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Adjuvant chemotherapy for uroepithelial transitional cell carcinoma

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Summary. The effectiveness of adjuvant chemotherapy in transitional cell carcinoma of the bladder (T_1/G_3 and $\geqq T_2$) and the upper urinary tract were evaluated. Among a group of 136 patients (male 107, female 29) with such tumors, complete tumor resection was possible in 108, in whom duration of survival and disease-free interval with or without chemotherapy were compared. The combination of antineoplastic agents used was changed from 5-fluorouracil (5-FU) + vincristine (VCR) + bleomycin (BLM) or peplomycin (PEP) + mitomycin C (MMC) or 5-FU + VCR + PEP + cyclophosphamide (CPM) + adriamycin (ADM) to CPM + ADM + *cis*-platinum (DDP) or methotrexate (MTX) + vinblastine (VBL) + ADM + DDP. Of the 59 patients in the chemotherapy group, 23 (39%) had side effects due to the treatment; however, fever and gastrointestinal symptoms were the chief adverse effects and were well tolerated. The 5-year survival rate and mean disease-free interval in the chemotherapy group were 76.3% and 24.6+ months, respectively, in bladder cancer patients, and 78.2% and 25.8+ months in those with upper urinary tract tumors. However, in the non-chemotherapy group ($n=49$) the corresponding values were 62.7% and 21.1+ months in patients with bladder cancer and 67.3% and 42.0+ months in those with upper urinary tract tumor. There was a statistically significant difference ($P<0.05$) in the disease-free intervals of the two treatment groups for bladder cancer patients. Recurrence, regardless of time, was observed in 25% of chemotherapy cases and in 65% of non-chemotherapy cases, and this difference was also statistically significant ($P<0.001$). These results suggest that adjuvant chemotherapy for uroepithelial transitional cell carcinoma may be effective in extending survival and significant by protracting the disease-free period, especially in cases of advanced bladder cancer.

Introduction

Recent studies of chemotherapy for patients with transitional cell carcinoma of the bladder have been focused on intravesical treatment and prophylaxis of superficial tumors, combination with radiation therapy for local control of deeply infiltrating tumors, and systemic therapy for metastatic tumors [10, 11]. In addition to these problems, extension of survival or of the disease-free interval after complete tumor resection is another important clinical target in the case of invasive bladder tumors or upper urinary tract tumors.

This report describes the result of adjuvant chemotherapy in such patients immediately prior to or after surgery and long-term oral administration of anticancer agents for the past 10 years.

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Materials and methods

A total of 263 patients with transitional cell carcinoma of the bladder, ureter and renal pelvis have been treated in our institute during the past 10 years. There were 213 patients with bladder tumors (178 male, 35 female patients), 10 with coexisting lower and upper urinary tract (UT) tumors (7 male, 3 female patients), and 40 upper UT tumors (29 male, 11 female patients). There were 86 cases of invasive bladder cancer of T_1G_3 and $\geqq T_2$. Postoperative stages and cell grades of the invasive bladder tumors and upper UT tumors are shown in Table 1. Resection was impossi-

Table 1. Pretreatment characteristics of patients

No. of cases (M:F)						136	(107:29)
Age range (average)						40–85	(65.3)
Diagnosis							
Bladder tumor (T_1G_3 & $\geqq T_2$) (BT)						86	(71:15)
Bladder tumor and upper UT tumor						10	(7: 3)
Renal pelvic or ureter tumor (RPT/UT)						40	(29:11)
By stage and cell grade							
T category	Tx	Tis	Ta	T_1	T_2	T_3	T_4
	2	4	12	23	38	32	25
Cell grade	Gx		G_1		G_2		G_3
	23		17		41		55
TNM classification							
	N_0M_0		N_+M_0		N_0M_+		N_+M_+
BT	74		3		6		3
BT + RPT/UT	8				2		
RPT/UT	32		5		1		2
Total	114		8		9		5
Observation period (average) 0–252 months (27.7)							

