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Intra-arterial chemotherapy for bladder cancer

Shori Kanoh[1], Ryosuke Noguchi[1], Mikinobu Ohtani[1], Satoru Ishikawa[1], Ryosuke Nemoto[1], Kenkichi Koiso[1], and Ryuichi Kitagawa[2]

[1] Department of Urology, Institute of Clinical Medicine, University of Tsukuba, Sakuramura, Niiharigun, Ibaragi Prefecture 305, Japan
[2] Department of Urology, Juntendo University, School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113, Japan

Summary. Intra-arterial infusion chemotherapy with adriamycin (ADM) was carried out in 32 patients with bladder cancer prior to total cystectomy. An oblique incision approximately 12 cm long was made in the gluteal region to expose either the superior or inferior gluteal artery, into which a Teflon catheter was inserted and fixed. The distal end of the catheter was taken out from under the skin in the precordial region. Via this catheter, a single dose of 10 mg ADM was injected twice a week. Superior-gluteal-artery infusion chemotherapy was performed in 7 patients; the 5-year survival rate was 14.3%, which was not as high as expected. Inferior-gluteal-artery infusion chemotherapy was performed in 25 patients. Cisplatin (CDDP) was used with ADM in 8 patients. Radiation and/or hyperthermia were used in 11 patients. The 5-year survival rate in these 25 patients was 58.4%, which was considered to be satisfactory. Of these 25 patients, 5 were stage-T4 cases; for these, the treatment was ineffective, and all 5 died within 2 years. Of the 6 patients at stage T2, 1 died, as did 1 patient with carcinoma in situ (CIS). Of the 13 patients with bladder cancer at stage T3, 3 died; lymph-node metastases were found in all 3 of these cases. Of the 25 patients who received inferior-gluteal-artery infusion chemotherapy, 9 died of cancer; all 9 died within 2 years due to distant metastases. There was no evidence of recurrence in any patient who survived for 2 years or more after total cystectomy. Therefore, inferior-gluteal-artery infusion chemotherapy may be effective as a preoperative adjuvant therapy with no serious side effects.

Introduction

Regional intra-arterial infusion of chemotherapeutic agents is a treatment modality designed to obtain a high concentration of the agent in the tumor in order to ensure effective treatment while minimizing the systemic side effects [2].

Since February 1977, we have been examining the effects of long-term intra-arterial infusion chemotherapy in patients with advanced bladder cancer who would be candidates for total cystectomy.

In our procedure, a Teflon catheter is inserted into the hypogastric artery via the superior gluteal artery, and the inferior gluteal artery is then catheterized to achieve very highly selective infusion of anticancer agents into the vesical artery. In a previous report, we recommended and assessed the effectiveness of a technique for the long-term intra-arterial infusion of 10 mg adriamycin (ADM) twice a week [1]. In the present study, we describe the longterm effects of the technique.

Offprint requests to: S. Kanoh

Materials and methods

We used our previously described catheterization technique [1] on patients with advanced bladder cancer who were candidates for total cystectomy. The criteria for the evaluation of the effectiveness of the treat were based on those of Yagoda [3]. Complete response (CR) required the complete disappearance of clinical, radiological, and biochemical evidence of tumor. Partial response (PR) was defined as being a greater than 50% reduction in the sum of the products of the dimensions of measurable tumors. Minimal response (MR) was defined being as any unequivocal shrinkage of measurable tumors of less than 50%.

Superior-gluteal-artery infusion chemotherapy with ADM was performed in 7 patients (Table 1). Ten milligrams of ADM was given intra-arterially once or twice a week, thus giving a total dose of 60–580 mg, the average being 376 mg. Inferior-gluteal-artery infusion chemotherapy was performed in 25 patients, i.e., 1 with CIS, 6 at stage T2, 13 at stage T3, and 5 at stage T4 (Table 2).

ADM was intra-arterially infused in a single dose once or twice a week for a total dose of 80–425 mg, with the average being 186 mg (Table 3). ADM alone was administered to 14 patients, while in 8 patients, it was combined with 10–20 mg CDDP, which was given twice a week for a total dose of 50–360 mg, the average being 196 mg.

