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Preoperative one-shot intra-arterial infusion chemotherapy for bladder cancer

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Summary. We have performed preoperative one-shot intra-arterial chemotherapy since 1976. However, in some cases, the results have not been satisfactory. Experimental studies were conducted to choose the drugs most suitable for this procedure. Drugs that were considered to be effective against bladder cancer, i. e., thio-TEPA, adriamycin (ADM), and cis-platinum (CDDP), were separately administered to groups of dogs via the common iliac artery or cephalic vein, and the concentrations of these drugs in the serum, bladder (mucosa and muscular layer), ileum, kidneys, and liver were measured 1 h later. The results revealed significantly high concentrations of intra-arterially injected ADM and CDDP in the bladder mucosa, suggesting that these drugs may be suitable for intra-arterial injection. It also appeared that thio-TEPA is unsuitable for this procedure. In clinical studies of 29 cases, preoperative one-shot intra-arterial injections were performed prior to total cystectomy or segmental resection of the bladder, and the effectiveness of the treatment was evaluated in terms of the histological effect, survival, and the relationship with the characteristics of the tumor. The results showed that the progonosis for cases showing therapeutic histological effectiveness (grade-IIb according to the classification of Shimosato et al.) was extremely good. Many patients in the grade-IIb group had stage-pT2 tumor or a tumor in the lateral wall. However, there seemed to be no significant differences between the drugs with respect to their histological effects.

Introduction

Although urinary bladder cancer is usually treated surgically, the value of pre- and postoperative adjuvant therapy is becoming increasing evident. In particular, preoperative treatment aims at improving the results of surgical treatment by minimizing the activity of local tumor cells for a short period before surgery is performed, preventing the dissemination of tumor cells during surgery, and inhibiting the growth of systemic micrometastases not detected in preoperative examinations.

A one-shot intra-arterial injection is suitable for preoperative treatment, as it is simple to perform and entails few complications. A one-shot injection can have satisfactory results when dose-dependent agents with high tissue affinity are used.

Since 1976, in the treatment of urinary bladder cancer, we have performed preoperative one-shot intra-arterial chemotherapy using four drugs, i. e., mitomycin C (MMC), cyclophosphamide (CPM), thio TEPA, and 5-fluorouracil (5-FU) [21]. In some cases, the results have not been satisfactory. Thus experimental studies concerning the one-shot intra-arterial injection of anticancer drugs were conducted in order to select the most suitable agents, with particular attention being paid to tissue affinity.

Using the drugs that appeared to be most appropriate on the basis of the results of these experiments we evaluated the histological effectiveness of a one-shot intra-arterial injection of these anticancer drugs (including commonly used agents). The relationship between survival rate, type of tumor, and the drugs used was also investigated.

Materials and methods

Experimental study. Thio-TEPA, adriamycin (ADM), and cis-platinum (CDDP) were applied in these experiments. Thirty hybrid female adult dogs weighing between 7.4 and 11.4 kg were divided into six groups of 5 animals, i. e., an intra-arterial and an intravenous group for each of the three drugs. All of the animals were given the appropriate drug while under intravenous anesthesia. In the intravenous injection groups, the drug was administered via the cephalic vein for over 5 min. In the intra-arterial injection groups, the right femoral artery was exposed to accept a 5 F catheter. The tip of the catheter was fixed directly above the bifurcation of the aorta. The bilateral femoral arteries were compressed with the fingers to create a condition of complete ischemia. The drugs used were infused over a period of about 5 min to prevent back-flow to the inferior mesenteric artery. The dogs were exsanguinated about 60 min after the drugs had been injected. From each dog, a blood specimen was collected, and the kidneys, the liver, the end of the ileum, and the urinary bladder were removed.

The concentration thio-TEPA, ADM, and CDDP was assayed using the NBP method, a fluorescence method [3], and atomic absorption [1], respectively.

The respective doses of thio-TEPA, ADM, and CDDP were 7, 10, and 5 mg/kg in order to ensure that the specimen concentration was within the standard curve.