ble in 28 patients due to poor performance status or advanced tumors. Therefore, 108 cases were studied. Adjuvant chemotherapy was administered in 59 cases, and 49 patients were observed following surgery alone. The initial treatment carried out for bladder cancer was transurethral resection (TUR) in 15 patients segmental resection in 29, and total cystectomy in 25 patients (Table 2). Adjuvant chemotherapy consisted in systemic administration of a combination of antineoplastic agents immediately before or after complete tumor resection, and long-term administration of 5-fluorouracil (5-FU) or its derivatives (≧6 months). Combinations were changed from 5-FU + vincristine (VCR) + bleomycin (BLM) or peplomycin (PEP) + mitomycin C (MMC) or 5-FU + VCR + PEP + cyclophosphamide (CPM) + adriamycin (ADM) to CPM + ADM + *cis*-platinum (DDP) or methotrexate (MTX) + vinblastine (VBL) + ADM + DDP. Dosages and schedules are presented in Fig. 1.

Results

The distribution of cell differentiation in transitional cell carcinoma with or without adjuvant chemotherapy is presented in Table 3. Although the non-chemotherapy group included a relatively large number of patients with disease in the Gx phase, there was no significant shift to one side in confirmed cases, indicating the possibility of comparing the two treatment groups (surgery alone vs combined surgery and chemotherapy).

The combinations used in this series were tolerable. Among 59 patients, side effects were observed in 23 (39%). However, almost all such adverse effects consisted of fever caused by BLM or PEP, or gastrointestinal symptoms because of DDP. Myelosuppression was mild, only 4 patients having a WBC of less than 3000/mm^3, with quick return to a normal range within 2 weeks. No mortality related to this treatment was observed (Table 4).

First, the effectiveness of the adjuvant chemotherapy in terms of survival time was studied with the Kaplan-Meier method. In patients with invasive bladder tumors (n=69), the 1-, 3- and 5-year survival rates in the chemotherapy group (n=31) were 100%, 76.3% and 76.3%, respectively. The group of non-chemotherapy cases showed respective survival rates of 91.5%, 67.5% and 62.7% (Fig. 2). No significant difference between these two groups was shown with the generalized Wilcoxon test. According to T categories, the 1-year survival rate in the chemotherapy

Table 2. Initial treatment for invasive bladder tumor and upper urinary tract tumor

Group	No. of cases	Curative operation			Chemotherapy alone	Palliative op./no treatment
		TUR	Segmental resection	Total cystectomy		
BT (≧T_1, G_3)	86	15	29	25	10	7
BT + RPT/UT	10		5		1	4
RPT/UT	40		34			6
Total	136		108		11	17

Table 3. Distribution of cell grade with or without adjuvant chemotherapy in invasive bladder tumor or upper urinary tract tumor

Group	Adjuvant chemotherapy	Cell grading (%)				
		Gx	G_0	G_1	G_2	G_3
Bladder tumor	Yes	2 (6)	0	0	9 (29)	20 (65)
	No	10 (26)	0	2 (5)	6 (16)	20 (53)
Renal pelvic or ureter tumor	Yes	1 (4)	0	15 (54)	9 (32)	3 (11)
	No	4 (36)	0	0	7 (64)	0
Total	Yes	3 (5)	0	15 (25)	18 (31)	23 (39)
	No	14 (29)	0	2 (4)	13 (27)	20 (41)

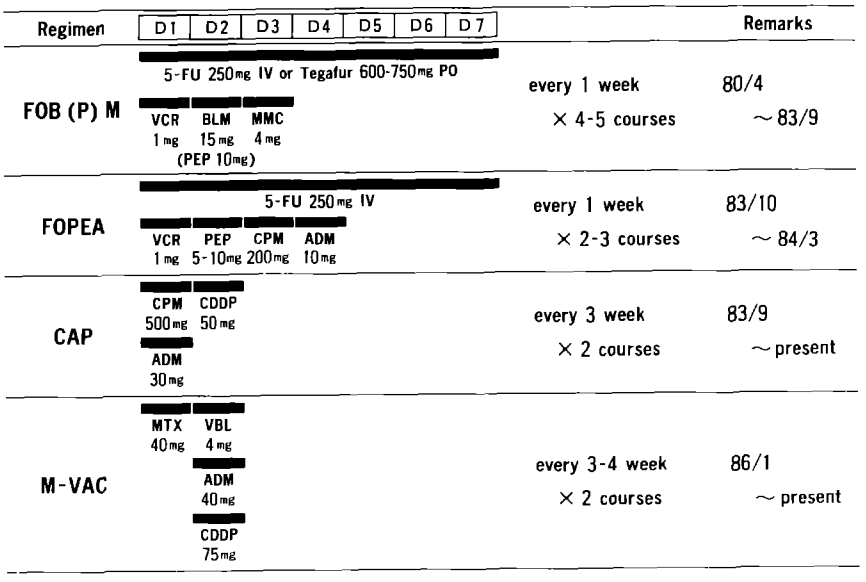

Fig. 1. Chemotherapeutic regimens, doses, and schedules

Table 4. Side effects appearing after adjuvant chemotherapy for invasive bladder tumor and upper UT tumor

