur-Seine, France), a Wisp automatic injector (710B; Waters Associates, Milford, Mass., USA), a 6000A pump (Waters), and a UV detector (Waters) set at 658 nm. The mobile phase consisted of water (adjusted to pH 4.3 with ammonium formiate) and acetonitrile (73:27, v:v) run at a flow rate of 1.5 ml/min. Under these conditions, the peak retention time was 4.48 min and the peak coeluted with a mitoxantrone standard. Quantifications were performed by the external standard method.

Pharmacokinetic analysis

The decrease in the plasma concentration versus time curve was triexponential after i.v., i.a.h. and i.t. injection. Pharmacokinetic parameters for each animal were evaluated by a model-independent method of estimation (APIS, Miips, Marseille, France). The slopes of the three exponential phases (α, β, and γ) were calculated by log linear regression, and half-lives were estimated as $Ln2/\alpha$, $Ln2/\beta$, $Ln2/\gamma$. The area under the concentration versus time curve (AUC) was calculated with the trapezoidal rule from 0 to 24 h, and extrapolated to infinity according to the log-linear regression of the last elimination phase. The total plasma clearance was calculated by dividing the dose by the AUC.

Antitumor effects of mitoxantrone

The antitumor effects were evaluated by comparing the tumor growth rates (TGRs) of six groups of six rabbits as previously mentioned. A laparotomy was performed at 14 days after the inoculation of cells, and measurements of the two visible tumor diameters were obtained. All treatments were given as single doses at that time. Then 9 days later, all rabbits were euthanized, tumors were measured again, and specimens were obtained for histologic assessment of the tumors' response to treatment. Tumor volumes were calculated as $(D \times d^2)/2$. Tumor growth was estimated by comparing the tumor volumes obtained before and after treatment using the following formula:

$$(\text{volume after treatment}/\text{volume before treatment} - 1) \times 100.$$

Statistical analysis

All biologic, pharmacokinetic, and tumor-growth-ratio results were compared using the Mann-Whitney non-parametric test. Significance was assumed for all tests at $P < 0.05$.

Results

Histologic effects of locoregional treatments

At 9 days after i.t. administration of mitoxantrone the tumor specimens bore heterogeneous blue-stained areas, evidence of the continued presence of the drug in the tumor. The histologic analysis of these stained tissues revealed complete necrosis, with dead tumor cells being surrounded by a lymphocyte-monocyte inflammatory infiltrate. The liver tissue at the periphery of the tumor showed moderate hepatocyte damage and a fibrotic organization around the tumor. No distant damage was observed in the liver, bile ducts or gallbladder. This histologic pattern was observed for up to 21 days after treatment, with the stained blue tissue persisting at that time. The i.a.h. administration of mitoxantrone caused moderate diffuse hepatocytic damage and incipient fibrosis of the portal triad along with a cellular inflammatory infiltrate, but there was no evidence of cholestasis. Tumors showed diffuse areas of necrosis with no blue stain in the tissue.

Tumors injected with ethanol showed coagulation necrosis following protein denaturation. The same effect was observed in the surrounding liver tissue that had been in contact with ethanol. Lesions remained localized and there was no injury to distant hepatic tissue or the biliary tree. Tumors injected with NaCl as repeated control injections showed no histologically visible damage nor did tumors in animals treated with i.v. mitoxantrone.

