Cancer Chemother Pharmacol (1992) 30 (Suppl): S 5–S 9

Cancer Chemotherapy and Pharmacology

Intra-arterial Adriamycin chemotherapy in combination with radiotherapy for advanced bladder cancer*

Yoshiteru Sumiyoshi[1], Takeshi Uyama[2], and Susumu Kagawa[3]

[1] Department of Urology, Shikoku Cancer Center, Horinouchi-13, Matsuyama, Japan
[2] Department of Urology, Seiwakai Kyoritsu Hospital, Hachiman, Tokushima, Japan
[3] Department of Urology, Tokushima University, Kuramoto, Tokushima, Japan

Summary. A total of 38 patients with locally advanced bladder cancer (T2, $n = 14$; T3, $n = 14$; T4, $n = 10$) were treated with intra-arterial Adriamycin chemotherapy in combination with radiotherapy. The clinical as well as the pathological efficacy of this treatment was evaluated in all patients. Clinically, 23 (60.5%) of the 38 patients achieved a complete remission (CR), 12 (31.6%) achieved a partial remission (PR), and 3 (7.9%) remained stable (NC). The pathological efficacy was evaluated according to the criteria of Shimosato et al., with 20 (52.6%) of the 38 patients being categorized as grade IV; 2 (5.3%), as grade III; 12 (31.6%) as grade II; and 4 (10.5%), as grade 0. The 5-year actuarial survival as a function of clinical stage amounted to 91.6% for T2, 50.0% for T3, and 37.4% for T4 (T2 vs T3, $P < 0.05$; T2 vs T4, $P < 0.01$). The 5-year actuarial survival determined according to the clinical and the pathological efficacy of treatment were 74.1% for CRs, 56.2% for PRs, and 0 for NCs (CR vs NC, $P < 0.01$; PR vs NC, $P < 0.01$). Surgery for preservation of the bladder was performed in 30 of the 33 patients who achieved clinical and pathological CRs or PRs. The 5-year actuarial survival of these 30 patients was 73.2%. These results demonstrate that this therapy is a useful method for the treatment of locally advanced bladder cancer and that preservation of the bladder might be feasible in patients who achieve clinical and pathological CRs or PRs during this treatment.

Introduction

One of the greatest concerns of urologists has involved the way in which advanced bladder cancer should be treated. Intra-arterial infusion chemotherapy has been shown to be effective in the treatment of bladder cancer [1, 12, 17]. We have also applied this procedure in the treatment of bladder cancer using Adriamycin [14]. Since the publication of our previous report on preoperative intra-arterial Adriamycin chemotherapy in combination with radiotherapy for bladder cancer [16], we have continued the follow-up of our patients and have treated several additional individuals. In the present study, we applied this treatment method to locally advanced bladder cancer and evaluated the results. We discuss the feasibility of preserving the bladder with this treatment.

Patients and methods

Between June 1979 and December 1988, a total of 38 patients (29 men and 9 women) with locally advanced bladder cancer were treated at Shikoku Cancer Center. The average age of the patients was 69.6 years (range, 45–86 years). This study was conducted in accordance with the General Rules for Clinical and Pathological Studies on Bladder Cancer (Japanese Urological Association and Japanese Pathological Society). The clinical stage was T2 in 14 patients, T3 in 14 subjects, and T4 in 10 patients. The tumor size ranged from 1 to 3 cm in 20 patients and was >3 cm in 18 patients. The number of tumors per patient amounted to 1 in 19 subjects and ≧2 in 19 patients. We performed transurethral biopsies on all 38 patients before the treatment. The histological type was transitional-cell carcinoma (TCC) in 30 patients and TCC with squamous-cell carcinoma (SCC) or adenocarcinoma (AC) in 8 individuals. The tumor grade was G2 in 17 patients and G3 in 21 patients. The growth pattern manifested as INF-α in 8 subjects, INF-β in 23 patients, and INF-γ in 4 individuals and was unknown in 3 patients. Lymph-duct involvement was positive in 31 patients, negative in 3 subjects, and unknown in 4 patients. Venous involvement was positive in 17 individuals, negative in 7 patients, and unknown in 14 subjects.

