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SESSION I

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Adjuvant and neoadjuvant chemotherapy for invasive bladder cancer

Abstract A total of 20 patients with primary invasive bladder cancer who underwent radical cystectomy received postoperative adjuvant chemotherapy using a CAP (cyclophosphamide, doxorubicin, and cisplatin) or modified M-VAC (methotrexate, vinblastine, pirarubicin, and cisplatin) regimen. In all, 16 of the patients were treated with CAP and 4 received the modified M-VAC regimen. Of the 20 patients, 17 had transitional-cell carcinoma with or without non-transitional-cell elements. All of the patients had tumors with a histological grade of G2 (6 cases) or G3 (14 cases). As for lymph-node metastasis, there were ten N0 cases, three N1 cases, six N2 cases, and one N3 case. Adjuvant chemotherapy was usually commenced 2 weeks after the surgery and was given every 3–4 weeks for two or three cycles. The 5-year survival rate of these 20 patients was 65.9%, whereas that of 49 patients who did not receive any adjuvant chemotherapy was 30.2%. Regarding toxicity, both of the adjuvant chemotherapy regimens used in this study were generally well tolerated. The most common toxic effects were gastrointestinal symptoms, alopecia, and myelosuppression. Another 19 patients with invasive transitional-cell carcinoma of the bladder received 2 or 3 cycles of neoadjuvant chemotherapy using the modified M-VAC or MEC (methotrexate, epirubicin, and cisplatin) regimen. Of 18 pathologically evaluable patients who underwent radical cystectomy or partial cystectomy, the stage was pT0 in 3 cases (17%), pTis in 3 (17%), pT1 in 3 (17%), and pT2 or higher in 9 (50%). The 4-year survival rate of 18 patients who received neoadjuvant chemotherapy was 71.5%. Regarding toxicitiy, one patient died of a bowel complication after surgery, and the complication was suggested to be drug-induced.

Key words Bladder cancer · Adjuvant chemotherapy · Neoadjuvant chemotherapy

Introduction

Patients with invasive bladder cancer have a poor prognosis, even if they are treated by radical surgery. Especially when the tumor infiltrates into the extravesical tissue, that is, T3b- or higher-stage tumors, the patients seldom survive for more than a few years. Of patients who undergo radical cystectomy for invasive bladder cancer, 40%–80% die of metastatic disease within a 2- to 3-year period [6–8]. Chemotherapy and radiotherapy have been thought to be the most useful adjuvant treatments for these patients. Because most patients with high-stage bladder cancer suffer from systemic rather than local disease, a significant improvement in their survival will require effective systemic chemotherapy.

In this article, we describe our experience with chemotherapy given in two or more cycles before or after radical cystectomy or partial cystectomy to patients with locally advanced bladder cancer.

Patients and methods

In the Center for Adult Diseases, Osaka, we performed adjuvant chemotherapy using a CAP (cyclophosphamide, doxorubicin, and cisplatin) or modified M-VAC (methotrexate, vinblastine, pirarubicin, and cisplatin) regimen in 20 patients who had undergone radical cystectomy for high-stage tumors. The patients' characteristics are shown in Table 1.

The histological findings for the bladder tumors indicated that almost all the patients had transitional-cell carcinomas. Squamous-cell carcinomas were found in two patients. Only one individual had an

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Table 1 Patients' characteristics (adjuvant chemotherapy)

Number of patients	20
Median age (years)	57 (range, 47–72)
Sex (M:F)	17:3
Cell type, number (%):	
Transitional-cell carcinoma	17 (85)
Squamous-cell carcinoma	2 (10)
Adenocarcinoma	1 (5)
Histological grade, number (%):	
G2	6 (30)
G3	14 (70)
Histological stage, number (%):	
pT2	1 (5)
pT3a	5 (25)
pT3b	9 (45)
pT4	5 (25)
Regional lymph node metastasis, number (%):	
pN0	10 (50)
pN1	3 (15)
pN2	6 (30)
pN3	1 (5)
Observation period (months)	5–136
Median (months)	45