Systemic tolerance of i.t. and i.a.h. mitoxantrone at the maximal tolerated dose

After i.v. administration, myelotoxicity was the limiting toxicity of mitoxantrone. Doses of 2 mg/kg provoked significant myelosuppression and weight loss, with the death of one-third of the treated animals occurring 20 days later. Doses of 1.5 mg/kg also gave rise to leukopenia, but recovery was observed at 14 days after treatment. This dose was retained as the maximal tolerated dose (MTD) for i.v. perfusions. Dose escalation for i.t. administration of mitoxantrone was started at 1.5 mg/kg, and 0.5-mg increments could be given up to a dose of 2.5 mg/kg. Unlike the situation with ethanol, drug diffusion throughout tissues was easier and uniform after i.t. injections of mitoxantrone. The dose of 2.5 mg/kg produced moderate leukopenia, although no weight loss was observed, and higher doses (3 mg/kg) were uniformly lethal. This MTD of 2.5 mg/kg represents a 66% increment is compared with the 1.5-mg/kg i.v. dose, and it provoked similar myelotoxicity. Thus, the dose-limiting side effect of i.t. mitoxantrone was myelosuppression, as was the case after i.v. treatments. The same dose (1.5 mg/kg) of mitoxantrone was given by the i.a.h. route and no hematologic toxicity was observed.

Plasma pharmacokinetics

The plasma concentration versus time curves generated following either i.v., i.t., or i.a.h. treatments with mitoxantrone at 1.5 mg/kg are depicted in Fig. 1 and the corresponding pharmacokinetic parameters are summarized in Table 1. The mean maximal plasma concentrations showed 2- and 8-fold decreases after i.t. and i.a.h. administration, respectively, as compared with i.v. administration ($P < 0.05$). Figure 2 shows the concentration versus time curves plotted for the 1st h after administration, which illustrate the differences observed between groups in terms of maximal plasma concentration. The plasma AUCs calculated after regional administration were significantly lower ($P < 0.05$) than those recorded after i.v. administration, with the i.v./i.t. and i.v./i.a.h. ratios being 1.5 and 3, respectively. In addition, the plasma AUC noted after

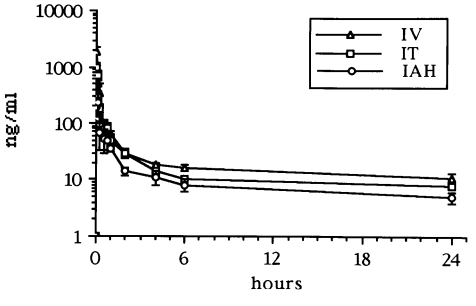

Fig. 1 Plasma concentrations of mitoxantrone (0–24 h) measured in three groups of six rabbits each following i.v. (*IV*), i.t. (*IT*), or i.a.h. (*IAH*) administration of a 1.5-mg/kg dose. Concentrations were determined by HPLC (*Triangles* i.v., squares i.t. *circles* i.a.h.). Each *point* represents the mean value ±SD

Table 1 Mean pharmacokinetic parameters of mitoxantrone obtained after i.v., i.t., and i.a.h. administration of 1.5 mg/kg in three groups of six rabbits

Route	AUC 0-$^{\infty}$ (ng h ml^{-1})	C max (ng ml)	V dγ (l)	Cl (l/h)	Half-lives		
					α(min)	β(min)	γ(h)
i.v.	1188 $\pm$215	1950 $\pm$647	233 $\pm$99	4.7 $\pm$1.3	2.5 $\pm$2	47 $\pm$15	34 $\pm$10
i.t.	761 $\pm$118	989 $\pm$608	241 $\pm$43	6.9 $\pm$1.4	1.7 $\pm$1.4	34 $\pm$18	25 $\pm$15
i.a.h.	414 $\pm$55	237 $\pm$178	433 $\pm$207	13.3 $\pm$3.9	7.7 $\pm$4.3	65 $\pm$29	22 $\pm$9

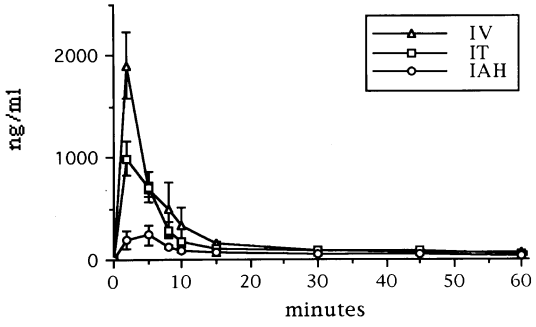

Fig. 2 Early plasma concentrations (0–60 min) of mitoxantrone measured in three groups of six rabbits following i.v. (*IV*), i.t. (*IT*) or i.a.h (*IAH*) administration of a 1.5-mg/kg dose (*Triangles*, i.v., *squares* i.t., *circles* i.a.h. Each *point* represents the mean value $\pm$SD