We used the previously described catheterization technique and treatment schedule [15]. Briefly, a catheter was inserted percutaneously through the femoral artery, fixed with its tip located 2 or 3 cm above the bifurcation of the common iliac arteries, and maintained in the vessel for 48 h. Adriamycin (20–30 mg/body) was dissolved in 100 ml physiological saline and infused over a period of about 15 min; during this time the femoral arteries were manually compressed. Radiotherapy consisted of a dose of 2 Gy/day and was confined to the bladder. The infusion was performed three times within 48 h after radiotherapy. Treatment courses were repeated at 3- to 4-week intervals to allow recovery from toxicity.

* Presented at the 4th International Conference on Treatment of Urinary Tract Tumors with Adriamycin/Farmorubicin, 16-17 November 1990, Osaka, Japan

Correspondence to: Y. Sumiyoshi, Department of Urology, Shikoku Cancer Center, Horinouchi 13, Matsuyama, Ehime 790, Japan

Table 1. Histological grading according to Shimosato et al. [8]

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, tumorstructures 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

Table 2. Correlation between the clinical and the pathological efficacy of intra-arterial Adriamycin

	Number of patients	Number of patients	
cCR	23	22	pCR
		1	
cPR	12	10	pPR
		1	
cNC	3	2	pNC
		2	

cCR, cPR, cNC: clinical CR, PR, NC
pCR, pPR, pNC: pathological CR, PR, NC

The clinical as well as the pathological efficacy of treatment against the tumors was evaluated at 4 weeks after a reasonable course of this therapy. The clinical efficacy was evaluated by intravenous pyelography, computed tomographic (CT) scan, bone scan, and cystoscopy. The efficacy was graded as follows: a complete remission (CR) was defined as the complete disappearance of the tumor and the resolution of all symptoms; a partial remission (PR) consisted of a reduction of $\geqslant 50\%$ in the tumor size; stable disease (NC) represented a decrease of <50% or an increase of <25% in the tumor size; and progressive disease (PD) was defined as an increase of >25% in the tumor size or the appearance of new lesions.

After the completion of three courses of this treatment, its clinical efficacy against the tumor was evaluated. We continued the therapy if we judged it to be efficacious; otherwise, we discontinued the treatment. Patients who were evaluated as showing CRs underwent transurethral biopsy and the bladder was preserved. Patients who were evaluated as showing PRs or more minor responses were subjected to one of the following surgical procedures: transurethral resection, segmental cystectomy, or total cystectomy.

The pathological efficacy was classified in accordance with the criteria of Shimosato et al. [8] (Table 1). Pathological grades III and IV were evaluated as CRs, grade II was classified as a PR, and grades I and 0 were classified as NCs.

All of the patients were maintained on oral chemotherapy with either tegafur, carmofur, or UFT. The duration of survival was calculated from the time of evaluation of the efficacy until September 1990. Survival and the vesical nonrecurrence rates were estimated by the method of Kaplan and Meier.

Table 3. Clinical and pathological efficacy related to the tumor

Details of tumor	Efficacy	CR or PR	NC	χ^2-test
Tumor number	1	15	4	
	2≦	18	1	N. S.[a]
Tumor size	1–3 cm	20	0	
	3 cm ≦	13	5	$P<0.05$
T stage	T2	14	0	
	T3	14	0	$P<0.05$
	T4	5	5	
Histological type	TCC	27	3	
	TCC with SCC or AC	6	2	N. S.
Tumor grade	G2	15	2	
	G3	18	3	N. S.
Growth pattern	INF-α	8	0	
	INF-β	19	4	N. S.
	INF-γ	3	1	

[a] N. S.: not significant

Results

Total course and dose

The total number of courses given to each patient ranged from 3 to 6 (3 courses, 8 patients; 4 courses, 16 subjects; 5 courses, 12 patients; 6 courses, 2 patients), with an average of 4.2 courses being given per patient. The total dose of Adriamycin given to each patient ranged from 180 to 540 mg (average, 298 mg), and the total dose of radiotherapy ranged from 18 to 42 Gy (average, 26 Gy/patient).