ADM and CDDP administration was combined with hyperthermia using Internova Novatherm IH 500 (Tokyo,

Table 1. Superior-gluteal-artery infusion chemotherapy with ADM

Histological type	Stage		Total
	T2	T3	
TCC G2	2	3	5
TCC G3	0	2	2
	2	5	7

Table 2. Inferior-gluteal-artery infusion chemotherapy with ADM

Grade	Stage				Total
	CIS	T2	T3	T4	
G2		3	1		4
G3	1	3	12	5	21
	1	6	13	5	25

Table 3. Combination regimens for inferior-gluteal-artery infusion chemotherapy

ADM	10 mg once or twice per week Total, 80–425 (186) mg	
CDDP	10–20 mg twice per week Total, 50–360 (196) mg	
Hyperthermia	10–23 (17) times Novatherm IH 500	
Radiation	2,000–4,000 (2,800) rad	
ADM		14 cases
ADM + Rad		2 cases
ADM + Hyp		1 case
ADM + CDDP + Hyp		4 cases
ADM + CDDP + Rad + Hyp		4 cases
Total cystectomy		15 cases
TUR		5 cases
Partial cystectomy		2 cases

(Means are given in parentheses)

Japan). In addition, 6 patients were given radiation to a dose of between 20 and 40 Gy (average, 28 Gy). After preoperative treatment, total cystectomy was performed in 15 patients. Of the patients in whom improvement with respect to stage was found, 5 had TUR, and the other 2 had partial cystectomy. Two other patients underwent an ileal conduit procedure, and 1 had biopsy only.

Results

Figure 1 shows the survival rate of patients treated with superior-gluteal-artery infusion chemotherapy with ADM. The 5-year survival rate was 14.3%, which was not as high as expected. Only 2 of the 7 patients died of cancer due to bone metastases; one of these survived for 1 year and 1 month, while the other survived for 3 years. Four patients died of other diseases with no evidence of recurrence.

Figure 2 shows the survival rate of patients treated with inferior-gluteal-artery infusion chemotherapy with ADM. The 5-year survival rate was fairly good, i.e., 58.4%. Nine patients died within 2 years, all of distant metastases. Of the 25 patients, 5 were at stage T4; their survival rate is shown in Fig. 3. All of these 5 patients died within 2 years.

Of the six patients at stage T2, 1 died of cancer due to metastases in the ribs after 1 year and 11 months. If this patient were excluded, the survival rate for stage-T2 cases would be satisfactory (Fig. 4).

Of the 13 patients at stage T3, 3 died 15–19 months later of cancer due to distant metastases. The 5-year survival rate for stage-T3 cases was very high, i.e., 75.2% (Fig. 5). Lymph-node metastases were detected during treatment in all of the patients at stage T3 who died: 1 of these had PR,

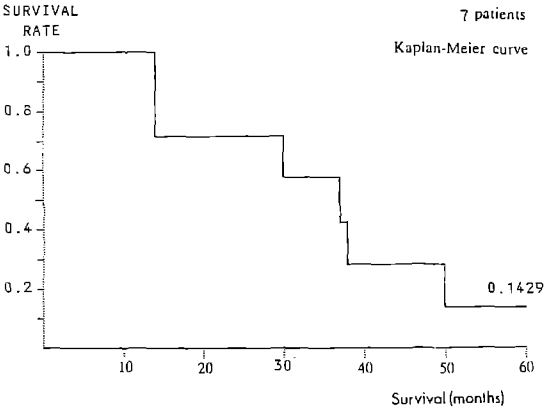

Fig. 1. Survival of patients treated with superior-gluteal-artery infusion chemotherapy

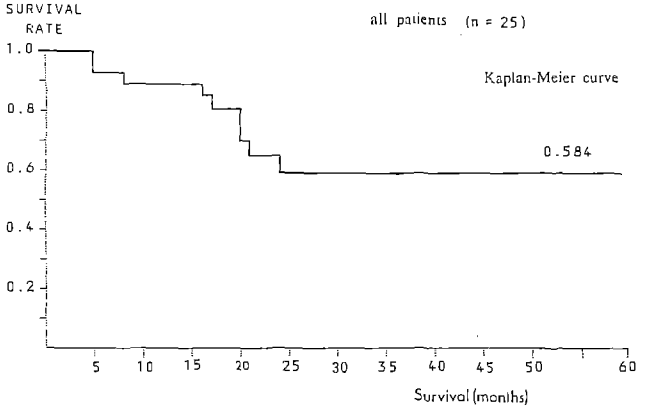

Fig. 2. Survival of patients treated with inferior-gluteal-artery infusion chemotherapy

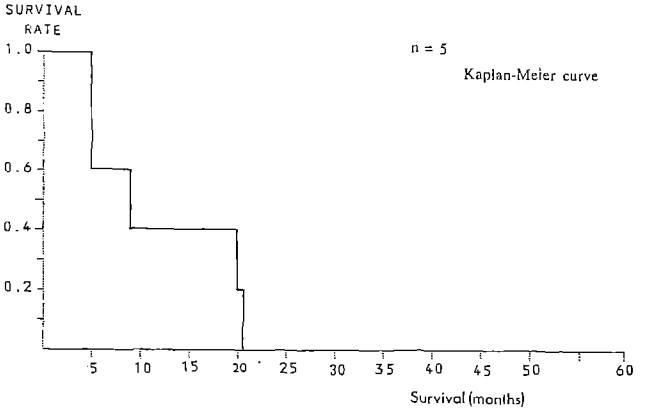

Fig. 3. Survival of patients at stage T4 treated with inferior-gluteal-artery infusion chemotherapy with ADM

while the other 2 had MR (Table 4). The 10 patients at stage T3 who are still alive showed G_3N_0; all had PR. The response rate for stage-T3 cases was satisfactory, i.e., 84.6%. No evidence of recurrence of the tumor has been recognized in any of the patients who are still alive.

