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Laboratory Investigations

Transcatheter Arterial Embolization as a Method of Cisplatin-Retention Enhancement on the VX2 Tumor Uterus Transplants

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Abstract

Purpose: Enhanced cisplatin (Pt) retention using transcatheter arterial chemoembolization (TAE) with Gelfoam particles was studied in rabbit uterine tumors.

Methods: Ten rabbit uteri were inoculated with 5×10^7 cells of VX2 carcinoma. Three to four weeks later cisplatin, 1 mg/kg, was injected, either with (TAE group) or without (IA group) being mixed with small Gelfoam particles, into the aortic bifurcation over 5 s. Blood and tissue concentration of cisplatin were determined.

Results: Slower arterial blood clearance of Pt was observed in the TAE group compared with the IA group, whereas the venous blood Pt clearance curves were similar for both groups. The uterine tumor Pt concentration at 80 min was found to be 2.52-fold higher after TAE compared with IA ($p < 0.01$). In the pelvic metastatic lymph nodes, the Pt concentration was 4.63 times higher after TAE than after IA ($p < 0.01$).

Conclusion: These data indicate that TAE is an effective means of increasing tissue concentration in uterine tumors.

Key words: Rabbit, VX2 uterine cancer—Embolization—Cisplatin—Tissue concentration

Chemoembolization has been studied as a method of cancer treatment in the liver [1] and pelvic [2–5] regions. The purpose of our experimental study was to investigate whether the addition of Gelfoam emboli to intraarterially infused cisplatin (cis-diamminedichloroplatinum II, increases the local concentration of the drug in the tumor tissue compared with arterial injection of platinum alone. VX2 tumor cells [6, 7] were inoculated into the rabbit uteri. Rabbits were treated either with intraarterial cisplatin (Pt) infusion alone (IA group) or with Pt mixed with Gelfoam particles (TAE group). The total Pt concentration in various tissues and the Pt clearance, from both the arterial and venous blood, were compared for the two treatment groups.

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Material and Methods

VX2 Tumor Inoculation into the Rabbit Uterus

Female New Zealand white rabbits (3.3–4 kg) were anesthetized with 25 mg/kg pentobarbital through the auricular vein. Anesthesia was maintained with ether inhalation. A median incision on the lower abdomen was made aseptically and the uterus was exposed. VX2 tumor cells (Funabashi Farm, Chiba, Japan, Fub:NZW) were maintained subcutaneously on the intact rabbits. Before inoculation, the tumor tissue specimen was taken aseptically, and a single cell suspension was prepared in saline. The vaginal side of the uterus was ligated, and a thread was applied to a site about 3–4 cm distal to the ligation. VX2 carcinoma cells (1×10^8 cells in 2 ml of saline) were inoculated from this site unilaterally into the bicornate uterus with an 18-gauge needle. Immediately after inoculation, the affected side was ligated. Lincomycin hydrochloride (30 mg; Upjohn, Kalamazoo, MI, USA) was sprayed over the peritoneal cavity, and the same dose of the drug was injected intramuscularly.

In a preliminary experiment, diagnostic laparotomy was performed 1 and 2 weeks after inoculation, during which both the appearance of the tumor and the degree of tumor growth were estimated. During this period, no tumor growth was observed. Three weeks after inoculation, the tumor size had increased to 15–20 mm in diameter, but pelvic lymph node metastases were negligible. Four weeks after inoculation, the tumor size was about 30–50 mm in diameter, and pelvic lymph node metastases 5–10 mm in size were observed in 40% of all inoculated rabbits. In addition, lymph node metastases, in the upper abdominal area and in the lungs had occurred, causing more than 80% animal lethality. Histology of the tumor tissue at that time showed papillary proliferation of tumor cells directed toward the uterine cavity. The interstitinum consisted of fine, vascular, connective tissue surrounded by proliferating tumor cells, arranged in layers in a pavement pattern. On the tumor periphery, necrosis combined with exfoliation was shown.

According to the pathomorphological evidence, uterine tumors 3–4 weeks after inoculation were considered appropriate for the current investigation (Fig. 1).

