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Intra-arterial Adriamycin chemotherapy for bladder cancer

Semiselective intra-arterial chemotherapy with compression of the femoral arteries at the time of injection

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Summary. *Twenty patients with bladder cancer were treated by semiselective intra-arterial chemotherapy with Adriamycin. Ten of them were given the agent while the femoral arteries were compressed, to prevent loss of the agent into the external iliac arteries. The other ten were given Adriamycin without this compression. Clinical and pathological responses of tumor and the side-effects were examined in these two groups. The results of the comparative study led us to the conclusion that the compression technique is a simple and valuable means of decreasing the side-effects of Adriamycin and increasing tumor response.*

Introduction

Adriamycin (doxorubicin) is an anthracycline antibiotic with a broad anticancer spectrum [4, 5, 7] and is also effective in urogenital cancer [8, 9]. Its activity is thought to be dose-dependent [1] and it is suggested that synergistic effects are obtained by combining Adriamycin with radiotherapy [10, 16]. Intravenously injected Adriamycin disappears rapidly from the blood, distributing to and accumulating in various organs [1, 12]. These properties of Adriamycin suggest that it would be effective if given by intra-arterial injection. Although Adriamycin is effective, such effects are limited when it is semiselectively injected into the common iliac arteries, since a considerable amount of the agent is lost into the external iliac arteries. The agent lost in this way causes such general side-effects [2] as bone marrow suppression, alopecia, stomatitis, and cardiac damage. Compression of the femoral arteries during semiselective injection of Adriamycin into the common iliac arteries was thought of as a solution to this problem.

Materials and methods

A total of 20 patients with bladder cancer were included in this study. The patients were divided into two groups: 10 patients were treated by semiselective intra-arterial injection of Adriamycin without compression of the femoral arteries when the agent was injected (control group). The other 10 were given Adriamycin by the same method while the femoral arteries were compressed (study group).

Analysis of the two groups. The control group consisted of four males and six females, ranging in age from 51 to 84 years, with an average age of 67.5 years. Tumors were categorized as follows: transitional cell carcinoma in nine cases and adenocarcinoma in one case; grade 1 in two, grade 2 in three, and grade 3 in five; T1 in one, T2 in two, T3 in one, and T4 in six. The study group was composed of nine males and one female, ranging in age from 62 to 79 years, with an average age of 72.2 years. Classification of tumors in these patients was as follows: transitional cell carcinoma in 10, including a pelvic recurrence; grade 1 in two, grade 2 in four, grade 3 in three, and grade X in the single pelvic recurrence; T1 in one, T2 in two, T3 in three, and T4 in four (Table 1).

Method of treatment. A Kifa green catheter was inserted through the femoral artery percutaneously. It was fixed with its tip 2 or 3 cm above the bifurcation of the common iliac artery and was kept indwelling in th vessel for 48 h. Heparinized physiological saline, 30 or 50 ml, was infused into the catheter once or twice per 24 h to prevent the congestion of the inner space by thrombus formation. Adriamycin (20–30 mg) was dissolved in 100 ml physiological saline and injected within a few minutes while the femoral arteries were manually compressed in the study group. In the control group, it was injected without compression. In general, Adriamycin was given to the patients three times in 48 h, and thereafter five or six times at 3- or 4-week intervals (Fig. 1).

Table 1. Patient groups

Group	Control	Femoral artery compression
Sex	Male = 4	Male = 9
	Female = 6	Female = 1
Age	51–84	62–79
(Mean)	(67.5)	(72.2)
Classification of disease[a]	Bladd. TCC = 9	Bladd. TCC = 9
	ADC = 1	Pelvic Rec. = 1
T category	T1 = 1	T1 = 1
	T2 = 2	T2 = 2
	T3 = 1	T3 = 3
	T4 = 6	T4 = 3
Grade	G1 = 1	G1 = 2
	G2 = 3	G2 = 4
	G3 = 5	G3 = 3
		Gx = 1

[a] TCC, transitional cell carcinoma; ADC, adenocarcinoma; Bladd. bladder; Rec., recurrence

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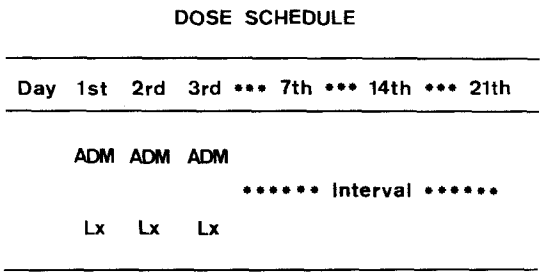