Figure 6 shows the survival rate among patients with bladder cancer according to treatment modalities. The 5-year survival rate was 80% for the 10 patients who had inferior-gluteal-artery infusion chemotherapy alone. The

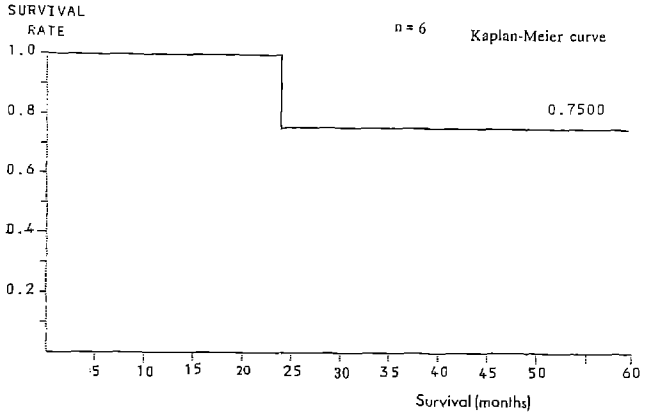

Fig. 4. Survival of patients at stage T2

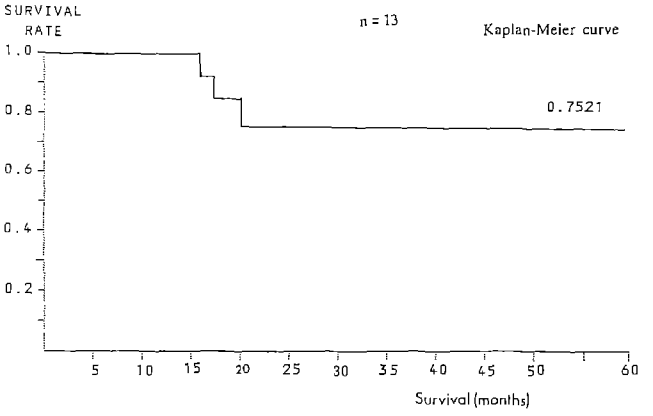

Fig. 5. Survival of patients at stage T3 treated with inferior-gluteal-artery infusion chemotherapy with ADM

Table 4. Response data of the 13 patients at stage T3 treated with inferior-gluteal-artery infusion chemotherapy with ADM

	Grade stage	Effect	Number of patients (n = 13)
Died of cancer	G2N2	MR	1
	G3N1	MR	1
	G3N4	PR	1
Alive	G3N0	PR	10
Response rates:	11	PR	(84.6%)
	2	MR	(15.4%)

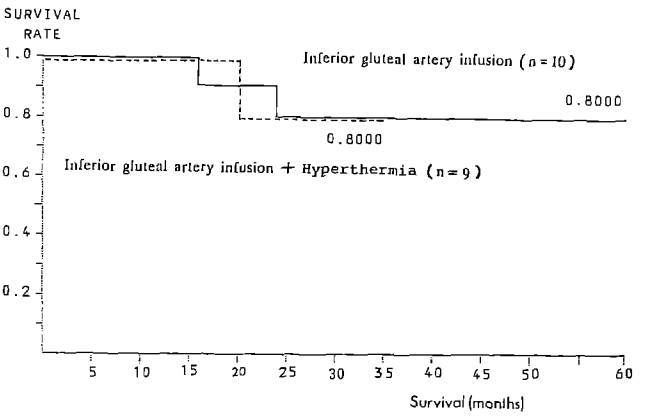

Fig. 6. Effect of a combination of inferior-gluteal-artery infusion and hyperthermia for 10 patients at stages T2 and T3

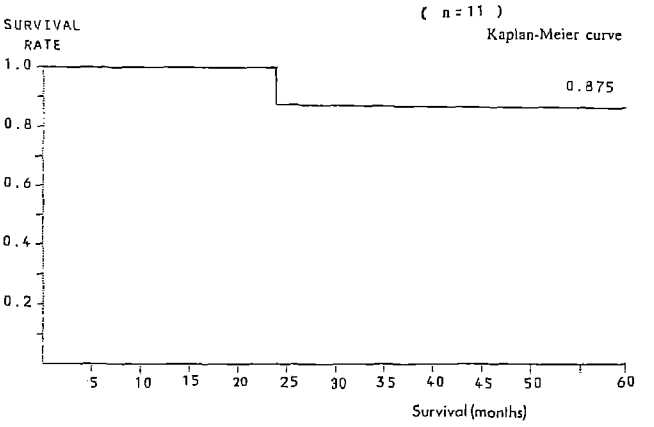

Fig. 7. Survival of patients with total cystectomy and ureterosigmoidstomy

3-year survival rate was 80% for the 9 patients who underwent hyperthermia with chermotherapy; however, such an observation period is relatively short. There were no differences between the two groups.