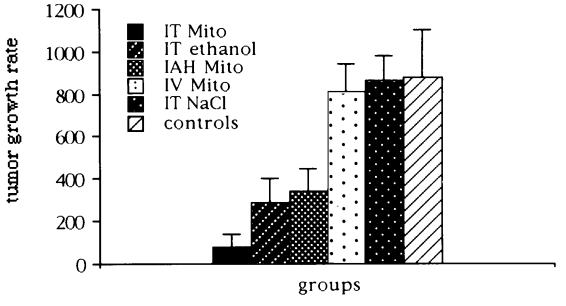

Fig. 3 Antitumor effects of mitoxantrone. Mean tumor growth rates obtained for rabbits following treatment with i.t. mitoxantrone (*IT Mito*, *black bars*), *i.t.* (*IT*) ethanol (*dark hatched bars*), i.a.h. mitoxantrone (*IAH Mito*, *gray dotted bars*), i.v. mitoxantrone (*IV Mito*, *white dotted bars*), or i.t. (*IT*) NaCl (*black dotted bars*) and for control animals (*white hatched bars*). Each *bar* represents the mean value for 6 rabbits

i.a.h. administration was significantly lower than that obtained after i.t. administration ($P < 0.05$). The total body clearance of mitoxantrone was significantly enhanced after i.t. and i.a.h. administration, but differences between the two routes were again in favor of the i.a.h. route ($P < 0.05$). Wide variability was noted in mean half-lives and volumes of distribution, and no significant difference was noted between groups.

Antitumor effects of mitoxantrone

The antitumor effects of i.t. and i.a.h. mitoxantrone were compared with those of i.v. mitoxantrone, i.t. ethanol (as standard local treatment), and i.t. 0.9% NaCl (to evaluate the effect of repeated tumor punctures) relative to control values. Significant reductions in TGRs were obtained after treatment with i.t. mitoxantrone (81 $\pm$62%), i.a.h. mitoxantrone (337 $\pm$110%) and i.t. ethanol (287 $\pm$117%) as compared with those obtained for controls (886 $\pm$223%; $P < 0.01$). Mitoxantrone given i.v. showed no antitumor activity (816 $\pm$132%), nor did the i.t. injections of 0.9% NaCl (868 $\pm$116%). Overall, i.t. mitoxantrone exhibited the highest antitumor effect; indeed, it resulted in a 3.5-fold reduction in TGRs as compared with i.a.h. mitoxantrone and i.t. ethanol ($P < 0.02$). Comparative data are shown in Fig. 3.

Discussion

Regional cancer therapy can induce better antitumor effects than can systemic therapy by improving the dose-response relationship of cytotoxic drugs. We explored the adequacy of mitoxantrone for direct injection into liver tumors and compared this modality with conventional i.a.h. and i.v. administration.

The i.t. administration of mitoxantrone was easy to perform and well tolerated, and no toxicity was found in distant normal liver tissue. In contrast, the i.a.h. administration of mitoxantrone induced diffuse lesions throughout the entire liver, like those observed after i.a.h. infusions in humans. These lesions were essentially localized in the biliary canaliculi and were probably related to vascular damage in the peribiliary plexus. They suggest that hepatic toxicity of mitoxantrone is a limiting factor, as has been seen with i.a.h. perfusions of fluorodeoxyuridine (FUDR) [4].