Fig. 1. Intra-arterial ADM chemotherapy. ADM, injection of Adriamycin; Lx, radiation therapy

Table 2. Total dose of Adriamycin and responses to treatment

Group	Control	Femoral artery compression
Total dose of Adriamycin	90–210 mg (148 ± 47 mg)	150–420 mg (295 ± 64 mg)
Clinical effects	CR = 7 PR = 1 NR = 1 NE = 1	CR = 6 PR = 2 NR = 1 NE = 1
(CR + PR)/Eval.	RR = 88.9%	RR = 88.9%
Pathologic effects	CR = 2 PR = 2 NR = 4 NE = 1	CR = 3 PR = 4 NR = 1 NE = 1
(CR + PR)/Eval.	RR = 50.0%	RR = 87.5%

Table 3. Side-effects of the treatment

Group	Control	Femoral artery compression
Number of cases	$n = 10$	$n = 10$
Stomatitis	10 (100%)	2 (20%)
Alopecia	10 (100%)	3 (30%)
Fever	7 (70%)	1 (10%)
Leukopenia	8 (80%)	2 (20%)
Thrombopenia	3 (30%)	1 (10%)
Cardiac Insufficiency	0	0

In some cases, radiation therapy was rapidly followed by Adriamycin injection. Bleomycin or *cis*-DDP was also combined with Adriamycin in several patients.

Evaluation of antitumor effects. In general, all patients in the two groups underwent pre- and postoperative examinations (transurethral biopsy or cystectomy, cystoscopy, cystography, urethrocystography in males, CT scan, and bimanual examination). These results for the two groups were compared.

Clinical effects were evaluated mainly by radiological findings, especially by CT scan, on the basis of a decrease in tumor size. Cystoscopic and bimanual examination of tumor were also taken into consideration. The results were evaluated as complete remission (CR) when tumor disappeared or was reduced in size by more than 90%, as partial remission (PR) when the tumor size was reduced by 25%–90%, and no remission (NR) when the tumor size was reduced by less than 25% or increased.

Histological evaluation of effectiveness was carried out using excised or biopsied specimens according to Shimosato's classification [17] summarized as follows:

Grade 0: No characteristic changes are noted in tumor cells and tumor structures.

Grade I: Characteristic changes are noted in tumor cells, but tumor structures have not been destroyed (there is no defect in tumor nests resulting from lysis of individual tumor cells).

Grade II: In addition to characteristic cellular changes, tumor structures have been destroyed as a result of disappearance of tumor cells. However, a variable number of 'viable cells' still remain:

a. Destruction of tumor structures is mild in degree, i.e., viable tumor cells are frequently observed.

b. Destruction of tumor structures is severe in degree, i.e., viable tumor cells are few in number.

Grade III: Markedly altered and presumably non-viable tumor cells are present singly or in small clusters, and viable tumor cells are hardly seen.

Grade IV: No tumor cells remain in any section (local cure):

a. Extensive areas of coagulation necrosis are present.

b. Granulation tissue with or without small foci of necrosis including keratotic debris remain.

c. Only cicatrix is observed.

Grades 0 and I were evaluated as NR, grade II as PR, and grades III and IV as CR.

Evaluation of side-effects. All patients underwent a blood test every other day and electrocardiography every 3 weeks. General condition, including loss of hair, fever, stomatitis, and appetite, was also checked every day. A leukocyte count under 2,000 was considered as leukocytopenia, and a thrombocyte count under 50,000 as thrombocytopenia.

Total dose of Adriamycin and combined treatment. The total dose of Adriamycin varied from 90 to 210 mg (148.0 ± 47.3 mg) in the control group and from 150 to 420 mg (295.0 ± 64.2 mg) in the study group. Radiation therapy was combined, at 30 Gy in four patients in the control group and at 28–42 Gy in all patients in the study group. Bleomycin was given to four patients in the control group, and a patient with pelvic recurrence in the study group received *cis*-DDP. After the intra-arterial chemotherapy with Adriamycin, all patients in both groups received maintenance chemotherapy with Tegafur (600 mg daily PO).