Table 2 Patients' characteristics (neoadjuvant chemotherapy)

Number of patients	19
Median age (years)	67 (range, 50–74)
Sex (M:F)	15:4
Prechemotherapy clinical stage, number (%):	
T4	4 (21)
T3	14 (74)
T2	1 (5)
Observation period (months)	3–56
Median (months)	22

adenocarcinoma. All patients had tumors with a histological grade of G2 or G3, and the majority had G3 tumors (14 patients). All patients underwent pelvic lymph-node dissection. Among the 20 patients, there were 10 pN0 cases, 3 pN1 cases, 6 pN2 cases, and 1 pN3 case. Lymph-node metastases were found in 10 patients. In all, 14 patients were treated with the CAP regimen and 6 were treated with the modified M-VAC regimen. The follow-up interval ranged from 5 to 136 months (median, 45 months).

In addition, we performed neoadjuvant chemotherapy using the modified M-VAC or an MEC (methotrexate, epirubicin, and cisplatin) regimen in 19 patients with clinically high-stage transitional-cell carcinoma of the bladder. The clinical stage of each case was assessed by physical examination, cystoscopy, excretory urography, computerized tomography (CT) scan, magnetic resonance (MR) imaging, and pathological examination of transurethral bladder resection specimens. The patients' characteristics are shown in Table 2.

All patients had tumors with a histological grade of G2 or G3, and the majority had G3 tumors (12 patients). Clinical staging of the bladder tumors of these patients showed 4 T4N0 cases, 2 T3N+ cases, 12 T3N0 cases, and 1 T2N+ case. In all, 18 patients were treated with the modified M-VAC regimen and 1 patient was treated with the MEC regimen. The follow-up interval ranged from 3 to 56 months (median, 22 months).

The adjuvant and neoadjuvant chemotherapy regimens are shown in Table 3. CAP consisted of 50 mg/m^2 Adriamycin (doxorubicin) and 500 mg/m^2 cyclophosphamide given i.v. on day 1 and 25 mg/m^2 cisplatin given i.v. on days 2 and 3. In the modified M-VAC regimen, 30 mg/m^2 methotrexate was given i.v. on days 1, 15, and 22; 3 mg/m^2 vinblastine was given i.v. on days 2, 15, and 22; 30 mg/m^2 pirarubicin was given i.v. on day 2; and 40 mg/m^2 cisplatin was given i.v. on days 2 and 3. As the MEC regimen, 30 mg/m^2 methotrexate was given i.v. on days 1 and 15, 50 mg/m^2 epirubicin was given i.v. on day 2, and 100 mg/m^2 cisplatin was given i.v. on day 2. The adjuvant chemotherapy was usually commenced 2 weeks after radical surgery and was given every 3 or 4 weeks for two or three cycles.

Results

Survival of patients treated with adjuvant chemotherapy

The survival curves generated the groups of patients treated with and without adjuvant chemotherapy are shown in Fig. 1. The patients who were treated with adjuvant chemotherapy survived longer than those who were not given any chemotherapy. The 5-year survival rate of the patients treated with adjuvant chemotherapy was 65.9%, whereas that of patients not given any adjuvant chemotherapy was 30.2%. The difference between these rates was statistically significant.

Figure 2 shows the cause-specific survival curves generated for the two patient groups. The patients who were treated with adjuvant chemotherapy survived significantly longer than those who were not given any chemotherapy. The 5-year survival rate of the patients treated with adjuvant chemotherapy was 78.0%, whereas that of the

Table 3 Chemotherapy regimens

1. CAP

Drug		Day		
		1	2	3
Doxorubicin	(mg/m^2)	50		
Cyclophosphamide	(mg/m^2)	500		
Cisplatin	(mg/m^2)		25	25

Every 3 weeks for 2 or 3 cycles

2. Modified M-VAC

Drug		Day				
		1	2	3	15	22
Methotrexate	(mg/m^2)	30			30	30
Vinblastine	(mg/m^2)		3		3	3
Pirarubicin	(mg/m^2)		30			
Cisplatin	(mg/m^2)		40	40		