Experimental Methods

Ten female, New Zealand white rabbits (3.3–4 kg) were divided equally into TAE and IA groups. VX2 tumor was inoculated by the method described in detail in the preliminary experiment. Three to four weeks after inoculation, the rabbits were anesthetized with 25 mg/kg of pentobarbital injected into the auricular vein. A 3 Fr polyethylene catheter (Cook Inc., Bloomington, IN, USA) was inserted via the right femoral artery. The tip of the catheter was placed at the aortic bifurcation, and another catheter was inserted into the left femoral vein by a similar method, and its tip was placed in the inferior vena cava.

IA Group

Pt bolus injection (1 mg/kg in 2 ml of saline) was performed over 5 s via the indwelling catheter into the bifurcation of the abdominal aorta. Arterial and venous blood samples were obtained via the catheters at 15-min intervals, starting immediately after Pt administration, for up to 1 h. The blood was centrifuged at 3,000 rpm for 5 min. Pt concentration in serum was determined by atomic absorption spectrometry [8].

TAE Group

Pt powder (1 mg/kg) was dissolved in 2 ml of saline, mixed with Gelfoam particles (about 1/4 sheet), divided into 1-mm squares, agitated, and bolusly injected for 5 s via the catheter into the bifurcation of the abdominal aorta under fluoroscopy. Arterial and venous blood samples were collected identically to the IA group, and the Pt concentration was determined.

Tissue Concentration

Eighty minutes after Pt infusion, in both groups, the rabbits were killed by rapid intravenous administration of pentobarbital. Uterine tumor, ipsilateral uterus, vagina, bladder, lungs, liver, kidneys, and the lymph node metastatic tumor specimens were immediately removed, washed with saline, and frozen at −80°C. The Pt concentration in each tissue sample was determined by atomic absorption spectrometry [8]. Tissue concentration was expressed as μg platinum per g wet weight of tissue.

Statistical Analysis

The paired values obtained from the IA and the TAE groups, were evaluated by the Student's t test for statistical significance. All calculated p values are two tailed. All p values < 0.05 were considered significant. All group data are presented as mean value ± one standard deviation (SD).

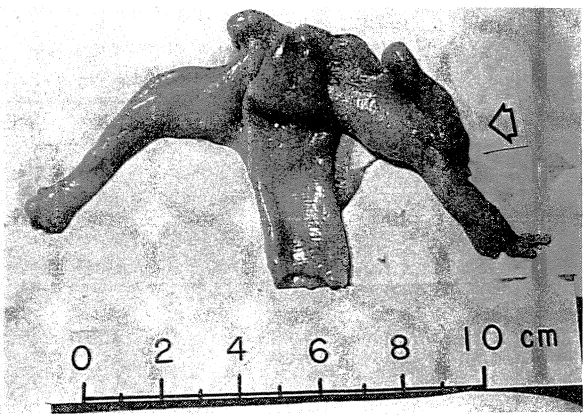

Fig. 1. The implanted uterine tumor 3 weeks after implantation (arrowhead).

Results

Blood Pt Clearance Curve

Rapid clearance (T1/2 = 6 min) of the arterial Pt concentration was registered in the IA group; a relatively slow one (T1/2 = 11 min) in the TAE group. The difference ($T = 5.34$, $p < 0.001$) between the TAE group (0.20 ± 0.04 μg/g, n = 5) and the IA group (0.09 ± 0.01 μg/g, n = 5) was significant (Fig. 2). In contrast, changes in the venous Pt concentration were not significantly different between the two groups (Fig. 3).

Tissue Pt Concentration (Fig. 4)

The Pt concentration in the normal uterus regions was 0.51 ± 0.21 μg/g on the intact side and 0.46 ± 0.14 μg/g on the tumor implant side in the TAE group. In the IA group, it was 0.40 ± 0.30 μg/g on the intact side and 0.48 ± 0.15 g/g on the implant side, which was virtually identical for the two groups. In contrast, the Pt concentration in the uterine tumor specimens was about 2.52 times higher in the TAE group compared with the IA group (1.21 ± 0.35 μg/g and 0.48 ± 0.09 μg/g, respectively). Pelvic lymph node metastases were observed in two rabbits in each experimental group. The Pt concentration in the metastatic tissue was 1.99 ± 0.86 μg/g in the TAE group and 0.43 ± 0.10 μg/g in the IA group, about 4.63 times higher in the TAE group ($n = 4$, $p < 0.01$). The Pt concentration was similar between the uterine tumors on the right side of the bicornate uterus and those on the left side.