Results

Responses to treatment (Table 2). Clinical response was evaluated in nine of 10 patients in the control group as CR in seven, PR in one, and NR in one, so that the clinical response rate of the control group was 88.9%. In the study group it was evaluated in nine of 10 patients, as CR in six, PR in two, and NR in one, so that the clinical response rate of the study group was also 88.9%. On the other hand, histological response was evaluated in eight patients of each group, and the results were as follows: in the control group, CR in two, PR in two, and NR in four; however, in the study group, CR in three, PR in four, and NR in one. The histological response rates were 50.0% in the control group and 87.5% in the study group. The non-response rates were 50.0% in the control group and 12.5% in the study group.

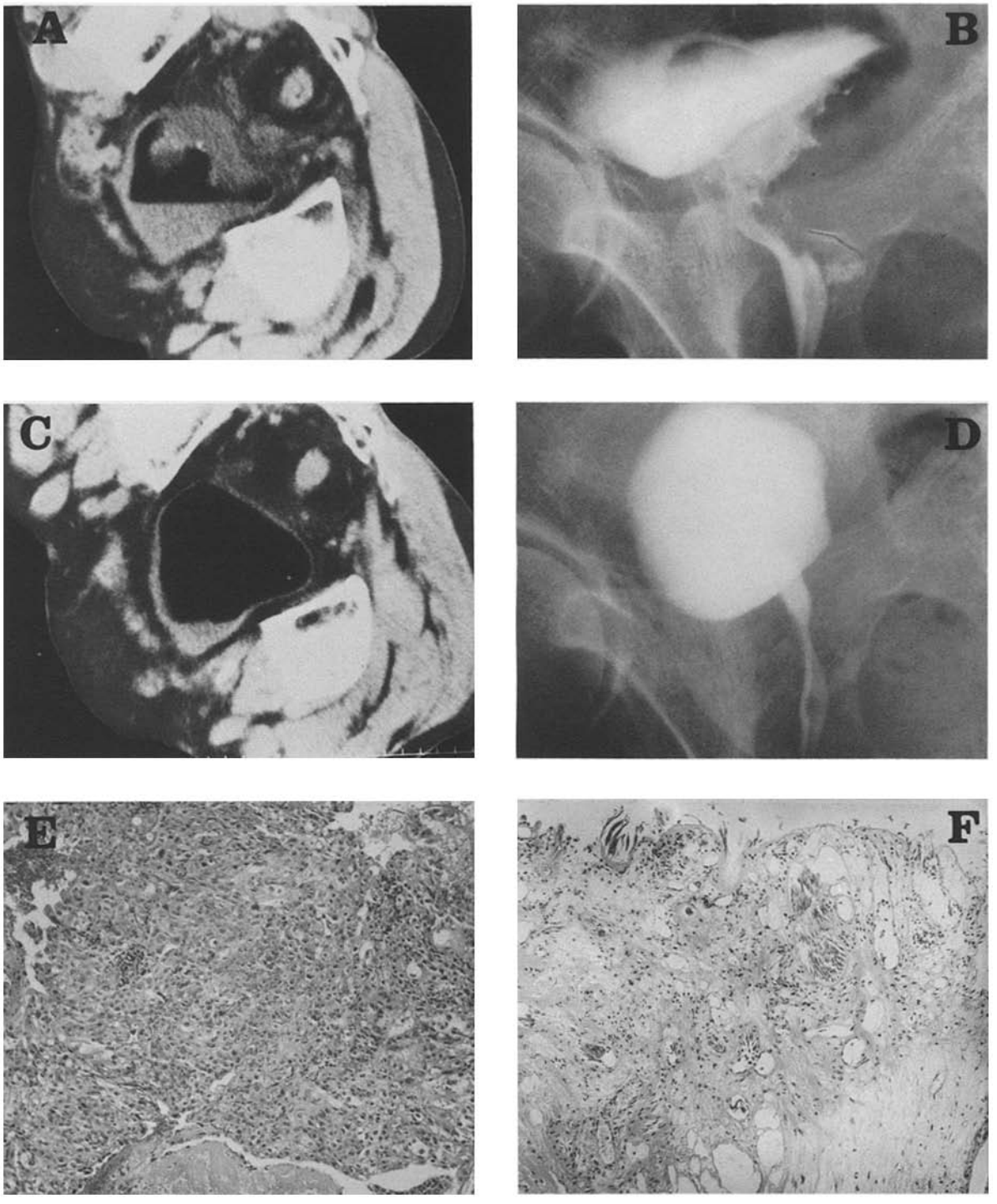

Fig. 2A–F. Radiographic and pathological findings in case 22. CT scan [**A**] and urethrocystography [**B**] prior to treatment, showing T4 tumor. Post-treatment findings [**C**, **D**] demonstrate complete remission of the tumor. Pre-operative biopsy [**E**] shows grade 3 transitional cell carcinoma, and post-operative biopsy [**F**] reveals grade III pathological effect