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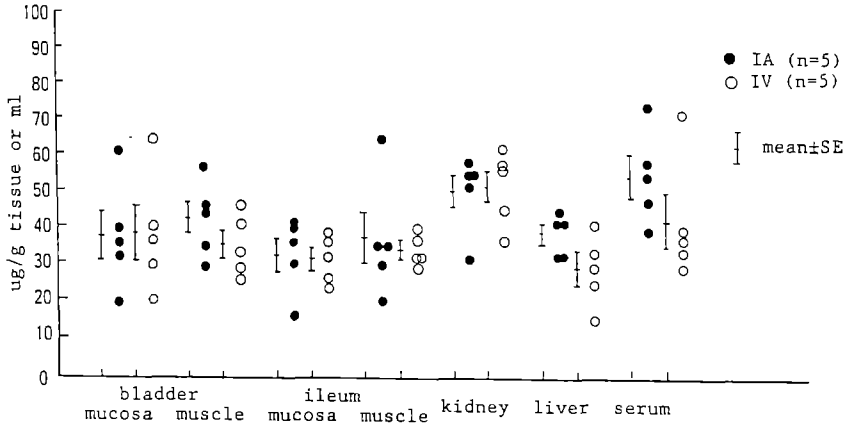

Fig. 1. Concentrations of thio-TEPA at various sites (7 mg i. a. or i. v.)

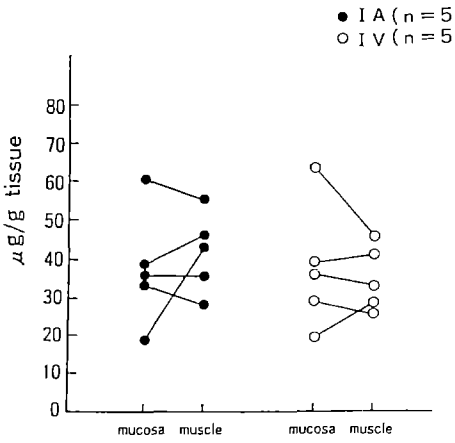

Fig. 2. Concentrations of thio-TEPA in the urinary bladder

A preliminary investigation revealed a significant variation in the concentration of CDDP in bladder tissues. This may be explained by the fact that the level of platinum, which is excreted in the urine, was measured. Therefore, prior to the administration of CDDP, urinary diversion was performed.

Student's *t*-test was used for statistical analyses.

Clinical study. The subjects consisted of 29 pT2 and pT3 cases (UICC) of urinary bladder cancer, which had first been detected between November 1976 and March 1986. The treatment was a one-shot intra-arterial injection prior to total cystectomy or segmental resection. The patients were given MMC (12 mg), CPM (300 mg), thio-TEPA (18 mg), and 5-FU (500 mg), by intra-arterial injection into the origin of the internal iliac artery, over a period of 4 years and 11 months (November 1976 to October 1981). Over a period of 2.5 years (November 1981 to May 1984), these drugs were replaced by ADM (30 mg) or CDDP (75 mg) injected intra-arterially into the internal iliac artery at the remotest possible site of the superior gluteal artery. After June 1984, MMC (6 mg), ADM (10–20 mg), and CDDP (50 mg) were administered. The blood flow of the internal iliac artery was temporarily blocked by a balloon, and intra-arterial injection was performed over a period of approximately 30 min. Surgery was performed an average of 14.3 days after the intra-arterial injection. Histological effectiveness was determined according to the classification of Shimosato et al. [4].

We investigated the relationship between histological effectiveness and prognosis, stage and grade of tumor, tumor characteristics, the technique of intra-arterial injection, and the drugs used.

Results

Experimental study

Concentration of thio-TEPA (Figs 1, 2). There were no differences between the intra-arterial and intravenous injection groups in terms of the concentration of thio-TEPA in serum and tissue. The concentration of this drug in the bladder mucosa was 36.7 ± 15.1 μg/g tissue in the intra-arterial injection group and 37.4 ± 16.5 μg/g tissue in the intravenous injection group. A comparison of the concentration of thio-TEPA in the bladder mucosa with that in the muscular layer revealed no significant differences either in the intra-arterial injection group or in the intravenous injection group.

Concentration of ADM (Figs. 3, 4). The serum ADM concentration was 1.7 ± 0.6 μg/ml in the intra-arterial injection group and 6.4 ± 3.9 μg/ml in the intravenous injection group; thus, it was significantly lower in the former group ($P < 0.05$). The concentrations of ADM in the kidneys and the ileal mucosa were also significantly lower in the intra-arterial injection group ($P < 0.01$). The concentration of ADM in the bladder mucosa was 21.6 ± 6.9 μg/g tissue in the intra-arterial injection group and 7.3 ± 2.5 μg/g tissue in the intravenous injection group; thus, it was significantly higher in the former group ($P < 0.01$).

The concentration of ADM in the muscular layer of the urinary bladder was also higher in the intra-arterial injection group ($P < 0.05$). A comparison of the concentration of ADM in the bladder mucosa with that in the muscular layer showed that it was significantly higher in the bladder mucosa in both groups.

