Cancer Chemother Pharmacol (1987) 20 (Suppl): S 10–S 14

Cancer Chemotherapy and Pharmacology

The role of preoperative intra-arterial doxorubicin chemotherapy in combination with low-dose irradiation for bladder cancer

Takeshi Uyama[1], Shoosuke Moriwaki[2], Akihide Yokozeki[1], Kozo Kitada[1], Isao Higa[1], Tomoyuki Shiotsu[1], and Jiro Fujita[1]

[1] Department of Urology, and [2]Department of Pathology, Shikoku Cancer Center Hospital, 13-Horinouchi, Matsuyama 790, Japan

Summary. Twenty patients with bladder cancer (T1, 3 patients; T2, 6 patients; T3, 8 patients; T4a, 3 patients) were preoperatively treated with intra-arterial doxorubicin chemotherapy in combination with low-dose irradiation. The originally scheduled operations were as follows: total cystectomy in 16 patients (T1 + cis, 1 patients; T2, 5 patients; T3, 7 patients; T4a, 3 patients), segmental cystectomy in 2 patients, and transurethral resection in 2 patients. The total dose of doxorubicin ranged from 120 to 540 mg (251.5 ± 100.2 mg), and that of irradiation was from 4 to 36 Gy (24.4 ± 7.3 Gy). Clinical and pathological effects were evaluated in all of the cases. Clinically, complete remission (CR) was observed in 14 cases (70.0%), partial remission (PR) was seen in 3 cases, a minor response (MR) occurred in 2 cases, and no response (NR) was seen in 1 patient; non patient showed progressive disease (PD). The pathological effects (according to the criteria of Shimosato et al.) were as follows: grade IV was seen in 10 cases, grade III in 3 cases, and less than grade II in 7 cases; however, viable tumor cells were not seen in 13 (65.0%) of the 20 cases. The bladder was preserved in 13 (81.3%) of the 16 cases for which total cystectomy had been recommended. All of the patients were followed up for periods ranging from 3 to 54 months (26.3 ± 16.5 months), durng which time 6 patients (30.0%) died (3 with cancer, 1 without cancer, and 2 unknown causes). The actual survival rate according to the stage of disease was 100.0% at 50 months in T1-T2 and 40.9% at 54 months in T3-T4a. In T3-T4a, the actual survival rate in pathologically complete responders was 60% (relative rate 68.8%) at 54 months, and the actual survival rate in incomplete responders was 25.0% (relativ rate 27.1%) at 36 months. The results of our study are encouraging, especially in T1-T2 and T3-T4a cases, who showed a complete response. It is concluded that doxorubicin intra-arterial chemotherapy combined with low-dose irradiation could be the first treatment of choice for locally invasive bladder cancer.

Introduction

Since the development of the concept of intra-arterial chemotherapy by Klopp et al. [9] in 1950, several groups of urological investigators [6, 8, 13, 14, 19] have discussed this unique procedure and have presented interesting and encouraging information; however, definitive conclusions are, as yet, lacking. We have also applied this procedure in the treatment of urological cancers using doxorubicin (doxorubicin-IAC [19]). It became clear that a good early-phase response could be obtained using a modified aortic method (even if it is not selective) in combination with (1) compression of the femoral arteries during the injection and (2) low-dose irradiation. In the present study, we discuss the role of preoperative doxorubicin chemotherapy performed in the same way for the treatment of locally invasive bladder cancer.

