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Percutaneous Mitoxantrone Injection for Primary and Secondary Liver Tumors: Preliminary Results

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Abstract

Purpose: To determine the effects of percutaneous intratumoral chemotherapy with mitoxantrone (PIM) in the palliative treatment of malignant liver lesions.
Methods: We treated 15 progressive lesions in nine patients in whom either previous therapy failed or serious complications developed as a result. Seven lesions were metastatic and eight were due to foci of hepatocellular carcinoma. Under computed tomography (CT) guidance, we percutaneously injected 10–20 mg of mitoxantrone mixed with 0.5 ml of contrast medium into the tumor, performing one to three treatments at intervals of 1 month.
Results: There were no complications. The morphologic responses of the tumors after treatment were: minor response in one case, no change in 11 cases, progressive disease in three cases. Mitoxantrone induced tumor necrosis with no viable cancer tissue in eight of 11 biopsies. Recurrence was observed in nine of the treated lesions 2–9 months after treatment. New lesions were observed in five of nine patients 1–9 months after treatment.
Conclusion: In patients with malignant liver lesions with no other therapeutic possibilities, minimally invasive intratumoral mitoxantrone injection was carried out safely with good tumor delivery of chemotherapy, and tumor necrosis was demonstrated at biopsy. We feel this approach warrants further investigation.

Key words: Liver neoplasms, percutaneous therapy—Mitoxantrone—Intratumoral chemotherapy

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During recent years, a wide choice of therapeutic modalities have been proposed for the treatment of inoperable malignant liver lesions. The methods most commonly used are systemic chemotherapy, transcatheter arterial embolization or chemoembolization (TAE) and percutaneous ethanol injection (PEI) [1, 2]. However, chemical toxicity or locally induced morphologic changes limit the number of therapies and the frequency of tumor recurrence is high [3].

Mitoxantrone (Novantrone, Laboratoire Lederle, Rungis, France) induces persistent intracellular DNA damage. It is currently used as an anticancer agent and has demonstrated clinical activity when administered via multiple routes: intravenous, intraperitoneal, intrapleural, intrapericardial, or intrathecal. It has been injected directly into locoregional recurrences of head and neck carcinomas as a coadjuvant of radiotherapy and has produced good results [4]. Mitoxantrone was selected for palliative local treatment of malignant liver lesions because of its low tissue toxicity, high intratumoral concentration after intratumoral instillation, and long dwelling time in the tumor, since it has a propensity to remain at the application site [5, 6]. Moreover, results of previous animal experimental studies comparing the tolerance and antitumor effects of mitoxantrone and ethanol on hepatic VX2 tumors in rabbits have established that intratumoral mitoxantrone induces the highest antitumor effects and is statistically superior to intratumoral ethanol injections ($p < 0.02$) [7].

Here we evaluate percutaneous intratumoral chemotherapy with mitoxantrone (PIM) and present the preliminary results of this clinical study.

Table 1. Summary of the nature and size of the lesions, number of PIM treatments, responses according to size, biopsy results, evolution of the lesions and outcome of the patients during follow-up

Patient age and sex	Lesion	Size (cm) before PIM	Treatments	Responses	Biopsy	Stable (months)	Increase in size (months after PIM)	New lesions (months after PIM)	Follow-up (months after PIM)
67 M	Hepatocellular carcinoma	3	3	MR	neg		6	6	Died (8 mo.)
59 M	Hepatocellular carcinoma	2	1	PD	neg	—	PD		Died (2 mo.)
	Hepatocellular carcinoma	4	3	PD	neg	—	PD		
	Hepatocellular carcinoma	3	3	PD	neg	—	PD		
75 M	Hepatocellular carcinoma	2	3	NC	neg	5	—		TAE; doing well (5 mo.)
	Hepatocellular carcinoma	1	3	NC	—	5	—		
48 F	Hepatocellular carcinoma	7	3	NC	—		9	9	Died (15 mo.)
	Hepatocellular carcinoma	6	3	NC	—		9		
76 M	Metastasis: adenocarcinoma of the colon	9	2	NC	neg		3	5	i.v. CH; died (8 mo.)
	Metastasis: adenocarcinoma of the colon	3	2	NC	neg		3		
45 M	Metastasis: leiomyosarcoma of the stomach	2	3	NC	pos	18			Doing well (18 mo.)
	Metastasis: leiomyosarcoma of the stomach	1	3	NC	pos	18			
66 M	Metastasis: adenocarcinoma of the colon	3	1	NC	—		7		Lost to follow-up
60 F	Metastasis: adenocarcinoma of the rectum	3	3	NC	neg	4	—	4	Hemihepatectomy (6 mo.)
42 F	Metastasis: adenocarcinoma of the ovary	5	3	NC	pos		2	1	Died (6 mo.)