Of the 11 patients who had total cystectomy and ureterosigmoidostomy after inferior-gluteal-artery infusion chemotherapy, 1 died of cancer due to metastases in the ribs 1 year and 11 months later (Fig. 7). The other 10 patients have survived with no evidence of recurrence. The 5-year survival rate was very high, i.e., 87.5%.

Of the patients in whom an improvement with respect to stage was observed after inferior-gluteal-artery infusion chemotherapy, 7 were treated with TUR or partial cystec-

Table 5. Conservative treatment after stagedown as a result of inferior-gluteal-artery infusion chemotherapy

Case	Age (years)	Grade	TNM	ADM (mg)	CDDP (mg)	Radiation (rad)	Hyper-thermia	Operation	Survival	
1	84	G3	T3NxM0	265				TUR	6Y	Alive
2	75	G3	T3NxM0	425				TUR	5Y9M	Alive
3	57	G2	T2NxM0	120				TUR	5Y3M	Alive
4	81	G3	T3N1M0	210		3000		TUR	1Y4M	Died of cancer
5	79	G3	T3N4M0	230	50	4000	20	TUR	1Y7M	Died of cancer
6	50	G3	T3N0M0	160	255		22	Partial cystectomy	1Y6M	Alive
7	52	G3	T2N0M0	190	360		20	Partial cystectomy	11M	Alive

Table 6. Side effects of inferior-gluteal-artery infusion chemotherapy in the 25 patients tested

Effects	Case	Percentage
Skin erosion	6	24
Hematological WBC $<3{,}000$	2	8
Platelet $<100{,}000$	1	4
Sciatic pain	1	4
Nausea	1	4
Cardiotoxicities	0	0
Nephrotoxicities	0	0
Alopecia	0	0

tomy alone in order to conserve the bladder. As shown in Table 5, cases 4 and 5 had lymph-node metastases during treatment and subsequently died of cancer. The other 5 patients are still alive. No evidence of recurrence has been found, except case 3 in whom one small papillary cancer recurred in the bladder after 4 years.

Table 6 shows the side effects caused by inferior-gluteal-artery infusion chemotherapy with ADM. Skin erosions were noted in the gluteal, perineal, and anal regions in 24% of the patients. Leukocytopenia was found in 8%, thrombocytopenia in 4%, sciatic pain in 4%, and nausea in 4%. There was no cardiotoxicity, nephrotoxicity, or alopecia. The side effects were only slight, and treatment did not have to be stopped in any patient.

Discussion

Superior-gluteal-artery infusion chemotherapy with ADM causes side effects such as skin erosion and sciatic pain, as the infused drug flows out through the inferior gluteal artery and internal pudendal artery. This makes it impossible to infuse a sufficient amount of this anticancer agent into the bladder-tumor region. Therefore, superior-gluteal-artery infusion chemotherapy with ADM is less effective than inferior-gluteal-artery infusion chemotherapy with ADM [1]. The 5-year survival rate after the former treatment is lower than that after the latter treatment.

Inferior-gluteal-artery infusion chemotherapy with ADM is not effective in patients with bladder cancer at stage T4 or lymph-node metastasis. It is now necessary to study further the possibility of increasing the single doses of ADM, the types of drugs that could be combined with ADM, the prolongation of the treatment period, and the possible combination of ADM with hyperthermia and/or radiation.

In all of the 9 patients who died within 2 years, death was due to distant metastases. No evidence of recurrence was detected in patients who survived for 2 years or more. This suggests that intra-arterial chemotherapy provides good control of the local cancer and prevents the possible dissemination of the tumor during total cystectomy. In conclusion, this method appears to be very effective as a preoperative adjuvant therapy for bladder cancer at stage T3 or less, and also has no serious side effects. It would appear to be the treatment of choice when a total cystectomy and ureterosigmoidostomy are planned.

In addition, this treatment may allow the bladder to be preserved by applying TUR and partial cystectomy with lymphadenectomy in patients in whom an improvement with respect to stage has been observed. Therefore, intra-arterial chemotherapy should now be used intensively in order to determine its limitations.

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