Materials and methods

The study included 20 patients with locally invasive bladder cancer (18 males, 2 females). The average age was 65.2 years, the range being from 45 to 81 years. Seventeen patients had initial tumors, while 3 had recurrent tumors. The tumor stage was T1 in 3 patients, T2 in 6 patients, T3 in

Table 1. Data for the patients studied

Total number of patients	20
Male	18
Female	2
Average age (years)	65.2
Age range (years)	41–81
Initial tumor	17
Recurrent tumor	3
T Stage	
T1 (+cis)	3 (1)
T2	6
T3 (M1 lung)	8 (1)
T4a	3
Grading of differentiation	
G1	2
G2	7
G3	10
Poor	1
Mode of infiltration (INF)	
INF-α	3
INF-β	7
INF-γ	4
Unknown	6

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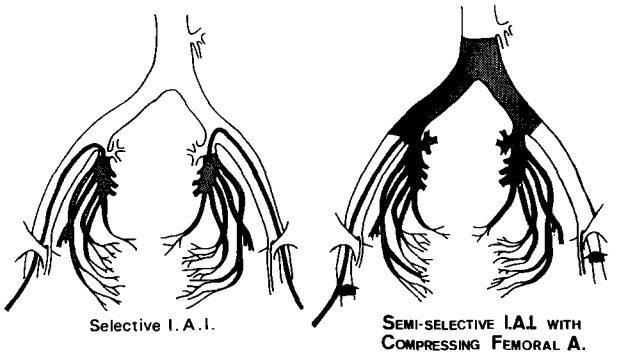

Fig. 1. Distribution of agents injected intra-arterially. Both selective, two-way hypogastric injection (*left*) and intra-aortic injection while compressing the femoral arteries (*right*) result in a similar distribution of agents in the hypogastric area

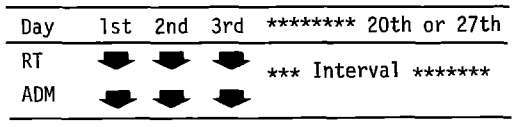

Fig. 2. Three-day courses of doxorubicin-IAC with low-dose irradiation. This was repeated four to six times. *RT*, irradiation (2 Gy); *ADM*, doxorubicin (20–30 mg)

8 patients including 1 case with a pulmonary metastatic lesion), and T4a in 3 patients. The grade of differentiation of the tumor was G1 in 2 patients, G2 in 7 patients, G3 in 10 patients, and poorly differentiated in 1 case of adenocarcinoma. The mode of infiltration (INF) was INF-α in 3 patients, INF-β in 7 patients, INF-γ in 4 patients, and unknown in 6 patients (Table 1).

Method of intra-arterial injection. A Kifa green catheter was inserted percutaneously through the femoral artery, fixed with its tip 2 or 3 cm above the bifurcation of the common iliac arteries, and maintained in the vessel for 48 h. Heparinized physical saline (30–50 ml) was infused into the catheter once or twice every 24 h to prevent the congestion of inner space by thrombus formation. Doxorubicin (20–30 mg) was dissolved in 100 ml physical saline and injected over a few minutes, during which time the femoral arteries were compressed manually (Fig. 1). The injection was performed three times in 48 h, and irradiation was rapidly followed by doxorubicin chemotherapy. The 3-day course was repeated four to six times, with a 3- to 4-week interval in most cases (Fig. 2).

Evaluation of response to the treatment. Clinically, the response was evaluated as follows: complete remission (CR) was taken to mean complete disappearance of the tumor according to all clinical criteria; partial remission (PR) indicated a more than 50% reduction of the tumor; minor response (MR) indicated a 25%–49% reduction of the tumor; no response (NR) indicated a less than 25% decrease or stable disease; progressive disease (PD) indicated a more than 25% increase in the tumor. Pathological effects were classified following the criteria of Shimosato et al. [17]. Pathologically, grade III and IV were evaluated as CR, grade II as PR, grade I as MR, and grade 0 as NR.

Table 2. Brief summary of the criteria for the classification of histological therapeutic effects according to Shimosato et al. [17]

Grade	Features
0	No characteristic changes in tumor cells and tumor structures
I	Characteristic changes in tumor cells, but tumor structures have not been destroyed
II	In addition to characteristic cellular changes, tumor structures have been destroyed as a result of the disappearance of tumor cells
III	Markedly altered and presumably nonviable tumor cells are present singly or in small clusters, and viable tumor cells are hardly seen
IV	No tumor cells remain in any section

Shimosato's classification of histological effects

This is briefly summarized in Table 2.