PIM = percutaneous intratumoral mitoxantrone; MR = minor response; NC = no change; PD = progressive disease; TAE = transcatheter arterial embolization; i.v. CH = intravenous chemotherapy.

Patients and Methods

We treated 15 histologically proven lesions in nine patients. Four patients presented eight foci of hepatocellular carcinoma (HCC) 1–7 cm in diameter; five patients had seven metastastic lesions 1–9 cm in diameter. Metastatic lesions were from colon adenocarcinoma (3 lesions in 2 patients), rectal adenocarcinoma (1 lesion), leiomyosarcoma of the stomach (2 lesions in 1 patient) and carcinoma of the ovary (1 lesion). The size of the lesions varied from 1 to 9 cm, with a mean size of 4 cm (Table 1).

All patients had previously received multiple treatments. Treatment modalities included partial hepatectomy (2 patients), locoregional radiotherapy (1 patient), intravenous chemotherapy administered over 2–6 years (6 patients), TAE with three to four treatments (3 patients) and PEI with three to six injections (3 patients). Initial treatment modalities could not be continued either because the patients had developed serious complications such as toxicity due to systemic chemotherapy (1 patient) or thrombosis of the hepatic artery (2 patients), or because of progression of lesions during therapy (6 patients). All lesions increased in size as demonstrated by two morphologic examinations [computed tomography (CT) or ultrasound] before treatment with mitoxantrone.

PIM was performed under CT guidance using an Elscint Prestige scan machine (Haifa, Israel). The liver was examined using 10-mm collimation thickness before and after the intravenous injection of 50 ml of contrast medium at 2 ml/sec, in arterial and portal phases. The puncture site was then marked and, after local anesthesia with 10 ml of lidocaine 1.0%, a 22-gauge needle was inserted into the middle of the lesion (Fig. 1). Intratumoral instillation results in a 1000-fold higher concentration in the tumor compared with intravenous administration. The dose used in the literature for local infiltration was 0.3–0.8 mg/cm^3 [4]. We injected 10 mg of mitoxantrone with 0.5 ml of contrast medium for lesions ≤3 cm in diameter (dose between 0.5 and 0.8 mg/cm^3) and 20 mg of mitoxantrone with 0.5 ml of contrast medium for lesions >3 cm in diameter (dose between 0.3 and 0.8 mg/cm^3). Three treatments were performed, 1 month apart, for each of 11 lesions. One patient who had two metastases from colon carcinoma received only two PIM treatments. Notwithstanding, in this patient the lesions continued to progress, tumor markers remained elevated and systemic chemotherapy was initiated. Two very small lesions situated in the hepatic dome received only one treatment because it was technically difficult to perform the puncture. CT and/or ultrasound were performed monthly for the first 3 months, and every 3 months thereafter.

The size and number of the lesions, serum alpha-fetoprotein levels and liver function parameters were recorded. The therapeutic responses of the tumors after treatment, based on size, were evaluated as follows: partial response (PR), >50% size reduction in bi-dimensional diameters; minor response (MR), 25%–50% size reduction in bi-dimensional diameters; no change (NC), <25% change in size; progressive disease (PD), >25% size increase.