Efficacy of treatment

The clinical as well as the pathological efficacy of the treatment was evaluated in all 38 patients. Clinically, 23 (60.5%) of the 38 patients achieved CRs, 12 (31.6%) achieved PRs, and 3 (7.9%) classified as NCs. Pathological evaluation revealed CRs in 22 (57.9%) of the 38 patients, PRs in 12 subjects (31.6%), and NCs in 4 patients (10.5%). Both the clinical and the pathological evaluations yielded CRs in 22 (57.9%) of the 38 patients, PRs in 11 (28.9%), and NCs in 5 (13.2%; Table 2).

Clinical CRs or PRs as determined according to the pretreatment clinical stage amounted to 14 (100%) for T2, 14 (100%) for T3, and 7 (70%) for T4. Pathological CRs or PRs as determined according to the clinical stage amounted to 14 (100%) for T2, 14 (100%) for T3, and 6 (60%) for T4. The clinical and pathological efficacy showed significant correlation with the clinical stage. As a function of the tumor size, a clinical CR or PR was achieved by all 20 patients with a tumor measuring 1–3 cm and by 15 (83.3%) of 18 patients with a tumor measuring >3 cm. Similarly, a pathological CR or PR was achieved by all 20 patients with a tumor measuring 1–3 cm and by 14 (77.8%) of the 18 patients with a tumor

Table 4. Incidence of overall toxicity

Symptom	Number of patients (%)
Leukopenia	32 (84.2)
Alopecia	26 (68.4)
Nausea and vomiting	25 (65.8)
Anemia	20 (52.6)
Diarrhea	5 (13.2)
Thrombocytopenia	3 (7.9)
Anal pain	2 (5.3)
Mucositis	2 (5.3)

measuring >3 cm. The clinical and pathological efficacy showed significant correlation with the tumor size.

As a function of the tumor number, a clinical and pathological CR or PR was achieved by 15 of the 19 patients with a single tumor and by 18 of the 19 patients with multiple tumors. As a function of the histological type, a clinical and pathological CR or PR was attained in 27 of the 30 patients with TCC and in 6 of the 8 patients with TCC and SCC or AC. As a function of the tumor grade, a clinical and pathological CR or PR was achieved by 15 of the 17 patients with grade 2 disease and by 18 of the 21 patients with grade 3 disease. As a function of the growth pattern, a clinical and pathological CR or PR was achieved by all 8 patients with INF-α, by 19 of the 21 patients with INF-β, and by 3 of the 4 patients with INF-γ. The clinical and pathological efficacy did not correlate significantly with the tumor number, histological type, tumor grade, or growth pattern (Table 3).

Survival

The average follow-up period was 59.1 months (range, 21–123 months). The 5-year actuarial survival of patients according to the clinical stage amounted to 91.6% for T2, 50.0% for T3, and 37.4% for T4 (T2 vs T3, $P<0.05$; T2 vs T4, $P<0.01$; Fig. 1). The 5-year actuarial survival according to the clinical and pathological efficacy was 74.1% for CRs, 56.2% for PRs and 0 for NCs (CR vs NC, $P<0.01$; PR vs NC, $P<0.01$; Fig. 2). Surgery for preservation of the bladder was performed in 30 of the 33 patients who achieved clinical and pathological CRs or PRs. The actuarial survival of these 30 patients amounted to 90.8% for 3 years and 73.2% for 5 years (Fig. 3). In all, 23 of these 30 patients are alive, 3 died of bladder cancer, and 4 died of other diseases. Two of the three patients who died of bladder cancer had been advised to undergo total cystectomy, but they refused it. The third patient developed lung cancer after 44 months and underwent a curative operation; he died of renal failure due to local recurrence of the bladder cancer. In all, 15 of the 23 living patients have not had any vesical recurrence, but the other 8 have shown evidence of such recurrence.