Side-effects (Table 3). In the control group, leukocytopenia appeared in eight of 10 patients (80.0%), thrombocytopenia in three (30.0%), fever (up to 38.0° C, lasting 3 days or more) in seven (70.0%), stomatitis in 10 (100%), and alopecia in 10 (100%). In the study group, leukocytopenia appeared in two of 10 (20.0%), thrombocytopenia in one (10.0%), fever in one (10.%), stomatitis in two (20.0%), and alopecia in three (30.0%).

Case report

Case 22, a 64-year-old male with a bladder tumor (T_4 N_x M_0). This patient received 300 mg Adriamycin and 30 Gy radiotherapy. After the treatment, the tumor disappeared and the results of multiple transurethral biopsy showed grade III histological effect. Oral chemotherapy has been continued with Tegafur (600 mg daily), and there is no clinical evidence

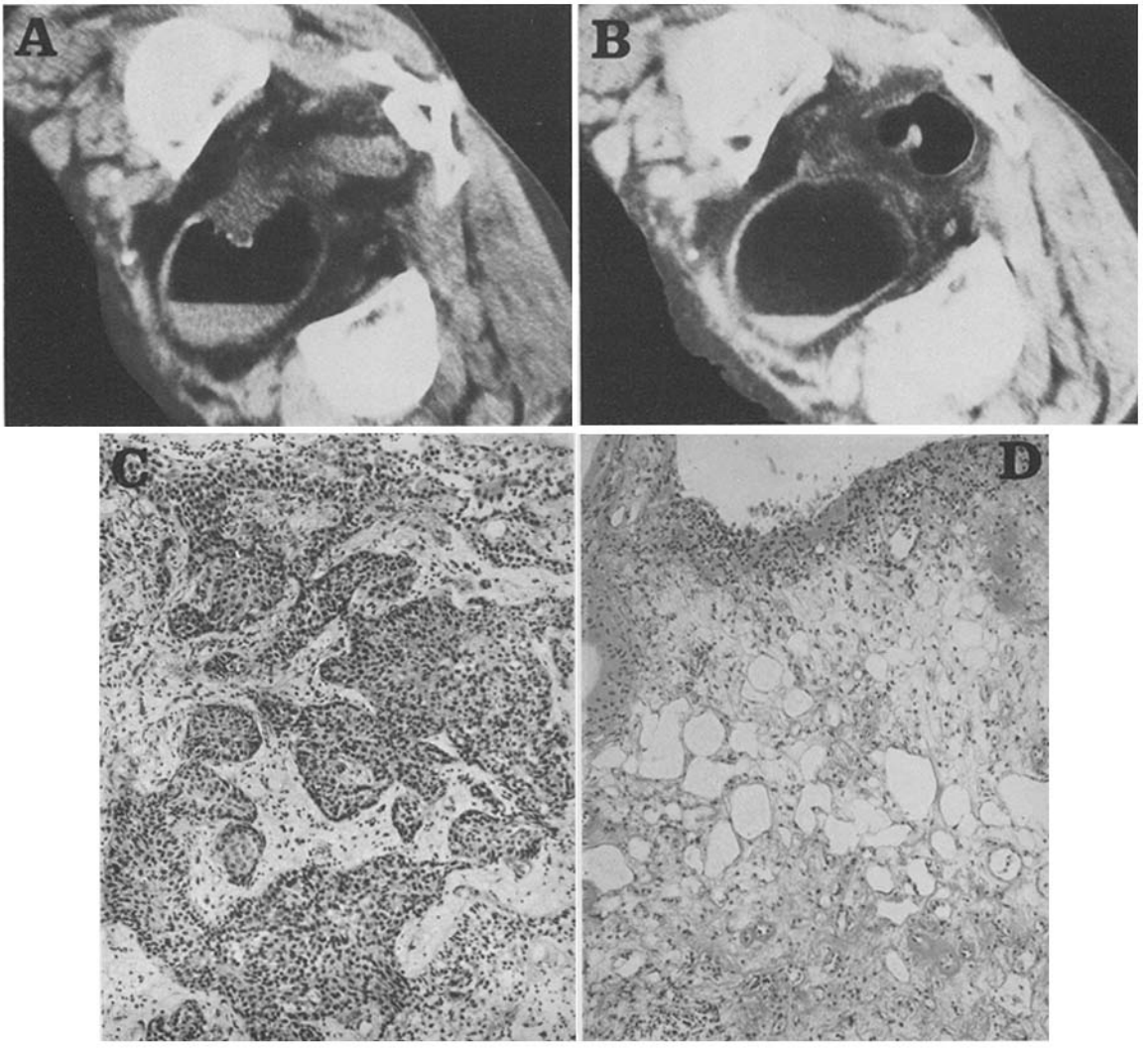

Fig. 3A–D. Radiographic and pathological findings in case 23. CT scan prior to the treatment [**A**] shows T3 bladder tumor; postoperative CT scan [**B**] reveals complete remission of the tumor. Pre-operative biopsy [**C**] shows grade 3 transitional cell carcinoma, and post-operative biopsy [**D**] reveals grade IVb pathological effect

of recurrent tumor at 13 months after initial admission (Fig. 2).

Case 23, a 78-year-old male with a bladder tumor (T_4 N_x M_0). The patient treated with 300 mg Adriamycin in combination with a course of 30 Gy irradiation. The postoperative examination revealed disappearance of tumor and grade IV pathological effect. This was considered as a local cure. Maintenance treatment was also administered in the form of oral chemotherapy with Tegafur (600 mg daily), and there was no tumor on the CT scan 12 months after initial admission (Fig. 3).

Discussion

The significance of intra-arterial chemotherapy for bladder cancer is as follows: highly concentrated antitumor agent can be delivered to the tumor, so that the agent acts directly on the tumor, and it is expected to transfer to the lymphatic vessels or lymph nodes, while a small amount of it distributes throughout the whole body as if injected IV [11, 14, 15, 18]. Although intra-arterial chemotherapy is an advantageous method for local management of tumor, the effectiveness of the procedure depends on the properties of the drugs employed [15]. Desirable properties of the agent used in intra-arterial chemotherapy include a wide antitumor spectrum, easy absorption by and storage in the tumor, and inactivation at a suitable speed.