To detect the presence of unexpected systemic toxicity a clinical examination and a complete blood test (blood count, liver parameters, creatinine) were performed at day 8 after the treatment. A biopsy specimen of 11 lesions (7 patients) was obtained at the periphery of the lesions before the last PIM treatment, using an 18-gauge needle.

Results

All injections were well tolerated; no other pain than that caused by the puncture was present during or after the injection of mitoxantrone. In one case a small pneumothorax occurred as a puncture-related complication but it resolved spontaneously without any further treatment. The injected product filled the entire volume of the lesion in seven cases

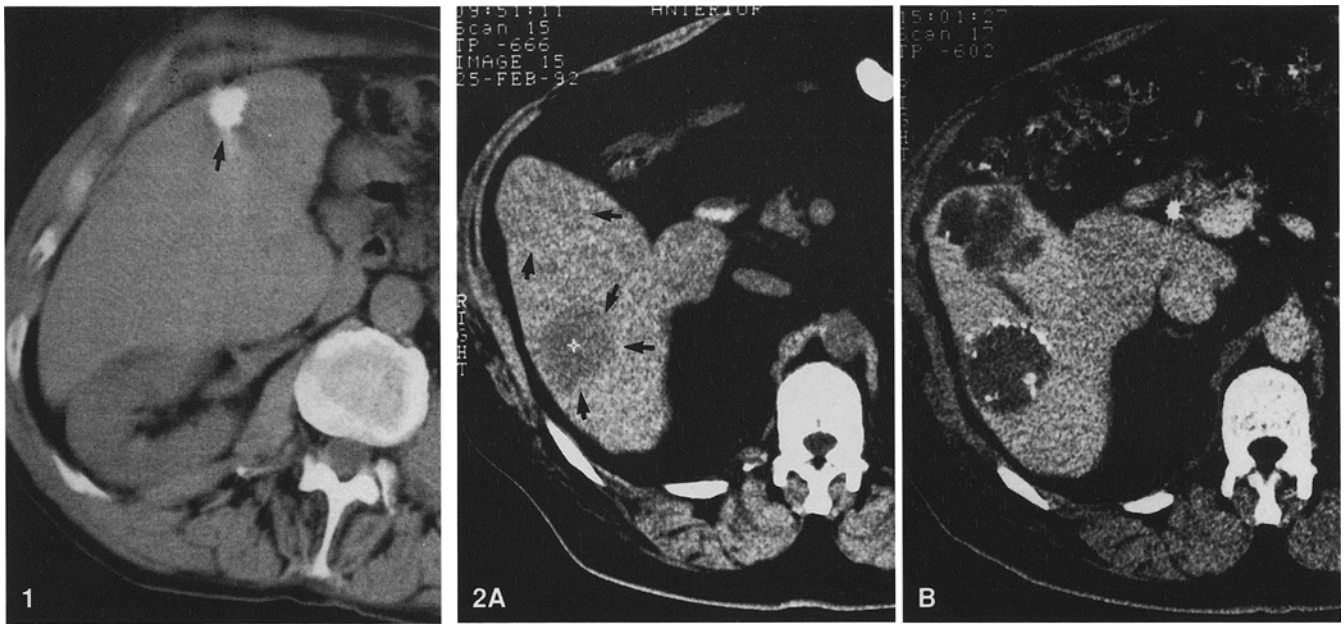

Fig. 1. CT scan showing the distribution of 10 mg of mitoxantrone mixed with 0.5 ml of contrast medium in a 3 cm hepatocellular carcinoma (arrow).