Vesical recurrence

The 5-year vesical nonrecurrence rate obtained for the 23 patients who underwent bladder-preservation opera-

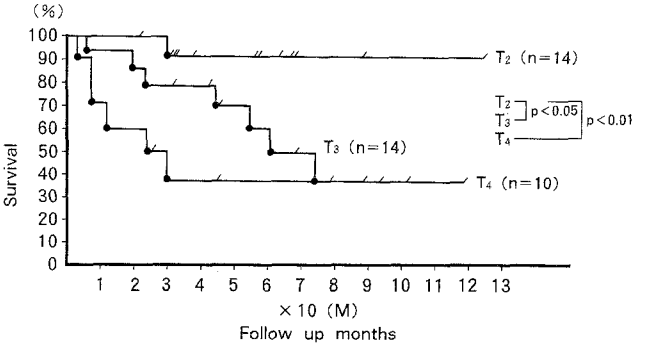

Fig. 1. Survival of patients according to clinical stage

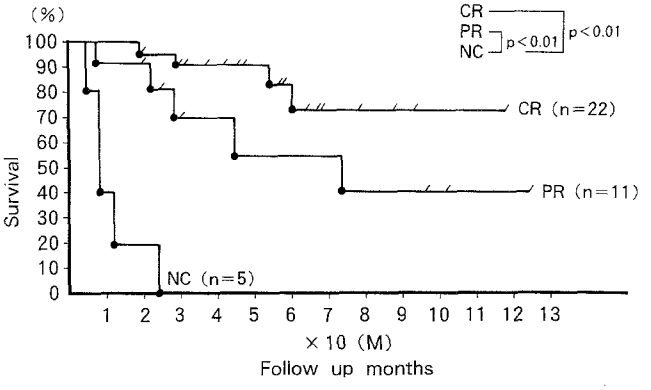

Fig. 2. Survival of patients according to treatment efficacy

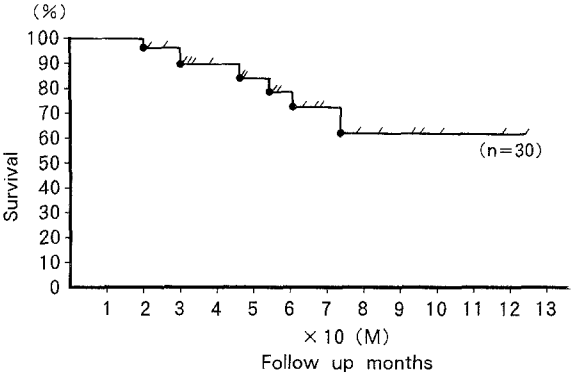

Fig. 3. Survival of patients whose bladders were preserved

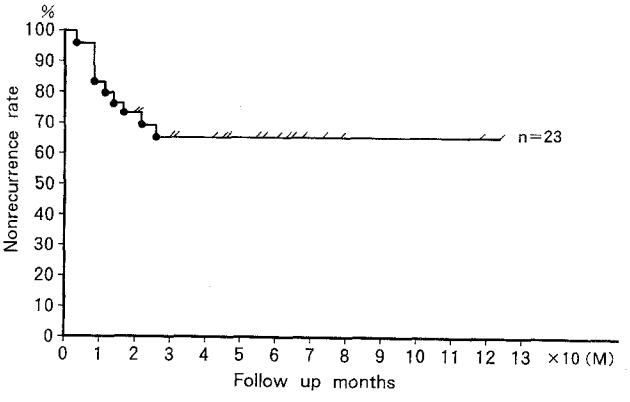

Fig. 4. Vesical nonrecurrence rate in patients whose bladders were preserved

tions and are currently alive was 65.5% (Fig. 4). In all, 8 of these 23 patients have had vesical recurrences; 6 of the 8 patients underwent transurethral resection and the bladder was preserved. The remaining 2 patients underwent total cystectomy due to in situ carcinoma of the urethra and to a tumor of advanced grade and stage, respectively.