Both i.t. and i.a.h. administration caused less systemic toxicity than did i.v. treatment, as expected for regional therapy. This finding correlated with our pharmacokinetic data, which reflected higher systemic exposure in rabbits after i.t. administration than after i.a.h. administration. A possible explanation could be related to the injection of a liquid volume into noncompliant solid tissue. This injection creates an increase in hydrostatic pressure as well as in the concentration

gradient of the drug. Misinjection into tumor neovessels may also occur, and all three of these three factors could result in the passage of mitoxantrone into the systemic circulation. On the other hand, the reduced systemic exposure obtained after i.a.h. administration was probably related to the distribution of the drug in the entire liver, which efficiently achieved a first-pass extraction, unlike treatment by the i.t. route. The hepatic extraction ratio of mitoxantrone can be estimated at 0.65, which corresponds to a 3-fold diminution in systemic exposure for i.a.h. versus i.v. administration. This advantage is 50% greater than that reported for doxorubicin when the same routes of administration are compared [9].

To our knowledge, data are not available on experimental i.a.h. perfusions of mitoxantrone, but a clinical study has suggested similar pharmacokinetic behavior in a comparison of i.v. and i.a.h. administration, albeit with a 3-fold difference in the peak plasma levels [28]. Other authors have found no significant difference in pharmacokinetic parameters after i.a.h. administration for infusion periods of 2 or 24 h [6]. Clinical antitumor effects after i.a.h. administration of mitoxantrone have been described in two reports, but no firm conclusion can be drawn due to large differences in response rates as well as in patient populations and administration schedules [12, 25].

The superiority of i.t. treatment can be related to various factors. The good diffusibility of mitoxantrone promoted satisfactory distribution throughout the tumor volume. We observed significant tumor staining by mitoxantrone after i.t. administration that lasted for as long as 3 weeks, as previously reported after i.p. or even after i.v. treatment [2, 15]. The prolonged retention of mitoxantrone in tissues is related to its extensive binding to proteins and DNA, which results in a prolonged cellular half-life [5]. The continucation of drug antitumor activity in these stained areas for even several days after treatment cannot be ruled out, since protein-bound mitoxantrone has been shown to maintain its cytotoxic activity against ovarian cell lines in vitro [16]. In the present study, the macroscopic blue-stained areas exhibited complete tumor necrosis at histologic analysis. The histologic patterns of the lesions in tumors or liver parenchyma suggest a cytotoxic effect of the drug rather than the chemical necrosis observed after tumor alcoholization. On the other hand, the extensive on-site fibrosis observed after i.t. administration of mitoxantrone and other cytotoxics [3] suggests that caution should be taken in the long-term assessment of tumor responses after i.t. therapy.

Other anticancer agents have also been tested by direct i.t. administration. Although these studies were performed on s.c. tumor models, they demonstrate the therapeutic efficacy of i.t. injections [3, 19, 21]. This effectiveness could be related to the more favorable dose-response obtained with i.t. administration. Indeed, tumor drug concentrations measured after i.t. administration have been reported to be 1000-fold higher than those measured after delivery of the same dose by the i.v. route [32], and are also probably higher than those achievable by the i.a.h. route.

The antitumor effects achieved with i.t. mitoxantrone were superior to those obtained with i.t. ethanol. The better efficacy of i.t. mitoxantrone may in part be attributable to its enhanced diffusibility's permitting a more homogeneous drug distribution. This is a critical issue, since ethanol diffusion in tissues is difficult and the total injectable volume must be limited to avoid pain or excessive passage into the biliary tree. In contrast, the administration of a larger diluted volume of mitoxantrone is possible and should improve the drug distribution and provide more effective treatment of the tumor boundaries. Therefore, i.t. administration of mitoxantrone is based on rationale opposite to that underlying treatment with ethanol, since the total volume of injected drug need not be limited by the tumor volume.

In conclusion, local i.t. treatment with mitoxantrone should be considered is a viable component of multimodality therapy for liver cancer. It should be worthwhile for hepatocarcinoma that remains localized within the liver even at advanced stages. This treatment could be further explored in a palliative setting. A preliminary clinical trial will be initiated on the present basis.