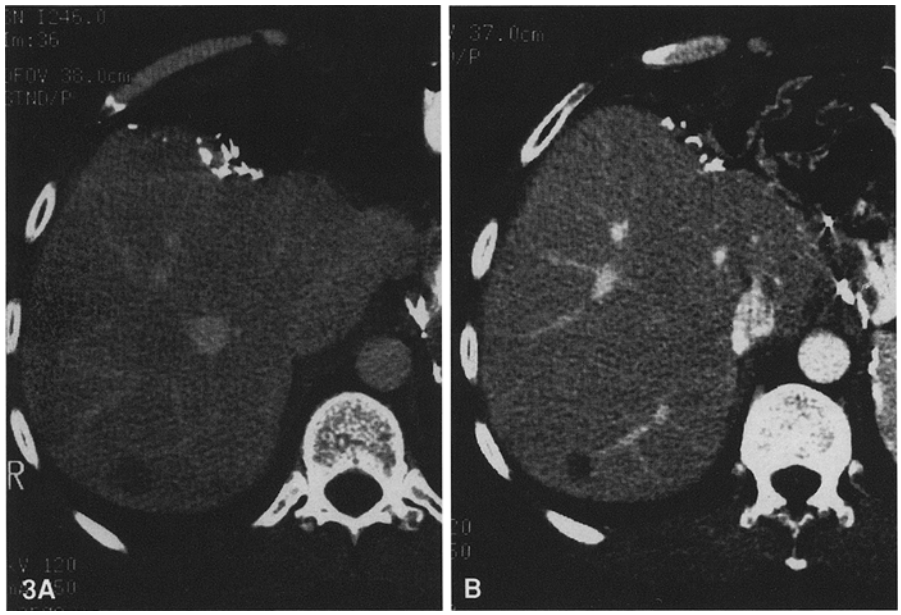

Fig. 2. **A** Two foci of hepatocellular carcinoma (arrows) previously treated over 2 years using percutaneous ethanol injection (six treatments) and transcatheter embolization (two treatments) until thrombosis of the hepatic artery occurred. **B** Follow-up CT of the liver demonstrating a slight increase in size despite three intratumoral injections of mitoxantrone.

Fig. 3. **A** Recurrence of liver metastasis of a leiomyosarcoma of the stomach after intravenous chemotherapy and partial hepatectomy in a 45-year-old patient. **B** The lesion was treated with an intratumoral injection of mitoxantrone and remained stable to slightly smaller for 18 months.

(Fig. 1), occupied the center of the lesion in six cases and concentrated at the periphery of the lesion, sparing the center, in two lesions.

Follow-up CT examinations, 1 month after therapy, showed very low attenuation of the lesion, indicating tumor necrosis. Biopsy specimens of 11 lesions showed necrosis with no viable tumor cells in eight lesions and the presence of tumor cells in three.

Tumor response after treatment based on size was minor in one lesion, no change in 11 lesions, and progressive disease in three. Nine lesions increased in size 2–9 months after treatment. Recurrence, with new lesions, was observed in five of nine patients 1–9 months after treatment (Table 1).

In the four patients with liver cirrhosis and HCC, PIM therapy obtained a minor response; the biopsy specimen was negative in one case, no response with a slight increase in the size of the foci in one patient in whom biopsy samples were negative (Fig. 2), and no change in two patients. In three of four patients, lesions stabilized between 5 and 9 months. Finally, disease progressed and new lesions emerged in two patients; three patients died of generalized disease or hepatic insufficiency 2 months to 15 months after PIM therapy and

5–9 years after the diagnosis of the HCC respectively (Table 1).

In the five patients with metastatic liver disease, lesions did not progress while they were under PIM therapy and for a period ranging between 2 and 18 months. Six of seven lesions recurred and metastatic disease continued to progress with the appearance of new lesions in four of five patients 1–6 months after PIM therapy. Of the five patients with metastatic disease, two died 3–4 years after the initial diagnosis, one had a partial hepatectomy, one is doing well, and one has been lost to follow-up.

Discussion

Surgery seems to be the most adequate treatment for HCC and liver metastasis [2, 8] but only a small percentage of patients benefit from such therapy [8]. In inoperable patients or in those presenting recurrences or multiple lesions, a number of alternative treatments can be proposed.

Chemoembolization is considered a therapy for unresectable HCC and has also been applied to liver metastases of colorectal carcinoma. After years of experience using this technique, there is no agreement on the optimal cytotoxic treatment nor whether embolization alone is more effective than chemoembolization [9]. Recent randomized controlled studies comparing chemoembolization with conservative treatment demonstrate that chemoembolization reduces tumor growth but there is no significant gain in survival [10]. Given the toxicity of chemoembolization (15% of patients suffer severe postembolization syndromes, 15% deterioration in hepatic function, and 14% gallbladder infarctions) and that the rate of mortality at 30 days is 2.6% [11], the persistent use of this technique remains controversial.