Every 4 weeks for 2 or 3 cycles

3. MEC

Drug		Day		
		1	2	15
Methotrexate	(mg/m^2)	30		30
Epirubicin	(mg/m^2)	50		
Cisplatin	(mg/m^2)		100	

Every 4 weeks for 2 or 3 cycles

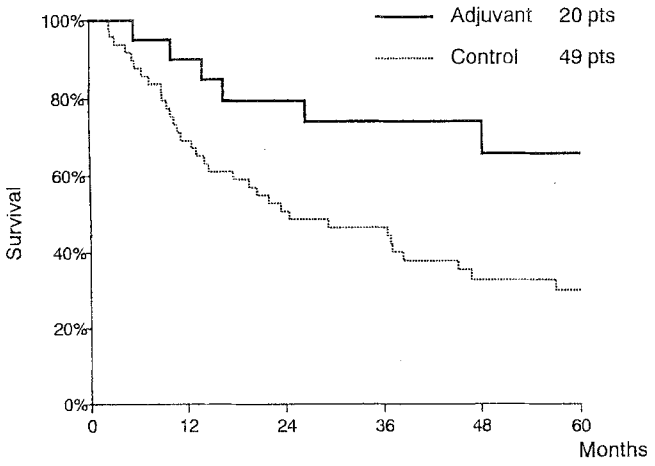

Fig. 1 Survival curves generated for patients treated with adjuvant chemotherapy and untreated control patients

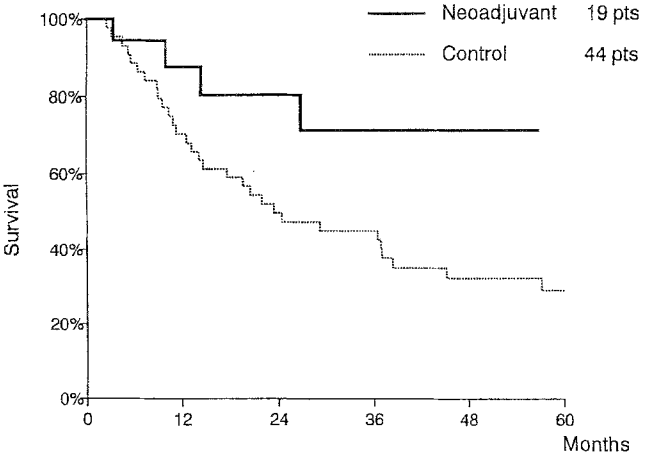

Fig. 3 Survival curves generated for patients treated with neoadjuvant chemotherapy and untreated control patients

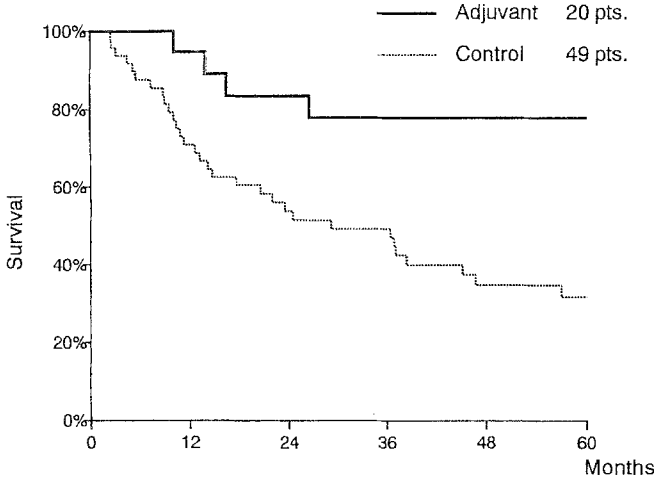

Fig. 2 Cause-specific survival curves generated for patients treated with adjuvant chemotherapy and untreated control patients