Toxicity

The overall toxic side effects of the treatment are shown in Table 4. None of the patients died of these treatment-related complications. The most common toxicities encountered were myelosuppression, alopecia, and nausea and vomiting. Leukopenia (<4000 leukocytes/mm^3) was noted in 32 patients (84.2%); anemia (Hb, <11 g/dl) in 20 (52.6%); and thrombocytopenia (<10 $\times$ 10^4 platelets/mm^3) in 3 (7.9%). There was no evidence of cardiovascular toxicity.

Discussion

Patients undergoing only radical cystectomy for locally advanced bladder cancer have a >50% probability of dying of their disease [3, 5, 13]. If perioperative adjuvant therapy were to be given, these patients would be subject to significantly less morbidity. These patients are usually managed with preoperative irradiation followed by cystectomy [9, 10]. Combination therapy with preoperative irradiation has produced a reduction of recurrence following cystectomy [18]. However, this combination therapy is not effective against occult metastatic disease. Currently used chemotherapy regimens include cisplatin, cyclophosphamide, and doxorubicin (CISCA) [2, 7] and methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) [6, 11]. Although CRs have been achieved by up to 50% of the patients treated with these combinations, adjuvant chemotherapy has not yet been proven to be superior to radical cystectomy alone in controlled trials.

Intra-arterial infusion chemotherapy is a treatment modality designed to obtain a high concentration of the antitumor agent(s) in the tumor so as to ensure effective treatment, whereas a small amount of drug is distributed throughout the body. For an agent to be used in this procedure, it should have a broad antitumor spectrum and should be easily absorbed by and readily accumulated in the tumor. We have applied this procedure in the treatment of bladder cancer using Adriamycin. We have found that (1) intra-arterial infusion chemotherapy is a useful treatment for bladder cancer, (2) Adriamycin is a suitable and effective agent for this treatment, and (3) a combination of Adriamycin and radiotherapy produces synergistic antitumor effects [4, 14, 15].

In the present study, we used intra-arterial Adriamycin chemotherapy in combination with radiotherapy for the treatment of locally advanced bladder cancer. Clinically and pathologically, 33 of the 38 patients, or 86.8%, achieved a CR or PR. Surgery for preservation of the bladder was performed in 30 of these 33 individuals. The most important questions that arose were:

1. What was the outcome in these patients?
2. What was the incidence of distant metastases in these subjects?

The 5-year actuarial survival of these 30 patients was 73.2%; only 3 patients died of bladder cancer, and they did not have any distant metastases. In all, 23 of these 30 patients are alive, and 8 of the 23 patients have had vesical recurrences. However, the recurrent tumors were ectopic and superficial and could be controlled by transurethral resection except in 2 cases.

These observations lead us to conclude that this combination therapy is a useful therapeutic method and could be a first-choice modality for the treatment of locally advanced bladder cancer. In patients who achieve a clinical and pathological CR or PR, it might be possible to preserve the bladder using this treatment. However, during the follow-up of patients whose bladders have been preserved, we never fail to perform total cystectomy if it is deemed to be necessary. We will continue this treatment and try to improve its efficacy by changing the antitumor agents and doses given to patients showing an incomplete response to this therapy.