The survival rate following PEI for small (<3 cm) HCC is comparable to that of surgical resection and in such cases it is considered an alternative to surgery [1]. However, response to alcoholization is very limited in the case of hepatic metastasis. Livraghi et al. [12] performed PEI for 21 metastases and obtained 52% complete responses, while 24% of lesions remained unchanged and 24% progressed. The major drawbacks with PEI are pain caused by the injection, for which analgesics are often needed [12], and the limited volume of ethanol that can be used in one session because of its toxicity. This fact implies numerous treatment sessions, exacerbating the risk of adverse effects such as portal vein thrombosis, cholangitis, liver infarct, and intraperitoneal hemorrhage [13].

Other procedures such as percutaneous acetic acid injection or hot saline injection have proven effective against small (<3 cm) HCC [11, 12]. Indications for less invasive treatments in bulky tumors (>3 cm), recurrences, or liver metastases have not been thoroughly evaluated.

In patients subjected over several years to multiple conventional treatment modalities whose disease relapses, persists, or who have malignant liver lesions or hepatic metastases, the question is whether treatment should be continued and how. Given the controversial results and the well-known side effects of standard therapies, we decided to test a new, less invasive therapeutic modality. Mitoxantrone was chosen because of its high anticancer effect in experiments on animals and a long intracellular dwelling time [6]. Administered intravenously, it has demonstrated clinical efficacy against breast, ovarian, and neck carcinomas [6] and against experimental liver tumors in rabbits. Intratumoral injections of mitoxantrone were able to induce complete tumor necrosis without major side effects [7]. We injected it percutaneously to obtain a higher drug concentration without systemic toxicity and to preserve the integrity of the healthy liver parenchyma. All injections were performed without side effects and in particular no deterioration of liver function, which is an advantage over TAE, PEI, or repeated surgery. This factor is of paramount importance as survival is dependent on the integrity of liver function [1].

PIM can be repeated several times and at different locations. This is a tremendous advantage compared with PEI and the more invasive TAE. All but four injections were painless and patients never required analgesics during or after the procedure. Doses of 10–20 mg intratumoral mitoxantrone produced no systemic side effects and no hematologic toxicity was observed.

Biopsies demonstrated necrotic lesions (HCC or metastasis), and no malignant tumor cells were found in eight of 11 cases. The histologic effects of locoregional mitoxantrone treatments are characterized by complete tumor necrosis in which dead tumor cells are surrounded by an inflammatory infiltrate and a fibrotic organization of liver tissue around the tumor [15]. This structure tends to isolate the lesions, preventing their expansion and promoting the persistence of the drug at the injected site. This fibrous rim reaction could also explain why lesions remained stable and did not shrink after PIM, as is usually reported with other anticancer treatments. Furthermore, this fibrous rim could prevent proliferation of residual cancer cells.

Although percutaneous injection of mitoxantrone in recurrent multitreated malignant liver tumors was not curative, it allowed 12 of 15 lesions to stabilize during treatment and beyond, for between 2 and 18 months (Fig. 3). The benefit was obtained with only limited distress to the patients.

The drawback of the PIM, as with all localized treatments, is that it does not preclude the emergence of other tumor foci or the progression of untreated tumors. Although PIM stabilized lesions and biopsy samples were negative in 73% of the lesions, the incidence of recurrences after treatment was high for metastatic liver disease. Faced with such pathology, extended treatment sessions, eventually modifying mitoxantrone doses, should be considered.

Our results indicate that percutaneous mitoxantrone can be considered a less invasive therapy for recurrent or bulky (>3 cm) HCC and eventually also for liver metastases. Further randomized and comparative studies will be needed to evaluate its effects and cost-effectiveness compared with other treatment modalities.

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