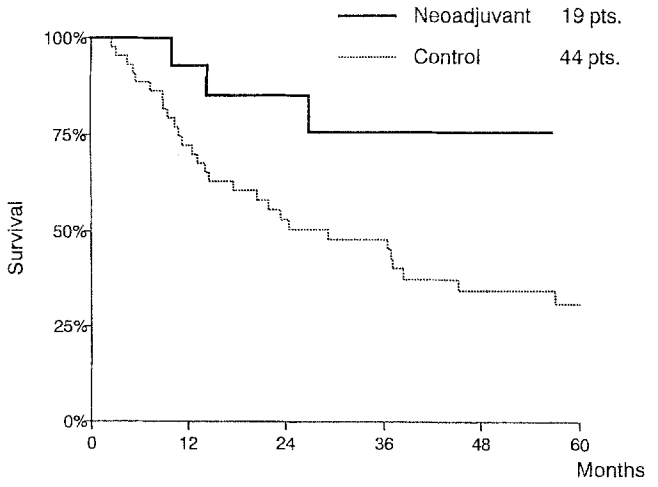

Fig. 4 Cause-specific survival curves generated for patients treated with neoadjuvant chemotherapy and untreated control patients

control patients not given adjuvant chemotherapy was 32.0%.

Response of the primary tumor to neoadjuvant chemotherapy

Of 18 evaluable patients who received neoadjuvant chemotherapy, a complete response was observed in 2 (11%); a partial response, in 10 (56%); and no change, in 6 (33%). The overall response rate was 67% (95% confidence interval, 45%–88%). In all, 17 patients underwent total cystectomy and 2 underwent partial cystectomy at the patient's request. One patient died of a bowel complication.

Table 4 shows the relationship between the prechemotherapy clinical T stage and the postchemotherapy pathological stage. In the 18 patients who were pathologically evaluated, 3 tumors were pT0, 3 were pTis, 3 were pT1, and 9 were pT2 or a higher stage. In this study, pT0 was achieved in 17% of cases. This rate was slightly lower than that reported for invasive bladder cancer treated with the M-VAC regimen [2].

Survival of patients treated with neoadjuvant chemotherapy

Figure 3 shows the survival curves generated for the groups of patients treated with and without neoadjuvant chemotherapy. The patients who were treated with neoadjuvant

Table 4 P- versus T-stage response to neoadjuvant chemotherapy

Prechemotherapy		Postchemotherapy pathological stage					
T-stage	Number of patients	P4	P3	P2	P1	Pis	P0
T4	3	2	1				
T3	14		2	4	3	3	2
T2	1						1

chemotherapy survived longer than those who were not given any chemotherapy. The 4-year survival rate of the patients treated with neoadjuvant chemotherapy was 71.5%, whereas that of the control patients not given any neoadjuvant chemotherapy was 32.4%. The difference between these rates was statistically significant.

Figure 4 shows the cause-specific survival curves generated for the two groups. The patients who were treated with neoadjuvant chemotherapy survived statistically longer than those who were not given any chemotherapy. The 4-year survival rate of the patients treated with neoadjuvant chemotherapy was 75.7%, whereas that of the control patients not given any neoadjuvant chemotherapy was 34.7%.

Toxicity

Table 5 compiles the toxic effects of the adjuvant and neoadjuvant chemotherapy regimens. The most common toxic effects were gastrointestinal effects, alopecia, and myelosuppression. Generally, the chemotherapy regimens given in this study were well tolerated by all of the patients. However, one patient who underwent radical cystectomy following neoadjuvant chemotherapy died of a bowel complication.

Table 6 compiles the incidence of myelosuppression for the adjuvant and neoadjuvant chemotherapy regimens. Leukopenia occurred in 90% of the patients who received the adjuvant chemotherapy and in all of the patients who received the neoadjuvant chemotherapy. Thrombocytopenia occurred in 60% and anemia, in 80% of the patients who received the adjuvant chemotherapy, and thrombocytopenia occurred in 79% and anemia, in 84% of the patients who received the neoadjuvant chemotherapy. Patients with these toxic effects must be given prompt treatment, including granulocyte colony-stimulating factor (G-CSF) and blood transfusions.