Among the normal tissues, the highest Pt concentration was observed in the kidneys, with only a slight difference between the two groups. The Pt concentra-

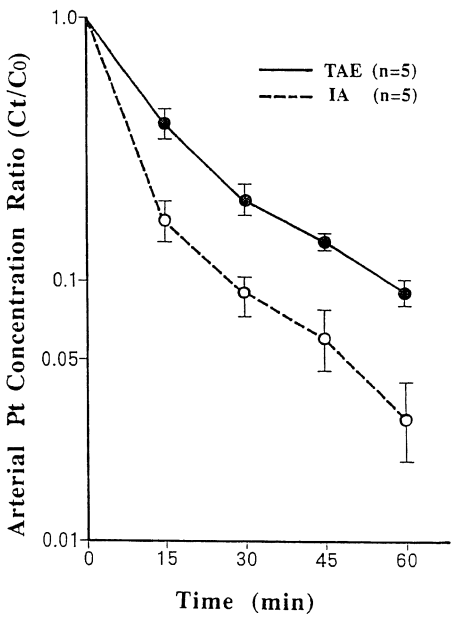

Fig. 2. Arterial serum platinum (Pt) clearance curves following intra-arterial infusion (○) and chemoembolization (●). On the Y axis, the concentration of Pt in the blood immediately after injection was regarded as 1. The Pt concentration changes with time (C_t) were expressed relative to initial level (C_0).

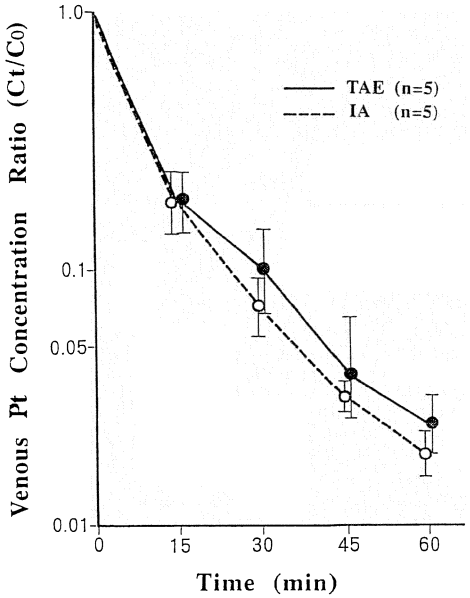

Fig. 3. Venous serum platinum clearance curves following Pt by intraarterial infusion (○) and chemoembolization (●). The Y axis shows the Pt concentration ratio as in Figure 2.

tion in the vagina, bladder, lungs, and liver did not differ significantly between the two groups.

Discussion

The VX2 tumor has been found to be a useful model for the study of regional cancer therapy [9]. In this tumor model, the TAE drug administration method was shown to be useful for treatment of liver cancer [10]. Nevertheless, experimental TAE studies using either this tumor model or other ones in the pelvic region have not been available, to our knowledge, up to this date. The vascular supply in the pelvic region is different from that of the upper abdomen, and that could cause different drug retention ratios for embolic materials. This method has already been applied in gynecologic practice with rather positive results [4, 5]. It is, therefore, desirable to undertake a quantitative study of the distribution of the drug. In the present experimental study, rabbit uterine tumors have been produced, and the malignancy of the transplanted tumor was histologically confirmed. This model was selected because of its relevance for regional chemotherapy.

The arterial Pt clearance was significantly slower in the TAE group than in the IA group. This means that in the TAE group, the outflow of Pt into the arterial blood is much more gradual, and the drug is accumulating for a longer time in the embolized area, whereas in the IA group, the drug can be easily eliminated by circulating blood. These data correspond to the findings reported by Daniels et al. [11], where the authors claim that the advantage of chemoembolization, meaning the intraarterial coadministration of chemotherapeutic agents and vascular occlusive agents, is prolongation of the dwelling time of the antineoplastic agent within the tumor, increasing first-pass extraction of the drug. We can confirm that for the pelvic region, with a much different vascularization (bilateral blood supply, large numbers of arteriovenous anastomoses), the occlusion of the main arterial systems can cause a dramatic increase in drug concentration within the tumor tissue. The venous Pt clearance was practically the same in both groups, proof of the similarity in this phase of drug elimination.