Concentrations of CDDP (Figs. 5, 6). The concentrations of CDDP in the serum and kidneys were lower in the intra-arterial injection group than in the intravenous injection group ($P < 0.05$). No significant differences between the two groups were observed with respect to the concentration of CDDP in the liver and the ileum. The concentration of CDDP in the bladder mucosa was 11.9 ± 2.2 μg/g tissue in the intra-arterial injection group and 8.4 ± 2.0 μg/g tissue in the intravenous injection group; it

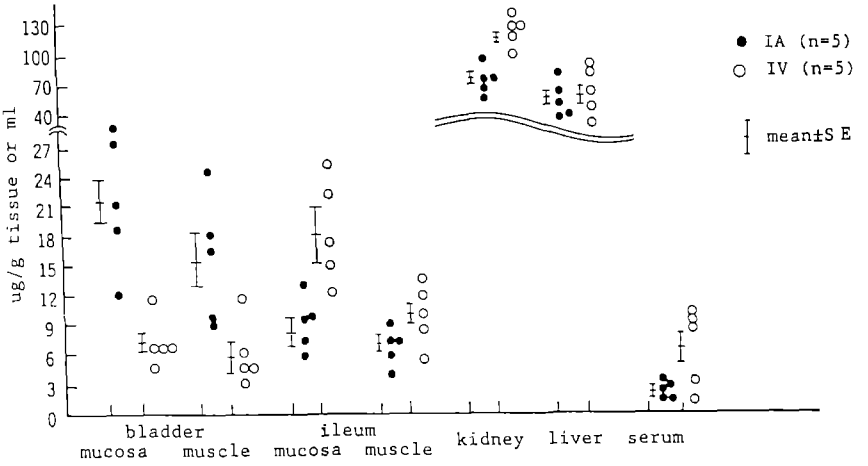

Fig. 3. Concentrations of ADM at various sites (10 mg/kg i. a. or i. v.)

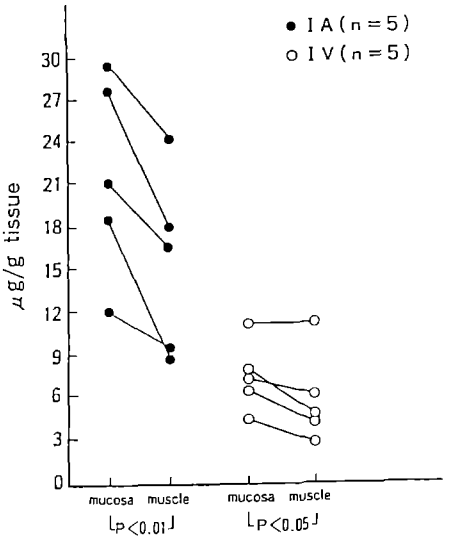

Fig. 4. Concentrations of ADM in the urinary bladder

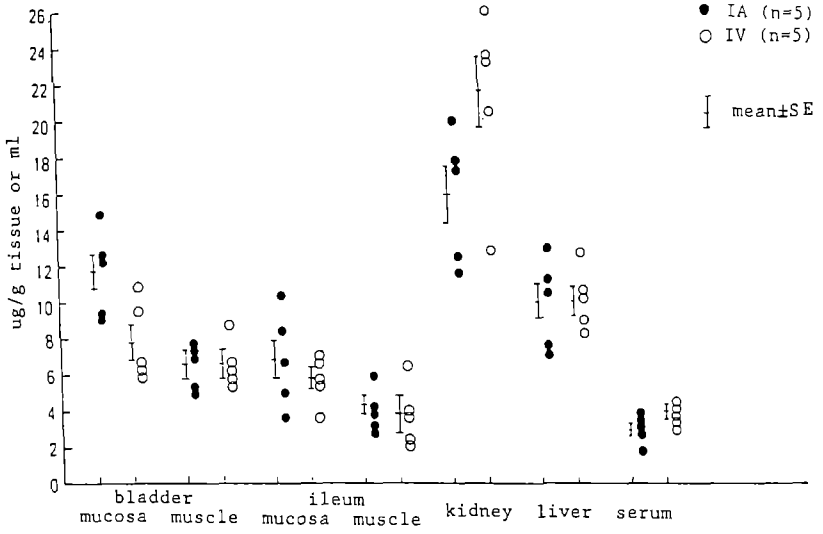

Fig. 5. Concentrations of CDDP at various sites (5 mg/kg i. a. or i. v.)