Table 5 Toxicity

Toxic effect	Adjuvant (n = 20)	Neoadjuvant (n = 19)
Gastrointestinal effect	20 (100)	19 (100)
Myelosuppressive effect	19 (95)	19 (100)
Skin, alopecia	18 (90)	17 (89)
Infection, fever	8 (40)	12 (63)
Hepatic effect	4 (20)	4 (21)
Renal effect	1 (5)	2 (11)
Cardiovascular effect	1 (5)	0

Table 6 Myelotoxicity

Myelotoxicity	Adjuvant (%) (n = 20)	Neoadjuvant (%) (n = 19)
Leukopenia	18 (90)	19 (100)
2000–2999	3 (15)	5 (26)
1000–1999	13 (65)	11 (58)
<1000	2 (10)	3 (16)
Thrombocytopenia ($\times 10^3$)	12 (60)	15 (79)
70–99	4 (20)	7 (37)
50–69	4 (20)	4 (21)
30–49	3 (15)	2 (11)
<30	1 (5)	2 (11)
Anemia	16 (80)	16 (84)

Discussion

Surgical treatment of high-grade, high-stage bladder cancer by radical cystectomy has not provided a satisfactory cure or long-term survival. Distant metastasis rather than local recurrence has been the major problem with invasive bladder cancer. It is thought that control of unidentified micrometastases with adjuvant or neoadjuvant chemotherapy is of benefit to long-term survival. In this study, we used the combination chemotherapy regimens of CAP, M-VAC, and MEC to test this hypothesis. Our treatment results were similar to those reported from previous studies [1, 2, 9].

Two prospective randomized trials demonstrated that adjuvant chemotherapy improved the disease-free survival of patients who had pT3, pT4, or pN+ tumors [3, 4]. Wallace et al. [5] reported on a randomized trial of neoadjuvant chemotherapy, but no significant improvement in survival was demonstrated. To date, no randomized trial has clearly demonstrated improved survival due to administration of neoadjuvant chemotherapy regimens.

It is unclear whether adjuvant chemotherapy or neoadjuvant chemotherapy achieves better prolongation of survival. The major advantage of adjuvant chemotherapy is that the cystectomy specimen is available for pathological evaluation. Patients can be assigned a chemotherapeutic regimen according to their pathological prognostic factors. There is no delay in definitive treatment when the cystectomy is performed initially. The major disadvantage is that there is no measurable lesion for the evaluation of response. An additional disadvantage is the delay of systemic therapy for micrometastases. The optimal time to treat micrometastases is when their volume in minimal.

The major advantage of neoadjuvant chemotherapy is that the response to chemotherapy can be evaluated since the primary bladder tumor remains as a marker lesion. This may permit the continuation of treatment to a maximal response or the termination of ineffective therapy. An additional advantage is the potential for bladder preservation. Chemotherapy can be started at the optimal time, when the volume of micrometastases is minimal. When chemotherapy is started prior to cystectomy, the delivery of drugs is better than after cystectomy because of the intact vascular bed. The major disadvantage is the difficulty of clinical staging. Patients have to be selected to receive chemotherapy on the basis of inaccurate clinical staging. An additional disadvantage is that neoadjuvant chemotherapy may be ineffective as initial treatment. Valuable time may be wasted in patients who do not respond.

Currently, we give neoadjuvant chemotherapy to patients definitely diagnosed as having T3b or T4 tumors by transurethral resection and imaging. Patients who have high-stage tumors but no demonstrable extravesical lesion should undergo radical cystectomy as initial treatment. Then, according to the pathological prognostic factors, adjuvant chemotherapy can be given.

The data available from reported nonrandomized and randomized trials have suggested the benefit of adjuvant or neoadjuvant chemotherapy. In the present study, the adjuvant and neoadjuvant chemotherapy regimens seemed to improve the survival of patients with high-stage bladder cancer. Because of these results, we will continue our study of adjuvant and neoadjuvant chemotherapies for invasive bladder cancer.

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