The highest Pt concentration in the normal tissues was registered in the kidneys, a relatively lower one in the liver, and the lowest in the lungs, consistent with the previously reported Pt distribution in rabbit organs [12]. These results indicate that the metabolism in the TAE and IA groups after first-pass extraction is similar to that of intravenous administration.

Regional modes of chemotherapeutic drug administration are intended to expose tumors to high concentrations and prolong tumor exposure to the drug [13]. The first step to improve the drug antitumor action was to change the intravenous infusion to an intraarterial one, where a drug is infused to a site very close to the

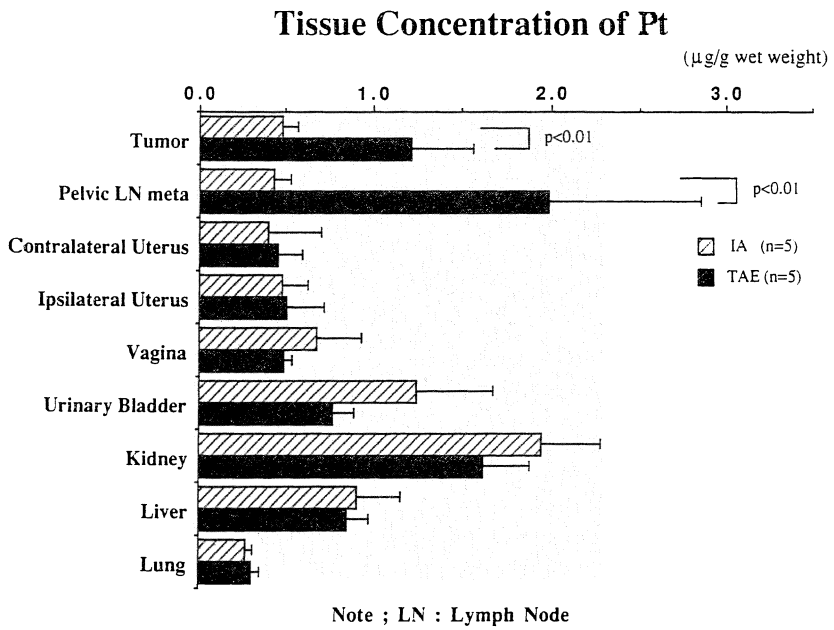

Fig. 4. Tissue platinum deposition 80 min after administration of 1 mg/kg Pt by intraarterial infusion (▨) and chemoembolization (□).

target tumor allowing its accumulation at a high concentration by the first-pass extraction and obtaining efficient pharmacological effects. Stephens [14] reported the benefit of intraarterial drug infusion compared with intravenous administration. He gave a clear quantitative picture for the advantage of IA: a 10 times higher concentration of agent can be active against the tumor while passing through the tumor circulation after injection into the artery supplying the tumor. Applying this to our results, we can conclude that the 2.5-fold increase in drug concentration in the tumor tissue by the embolization (TAE group) is equal to 25 times higher concentration of agent compared with intravenous injection. A 4.6-fold higher Pt concentration in the pelvic lymph node metastatic tumor in this group is equal to 46 times higher drug activity against the tumor during first circulation. Thus, this method can increase tumor cure rates in the pelvic region.

Concerning the association between the Pt concentration in the tumor and the antitumor effects, Jaffe et al. [15] made a comparison between the drug concentration in the tumor and the tumor necrosis rate in patients with osteosarcoma. A tumor necrosis rate of 60%–100% was obtained at a Pt concentration in the tumor of 17–40 μg/g, suggesting the necessity of a high drug concentration in the tumor. In our study, the Pt concentration in the uterine tumor was significantly higher in the TAE group than in the IA group after Pt infusion into the bifurcation of the abdominal aorta. In clinical TAE, a catheter is introduced into the internal iliac artery or the uterine artery. Therefore, in clinical practice, higher Pt accumulation in the tumor can be expected compared with the experimental study.

In conclusion, chemoembolization by intraarterial infusion of Pt in combination with Gelfoam is a useful drug delivery system that enhances the antitumor effects of Pt in the treatment of gynecologic malignancies [4, 5].

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