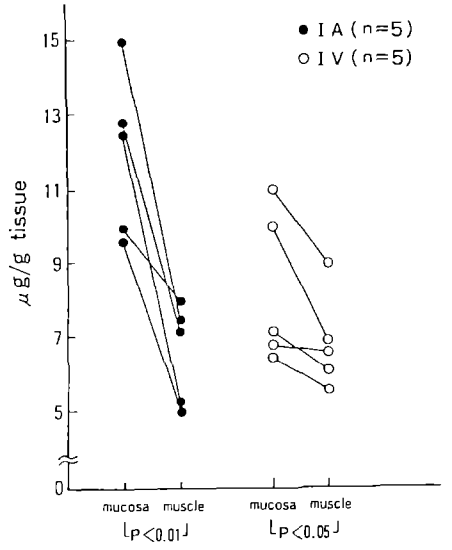

Fig. 6. Concentrations of CDDP in the urinary bladder

was thus significantly higher in the former group ($P < 0.05$). There were no significant differences between the two groups with respect to the concentration of CDDP in the muscular layer. A comparison of the concentration of CDDP in the bladder mucosa with that in the muscular layer showed that it was higher in the former in both the intra-arterial ($P < 0.01$) and intravenous ($P < 0.05$) injection groups.

Clinical study

In our study of 29 patients, 6 showed grade-IIb histological effectiveness, 16 exhibited grade-IIa, and 6 showed grade I (Table 1), this being according to the classification of Shimosato et al. ([4]; Table 2). No patient showed grade III or more. An analysis of the relationship between histological effectiveness and survival rate revealed that the 3-year survival rate was 41.7% in the grade-I group. In the grade-IIa group, the 3-year survival rate was 37.5%, and the 5-year survival rate was 28.1%; this difference was not significant. The 3- and 5-year survival rates were 100% in the grade-IIb group (Fig. 7); there were significant differences between this group and the other groups ($P < 0.05$).

Table 1. Histological effects of intra-arterial infusion

Histological effects	No. of cases	Intervals before operation (mean ± SE)
Grade II b	6 (20.7%)	14.0±2.7
Grade II a	16 (55.1%)	14.9±2.1
Grade I	6 (20.7%)	10.0±1.8
Grade 0	1 (3.5%)	33
	29 (100%)	14.3±1.5

A comparison of tumor-related factors between the groups revealed that many patients in the grade-IIb group had a stage-pT2 tumor; however, the degree of dysplasia of the tumor was similar among the various groups

Table 2. Histological grading (employed at the National Cancer Center Hospital)

Grade I:	Characteristic changes are noted in tumor cells, but tumor structures have not been destroyed
Grade II:	In addition to characteristic cellular changes, tumor structures have been destroyed as a result of the disappearance of tumor cells. However, variable numbers of "viable tumor cells" still remain
II a:	Destruction of tumor structure is of a mild degree, i. e., "viable cells" are frequently observed
II b:	Destruction of tumor structure is of severe degree, i. e., "viable tumor cells" are few in number
Grade III:	Markedly altered, presumably nonviable, tumor cells are present singly or in small clusters, and "viable cells" are very infrequently seen
Grade IV:	No tumor cells remain in any of the sections

Table 3. Characteristics of patients

Histological effects		Grade II b	Grade II a	Grade I
Age years		69.3 ± 2.04	66.6 ± 2.54	64.7 ± 4.96
Stage	pT2	4 (66.6%)	4 (25.0%)	2 (33.3%)
	pT3	2 (33.3%)	12 (75.0%)	4 (66.6%)
Grade	G2	0 (0%)	1 (6.3%)	1 (16.7%)
	G3	6 (100%)	15 (93.7%)	5 (83.3%)

Table 4. Size, form, and site of tumor, and histological effect

		Grade II b	Grade II a	Grade I
Size:	3 cm ≤	6 (100%)	10 (62%)	6 (100%)
	< 3 cm	0 (0%)	6 (38%)	0 (0%)
Form:	papillary	1 (17%)	1 (6%)	2 (33%)
	non-papil	5 (83%)	15 (94%)	4 (67%)
Site:	lateral	5 (83%)	6 (38%)	3 (50%)
	dome		1 (6%)	1 (17%)
	anterior		1 (6%)	
	posterior	1 (17%)	4 (25%)	2 (43%)
	trigone		3 (19%)	
	neck		1 (6%)	

Table 5. Infused drugs and histological effects

Histological effects / Infused drugs	Grade II b	Grade II a	Grade I	No. of cases
MMC, thio-TEPA 5-FU, CPM	2 (16.7%)	9 (75.0%)	1 (8.3%)	12
ADM	1 (16.7%)	2 (33.3%)	3 (50.0%)	6
CDDP	1 (33.3%)	2 (66.7%)	0 (0%)	3
MMC, ADM CDDP (BOA)	2 (28.6%)	3 (42.8%)	2 (28.6%)	7