The properties of Adriamycin suggested that it would be extremely suitable for intra-arterial chemotherapy. On the other hand, Adriamycin accumulating in the heart causes cardiac damage, which is the main limiting factor of this agent [3, 6]. In a simple semiselective intra-arterial chemotherapy for bladder cancer, a considerable amount of the agent was observed to run out and be lost into the external iliac arteries, distributing systemically and causing systemic side-effects [18]. To solve this problem, selective [14, 15] or very highly selective [11] techniques of intra-arterial chemotherapy have been designed, but these are difficult. Local side-effects have frequently been seen with these procedures [14, 19].

alpha-Tocopherol (vitamin E) has been administered in combination with Adriamycin to prevent side-effects, with some promising preliminary results [13].

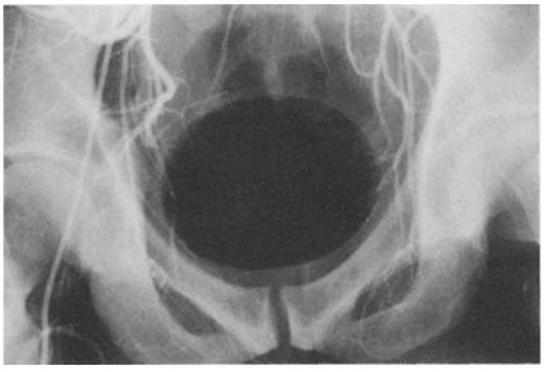

Fig. 4. Pelvic arteriography with compression of the femoral arteries demonstrates no agent proceeding into the external arteries

We designed a semiselective method of iliac arterial chemotherapy with compression of the femoral arteries at the time of Adriamycin injection. A hypogastric arteriogram demonstrated that the compression technique effectively prevented loss of agent into the external iliac arteries (Fig. 4). This preliminary comparative study showed that a larger amount of Adriamycin could be given to the patients without increasing side-effects. Although radiotherapy and vitamin E were given in some cases, we are of the opinion that the compression of the femoral arteries played a very important role in decreasing the side-effects and increasing the antitumor effects. Since our preliminary results seem encouraging, a further study in a larger number of patients is planned.

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