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References

1. Alberts D, Young L, Mason N, Salmon S (1985) In-vitro evaluation of anticancer drugs against ovarian cancer at concentrations achievable by intraperitoneal administration. Semin Oncol 12 [Suppl 4]: 38–42
2. Alberts D, Peng Y, Leigh S, Davis T, Woodward D (1985) Disposition of mitoxantrone in cancer patients. Cancer Res 45:1879–1884
3. Andrews P, Johnson C (1989) Regional chemotherapy in an experimental model of Wilms' tumor in rats. Cancer Chemother Pharmacol 23:31–36
4. Bognel C, Degott C, Rougier P, Lasser P, Elias D, Grandjouan S, Duvillard P, Charpentier P, Prade M (1989) Etude anatomopathologique de la toxicité hépatique de la chimiothérapie intra-artérielle hépatique. Gastroenterol Clin Biol 13:125–131
5. Canal P, Attal M, Chatelut E, Guichard S, Huguet F, Muller C, Schlaifer D, Laurent G, Houin G, Bugat R (1993) Plasma and cellular pharmacokinetics of mitoxantrone in a high-dose chemotherapeutic regimen for refractory lymphomas. Cancer Res 53:4850–4854
6. Czejka M, Jäger W, Georgopoulos A, Schüller J (1990) Pharmacokinetics of mitoxantrone in patients after 2 h and 24 h intra-arterial administration. Eur J Drug Metab Pharmacokinet 15:219–222
7. Doria M, Shepard K, Levin B, Riddell R (1986) Liver pathology following hepatic arterial infusion chemotherapy. Cancer 58:855–861