References

1. Kubota Y, Kakizaki H, Numasawa K, Suzuki K, Kato H (1989) Preoperative intra-arterial infusion chemotherapy for patients with bladder cancer. Eur Urol 16: 189
2. Logethetis CJ (1981) CISCA chemotherapy for bladder cancer. Cancer Bull 33: 79
3. Montie JR, Straffon RA, Stewart BH (1984) Radical cystectomy without radiation therapy for carcinoma of the bladder. J Urol 131: 477
4. Nevin JE, Melnik I, Baggerg JT (1974) Advanced carcinoma of bladder: treatment using hypogastric artery infusion with 5-fluorouracil, either as a single agent or in combination with bleomycin or Adriamycin and supervoltage radiation. J Urol 112: 752
5. Pearse HD, Reed RR, Hodge CV (1978) Radical cystectomy for bladder cancer. J Urol 119: 216
6. Scher HI, Yogoda A, Herr HW, Sternberg CN, Morse MJ, Sogani PC, Watson RC, Reuter V, Whitmore WF Jr, Fair WR (1988) Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for extravesical urinary tract tumors. J Urol 139: 475
7. Schwartz S, Yogoda A, Natale RB, Watson RC, Whitmore WF Jr, Lesser M (1983) Phase II trial of sequentially administered cisplatin, cyclophosphamide and doxorubicin for urothelial tract tumors. J Urol 130: 681
8. Shimosato Y, Oboshi S, Baba K (1971) Histological evaluation of effects of radiotherapy and chemotherapy for carcinomas. Jpn J Clin Oncol 1: 19
9. Skinner DG, Tift JP, Kaufman JJ (1982) High dose, short course preoperative radiation therapy and immediate single stage radical cystectomy with pelvic node dissection in the management of bladder cancer. J Urol 127: 671
10. Smith JA Jr, Batata M, Grabstald H, Sogani PC, Herr H, Whitmore WF (1982) Preoperative irradiation and cystectomy for bladder cancer. Cancer 49: 869
11. Sternberg CN, Yogoda A, Scher HI, Watson RC, Herr HW, Morse MJ, Sogani PC, Vaughan ED Jr, Bander N, Weiselberg LR, Geller N, Hollander PS, Lipperman R, Fair WR, Whitmore WF Jr (1988) M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. J Urol 139: 461

12. Stewant DJ, Futter N, Maroun JA, Murphy P, Mckay D, Rasuli P (1984) Intra-arterial cisplatin treatment of unresectable or medically inoperable invasive carcinoma of the bladder. J Urol 131: 258
13. Sumiyoshi Y, Kagawa S, Takigawa H, Kurokawa K (1987) Clinical study of total cystectomy: simple total cystectomy for transitional cell carcinoma of the bladder. Nishinihon J Urol 49: 797
14. Uyama T, Nakamura S, Yamamoto A, Moriwaki S (1980) Treatment of advanced bladder cancer by intra-arterial infusion of Adriamycin. Jpn J Cancer Chemother 7: 1964
15. Uyama T, Moriwaki S, Yonezawa M, Fujita J (1983) Intra-arterial Adriamycin chemotherapy for bladder cancer. Semiselective intra-arterial chemotherapy with compression of the femoral arteries at the time of injection. Cancer Chemother Pharmacol 11 [Suppl]: S59
16. Uyama T, Moriwaki S, Yokozeki A, Kitada K, Higa I, Shiotsu T, Fujita J (1987) The role of preoperative intra-arterial doxorubicin chemotherapy in combination with low dose irradiation for bladder cancer. Cancer Chemother Pharmacol 20 [Suppl]: S10
17. Wallace S, Chaung VP, Samuels M, Johnson D (1982) Transcatheter intraarterial infusion of chemotherapy in advanced bladder cancer. Cancer 49: 640
18. Whitmore WF Jr, Batana MA, Ghoneim MA, Grabstald H, Ural A (1977) Radical cystectomy with or without prior irradiation in the treatment of bladder cancer. J Urol 118: 184