Evaluation of side effects. All of the patients were evaluated initially and at variously intervals as follows: general physical studies were performed every day, complete blood and platelet counts were obtained every other day, and a routine chemical profile, chest X-rays, and cardiography were performed at 4- to 8-week intervals.

Schedule of the treatment of patients. After a reasonable course of doxorubicin-IAC, the clinical response of the tumor was evaluated primarily by a computed-tomography (CT) scan. The patients evaluated as CR underwent a transurethral biopsy study, and the bladder left intact. The patients with a clinical response of PR or less were subjected to surgery, i. e., total cystectomy, segmental cystectomy, or transurethral resection. All of the patients in these two groups (CR and PR or less) were maintained on oral chemotherapy with either tegafur, carmofur or UFT (a compound containing uracil and tegafur; 4:1). The daily dose of these agents was 400–600 mg tegafur, 200–300 mg carmofur and 200–300 mg UFT (estimated in terms of tegafur value). The aim was to continue long-term oral chemotherapy for at least 3 years.

Method of statistical study. The duration of the response and survival were calculated from the time of the onset of treatment, and the survival and nonrecurrent rates were obtained according to Kaplan-Meier.

Results

Doses employed

The total dose of doxorubicin ranged from 120 to 540 mg, with an average of 251.5 mg and a median of 290 mg. The total of dose of irradiation was 4–36 Gy, with an average of 24.4 Gy, the median being 24.0 Gy.

Side effects

Slight and temporary lassitude and/or anorexia were frequently encountered, while nausea and/or vomiting were noted in 3 patients (15.0%), stomatitis in 2 patients (10.0%), fever in 1 patients (5.0%). Loss of hair to a mild degree was common; however, alopecia was observed in only 3 pa-

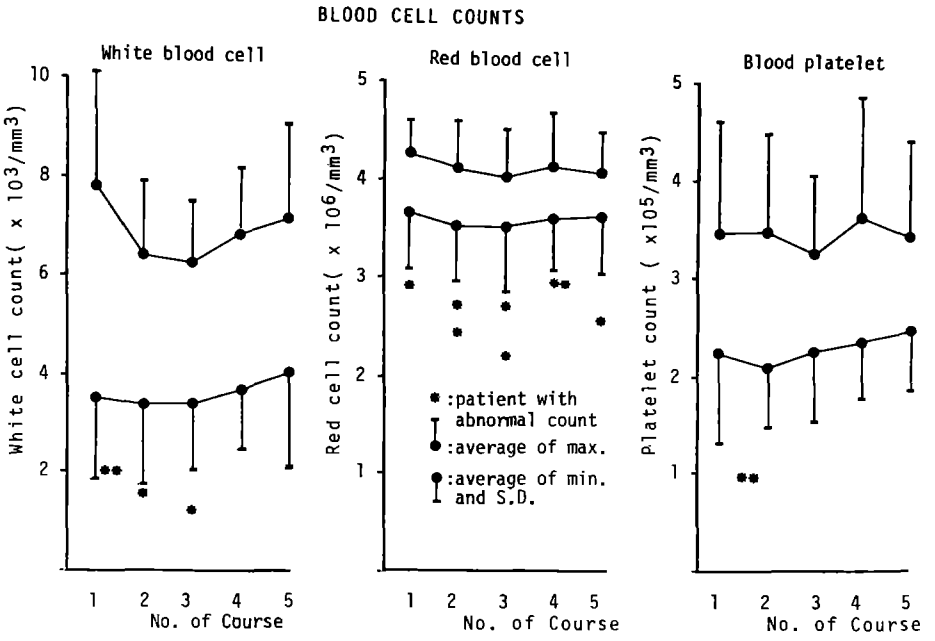

Fig. 3. Changes in blood cell and platelet counts following treatment

tients (15.0%). No patient exhibited cardiovascular, hepatic, or renal side effects. Local thrombus formation and erosion and/or necrosis of the skin were not encountered. Hematologically, 3 patients had a white blood cell count under 2,000 (15.0%), anemia (less than 3 million) occurred in 4 patients (20.0%), and thrombocytopenia (less than 100,000) was seen in 2 patients (10.0%) Fig. 3). Blood cytopenia were controllable without blood transfusion.