8. Dorr R, Alberts D, Soble M (1986) Lack of experimental vesicant activity for the anticancer agents cisplatin, melphalan, and mitoxantrone. Cancer Chemother Pharmacol 16:91–94
9. Garnick M, Ensminger W, Israel M (1979) A clinical-pharmacological evaluation of hepatic arterial infusion of adriamycin. Cancer Res 39:4105–4110
10. Gordon I, Kar R, Opfell RW, and Wile AG (1987) Pharmacokinetics of hexamethylmelamine in intralipid following hepatic regional administration in rabbits. Cancer Res 47:5070–5073
11. Hohn D, Stagg R, Friedman M, Hannigan J, Rayner A, Ignoffo R, Acord P, Lewis B (1989) A randomized trial of continuous intravenous versus hepatic intraarterial floxuridine in patients with colorectal cancer metastatic to the liver: the Northern California Oncology Group trial. J Clin Oncol 7:1646–1654
12. Jones D, Patt Y, Ajani J, Abbruzzese J, Carrasco C, Charnsangavej C, Levin B, Wallace S (1993) A phase I–II trial of mitoxantrone by hepatic arterial infusion in patients with hepatocellular carcinoma or colorectal carcinoma metastatic to the liver. Cancer 72:2560–2563
13. Kirk Martin J, O'Connell M, Wieand H, Fitzgibbons R, Mailliard J, Rubin J, Nagorney D, Tschetter L, Krook J (1990) Intra-arterial floxuridine vs systemic fluorouracil for hepatic metastases from colorectal cancer. A randomized trial. Arch Surg 125:1022–1027
14. Livraghi T, Solbiati L (1993) Percutaneous ethanol injection in liver cancer: methods and results. Semin Interv Radiol 10:69–77
15. Markman M, George M, Hakes T, Reichman B, Hoskins W, Rubin S, Jones W, Almadrones L, Lewis J Jr (1990) Phase II trial of intraperitoneal mitoxantrone in the management of refractory ovarian cancer. J Clin Oncol 8:146–150
16. Markman M, Alberts D, Rubin S, Hakes T, Lewis J, Reichman B, Jones W, Curtin J, Barakat R, Brodar F, Peng Y, Pennie K, Almadrones L, Hoskins W (1993) Evidence of persistence of mitoxantrone within the peritoneal cavity following intraperitoneal delivery. Gynecol Oncol 48:185–188
17. Miller DL, O'Leary J, Girton M (1987) Distribution of iodized oil within the liver after hepatic arterial injection. Radiology 162:849–852
18. Munck JN, Riggi M, Rougier P, Chabot GG, Ramirez LH, Zhao Z, Bognel C, Ardouin P, Hérait P, and Gouyette A (1993) Pharmacokinetic and pharmacodynamic advantages of pirarubicin over adriamycin after intraarterial hepatic administration in the rabbit VX2 tumor model. Cancer Res 53:1550–1154
19. Nagase M, Nomura T, Nakajima T (1987) Effects of intralesional versus ip administration of cisplatin on squamous cell carcinoma of mice. Cancer Treat Rep 71:825–829
20. Nordic Gastrointestinal Tumor Adjuvant Therapy Group (1992) Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: randomized trial. J Clin Oncol 10:904–911
21. Ohanian S, Schlager S, Goodman D (1980) Analysis of the intralesional adriamycin-induced regression of primary and metastatic growth of line-10 guinea-pig hepatoma. Cancer Immunol Immunother 8:179–187
22. Piedbois P, Buyse M, Rustum Y, Machover D, Erlichman C, Carlson R, Valone F, Labianca R, Doroshow J, Petrelli N (1992) Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 10:896–903
23. Richard B, Fabre G, Fabre I, Cano JP (1989) Excretion and metabolism of mitoxantrone in rabbits. Cancer Res 49:833–837
24. Rougier P, Laplanche A, Huguier M, Hay J, Ollivier J, Escat J, Salmon R, Julien M, Roullet-Audy J, Gallot D, Gouzi J, Pailler J, Elisa D, Lacaine F, Roos S, Rotman N, Luboinski M, Lasser P (1992) Hepatic arterial infusion of floxuridine in patients with liver metastases from colorectal carcinoma: long term results of a prespective randomized trial. J Clin Oncol 7:1112–1118
25. Shepherd F, Evans W, Blackstein M, Fine S, Heathcote J, Langer B, Taylor B, Habal F, Kutas G, Pritchard K, Kuruvilla P (1987) Hepatic arterial infusion of mitoxantrone in the treatment of primary hepatocellular carcinoma. J Clin Oncol 5:635–640
26. Shiina S, Tagawa K, Unuma T, Takanashi R, Yoshiura K, Komatsu Y, Hata Y, Niwa Y, Shiratori Y, Terano A, Sugimoto T (1991) Percutaneous ethanol injection therapy for hepatocellular carcinoma. A histopathologic study. Cancer 68: 1524–1530
27. Stewart D, Green R, Mikhael N, Montpetit V, Thibault M, Maroun J (1986) Human autopsy tissue concentrations of mitoxantrone. Cancer Treat Rep 70:1255–1261
28. Van Belle S, M Planque de, Smith I, Oosterom A van, Schoemaker T, Deneve W, McVie J (1986) Pharmacokinetics of mitoxantrone in humans following single-agent infusion or intra-arterial injection therapy or combined-agent infusion therapy. Cancer Chemother Pharmacol 18:27–32
29. Vilana R, Bruix J, Bru C, Ayuso C, Solé M, Rodés J (1992) Tumor size determines the efficacy of percutaneous ethanol injection for the treatment of small hepatocellular carcinoma. Hepatology 16:353–357
30. Von Hoff D, Coltman C, Forseth B (1981) Activity of mitoxantrone in a human tumor cloning system. Cancer Res 41:1853–1855
31. Von Hoff D, Clark G, Weiss G, Marshall M, Buchok J, Knight W, LeMaistre C (1986) Use of in-vitro dose response effects to select antineoplastics for high-dose or regional administration regimens. J Clin Oncol 4:1827–1834
32. Zamboglou N, Wurm R, Pape H, Schnabel T, Kuhn F, Streffer C, Schmitt G (1991) Simultaneous radiotherapy and intratumoral instillation of mitoxantrone in locoregional recurrence of head and neck carcinoma. Reg Cancer Treat 4:79–84