Table 6. Histological effects and postoperative therapy

Histological effects / Therapy	Grade II b	Grade II a	Grade I
FT-207 ara-C TY	1 (16.6%)	2 (12.5%)	1 (16.6%)
CDDP FT-207 ara-C	3 (50.0%)	3 (18.8%)	4 (66.6%)
FT-207 only or FT-207 and others	2 (33.0%)	6 (37.5%)	0
Radiation	0	3 (18.8%)	0
No therapy	0	2 (12.5%)	1 (16.6%)

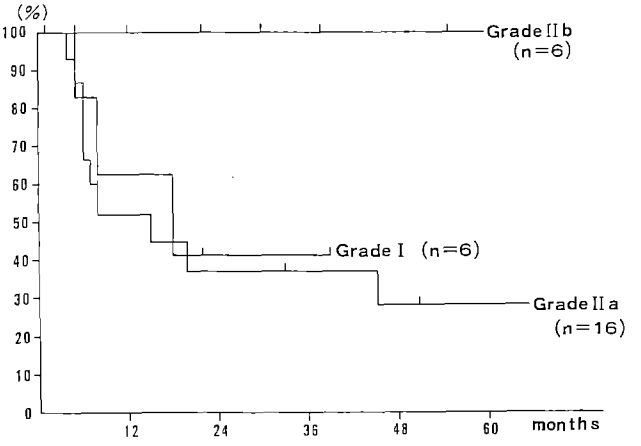

Fig. 7. Survival and histological effects

(Table 3). The tumors exhibited a similar growth pattern in all of the groups. In the grade-IIb group, many patients had a tumor in a lateral wall (Table 4).

Administration of the drugs by various methods produced grade-IIb histological effectiveness in 16.7%–33.3% of the patients (Table 5). There were no significant differences between the chemotherapy groups. There was no significant correlation between postoperative chemotherapy and histological effectiveness (Table 6). Postoperative therapy did not seem to be a major factor in increasing the survival rate in the grade-IIb group.

No severe side effects were observed, but vomiting (CDDP), liver dysfunction (CDDP), slight alopecia (ADM), and slight leukopenia (ADM) were encountered. Surgery had to be postponed in 1 patient because of liver dysfunction.

Discussion

When performing a one-shot intra-arterial injection, it is important to select anticancer drugs that act effectively against tumors when administered by this procedure. The prerequisite for making better use of the characteristics of a one-shot intra-arterial injection is to use dose-dependent drugs with high tissue affinity. We selected thio-TEPA,

ADM, and CDDP for application against bladder tumors, and we evaluated their affinity for bladder tissues after a one-shot intra-arterial injection.

There were no differences between the intra-arterial and intravenous injection groups in terms of the concentration of thio-TEPA detected in bladder tissues. This suggests that the anticancer effects of thio-TEPA after a one-shot intra-arterial injection would be comparable to those obtained by intravenous injection. No differences were observed between the intra-arterial and intravenous injection groups with respect to the concentration of thio-TEPA in other tissues. Thus, if significantly better results are not achieved by intra-arterial infusion, it would seem to be pointless to use this approach in preference to intravenous infusion.

The concentration of ADM in bladder tissues in the intra-arterial injection group was about three times higher than that observed in the intravenous injection group. This indicates the high affinity of this drug for bladder tissues when delivered by the former route. It may also be possible to reduce side effects by this procedure, as the concentration of ADM in the serum, kidneys, and ileum was lower in the intra-arterial injection group than in the intravenous injection group. These results suggest that ADM is a suitable drug for a preoperative one-shot intra-arterial injection.

The same was true for CDDP, which would therefore also seem to be suitable for one-shot intra-arterial injections.

The high tissue affinity of ADM and CDDP may account for the fact that, after a one-shot intra-arterial injection, their concentrations in bladder tissues were high, whereas their concentrations in other tissues were low. We consider that ADM and CDDP have a high affinity for bladder tissues during the first circulation after an intra-arterial injection. A reduced volume of these drugs then enters the systemic circulation, resulting in lower concentrations of these drugs in other tissues as compared to the concentrations observed after intravenous injection.

Our clinical study showed that there was a better prognosis for patients with grade-IIb (according to the classification of Shimosato et al. [4]) after an intra-arterial injection. The drugs that we studied were more effective histologically in patients with a stage-pT2 tumor located in the lateral wall. However, there were no differences in the histological effects of the drugs and techniques tested in our study. The number of patients was small, and the relationship between histological effects and prognosis requires further study.

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