Response during the early phase of treatment

Clinically, 14 of the 20 patients (70.0%) were evaluated as CR, 3 patients (15.0%) exhibited PR, 3 patients (15.0%) showed MR, and none was evaluated as PD. Pathologically, CR was recognized in 13 of the 20 patients (65.0%), PR in 5 patients (25.0%), and NR in 2 patients (10.0%). The complete-response rate was 70.0% clinically and 65.0% pathologically. The pathological complete-response rate according to the stage of the tumor was 0 out of 3 patients (0%) in T1, 6 of the 6 patients (100%) in T2, 6 of the 8 patients (75.0%) in T3, and 1 of the 3 patients (33.3%) in T4a. In the early phase response, the clinical and pathological response were mutually related.

Tumor-free duration of treatment

Overall, the disease-free duration ranged from 0 to 54 months (0 : M1 case), with an average of 21.0 months and a median of 16.5 months. In 17 of the bladder-preservation cases, the vesical nonrecurrence rate was 61.1% at 54 months (Fig. 4), during which time 4 patients exhibited a recurrent tumor. In 3 cases, the recurrence (RTa-RT1) was controllable by TUR, while 1 case (RT3) failed to respond.

Survival following treatment

Overall, the expected survival rate of the patients was 88.9% at 54 months, but the actual survival rate was 57.6%;

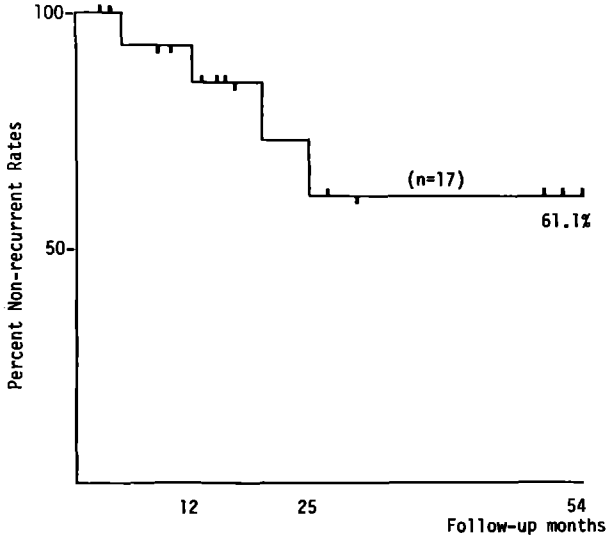

Fig. 4. Vesical nonrecurrence rate following treatment in cases in which the bladder was preserved

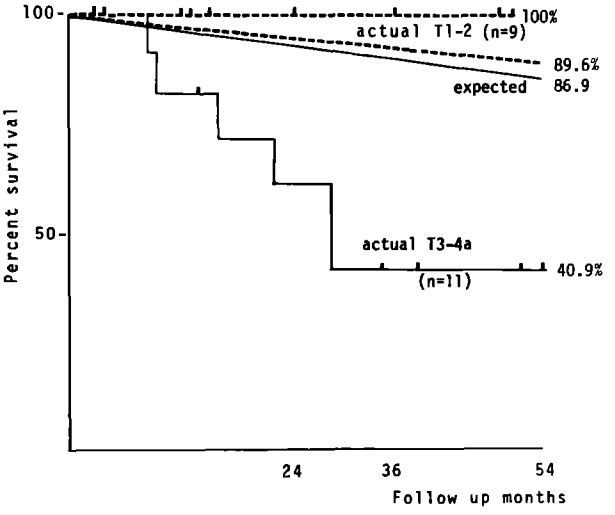

Fig. 5. Survival following treatment according to T stage

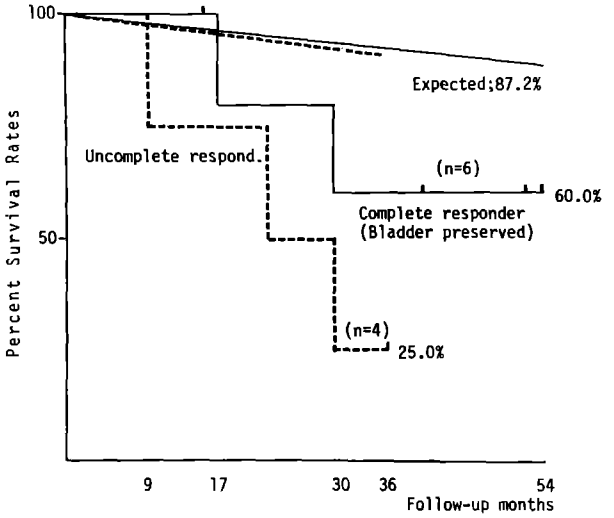

Fig. 6. Survival in T3 and T4a tumors according to pathological response

consequently, the relative survival rate was 64.8% at 54 months. The survival for the T stage of the disease was 100% at 50 months in the T1 and T2 group ($n=9$), and was 40.9% at 54 months in the T3 and T4a group ($n=11$), as expected (Fig. 5). The survival in the T3 and T4a group according to pathological response is shown in Fig. 6. The actual survival rate among patients who showed pathological CR was 60.0% (relative rate, 68.8%) at 54 months, while the actual survival rate in incomplete responders was 25.0% (relative rate 27.1%) at 36 months.

Discussion

Radical cystectomy may be curative in patients with locally invasive bladder cancers; the 5-year survival rate ranges between 62% and 87% for stage-B1 bladder cancers [12, 22], between 25% and 73% for stage-B2 tumors [10, 11, 12], and between 11% and 61% for stage-C cancers [12, 21, 22]. This procedure is unsatisfactory for the maintenance of voiding and sexual functions. High-energy, external-beam irradiation could, theoretically, counter the events caused by surgical cystectomy, but the survival rate is disappointingly low. This procedure was been found to result in a 5-year survival rate ranging from 18% to 38% in stage-B2 and -C cancers [5, 20].

Radiation therapy followed by cystectomy has been reported to produce a 5-year survival rate of 56% in radiosensitive T3 tumors [1] and 53% in T3 tumors without lymph-node metastasis [2]. Systemic cis-platin and full-dose irradiation have been shown to achieve a good early phase response [18]. These results are unsatisfactory, and there is much room for further improvement by applying other procedures either singly or in combination. Regional intra-arterial chemotherapy has been thought to be an advantageous approach [6, 8, 13, 14, 19], but there has been no discussion about survival following this procedure. Selective hypogastric chemotherapy [6, 13, 14] is an important method for treating bladder cancer. In the present study, we took an aggressive approach by performing intra-aortic injections using the compressing technique; this procedure is simple and requires only a single catheter, and the application of the compressing technique can result in good movement of the agents as is achieved by selective injection. It has been demonstrated by clinical [3, 16] and experimental [4, 7, 15] studies that a combination of doxorubicin and irradiation results in synergistic antitumor effects. Our use of irradiation in combination with doxorubicin produced 100% survival of 50 months in T1 and T2 tumors, 40.9% survival at 54 months in T3 and T4a tumors, and 60% survival at 54 months in pathologically complete responders (T3 and T4a) with an intact bladder. The results of our study are encouraging with respect to several problems, i. e., how to treat undetectable dissemination, how to treat incomplete responders, how to treat patients with arterial sclerosis, and what the best combination is. Long-term oral chemotherapy with a 5-fluorouracil derivative would seem to provide a partial solution to the problem of undetectable metastatic disease.

Acknowledgements. This study was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare, Japan.

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