Group	No. of cases	No. of cases with (%) side effect	Type of side effect			
			Fever ↑	Nausea/vomiting	Anorexia	WBC <3000
Bladder tumor	31	7 (23)	5	1	0	2
Upper UT tumor	28	16 (57)	9	3	3	2
Total	59	23 (39)	14	4	3	4

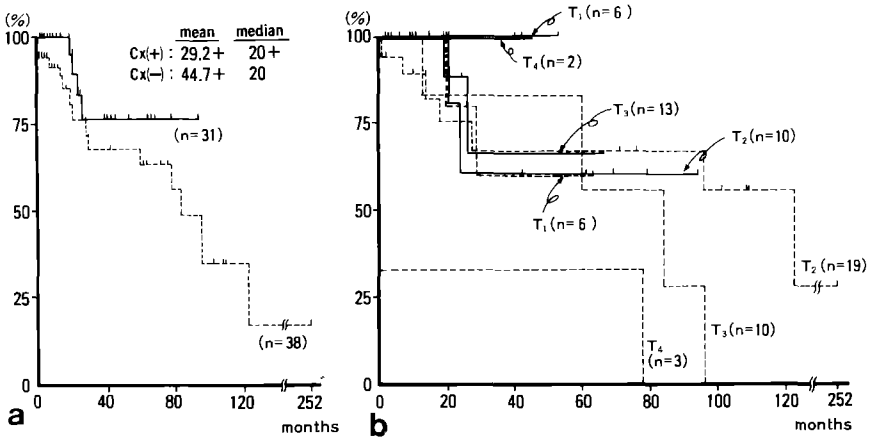

Fig. 2. Effect of adjuvant chemotherapy in terms of patient survival rate in invasive bladder tumor. *Solid lines*, chemotherapy group; *dotted lines*, non-chemotherapy groups. **a** All cases ($n=39$); **b** by T category

group was 100%, but no figures were available for 5-year survival (the longest case was still at 53+ months) in G_3 of T_1 cases ($n=6$), while the 1- and 5-year survival rates were 100% and 60% in T_2 ($n=10$) and 100% and 65.6% in T_3 ($n=13$). In T_4 ($n=2$) the 1-year survival was 100% but the longest survival was 45+ months. In the non-chemotherapy group, the corresponding values were 100% and 60% in G_3 of T_1 ($n=6$), 88.5% and 66.9% in T_2 ($n=19$), 83.3% and 55.6% in T_3 ($n=10$), and 33% and 33% in T_4 ($n=3$). Although in every T category higher survival rates were obtained in the chemotherapy group than in the non-chemotherapy group, no significant difference was observed. In patients with upper UT tumors, including coexisting lower and upper UT tumors, 1-, 3-, and 5-year survival rates were 95.8%, 91.2%, and 78.2%, respectively, in the chemotherapy group ($n=28$), and 100%, 80.8%, and 67.3% in the non-chemotherapy group ($n=11$) (Fig. 3). According to T category, as shown in Fig. 4, the groups with Tis, Ta and Tx could not be compared due to lack of one or other treatment groups. In all groups from T_1 to T_4, there was a tendency toward longer survival in the chemotherapy group, but the difference was not statistically significant.

Disease-free intervals were compared in these two groups. In Fig. 5, the durations of remission of invasive bladder tumors are shown. The chemotherapy group showed a higher disease-free rate in every follow-up period; the 1-, 3-, and 5-year disease-free rates in this group were 85.1%, 57.5%, and 57.5%, respectively, whereas the non-chemotherapy groups had rates of 61.3%, 42.9%, and 30.7%. There was a significant statistical difference between these two groups ($P<0.05$). The median disease-free interval in all cases was 19 months in the chemother-

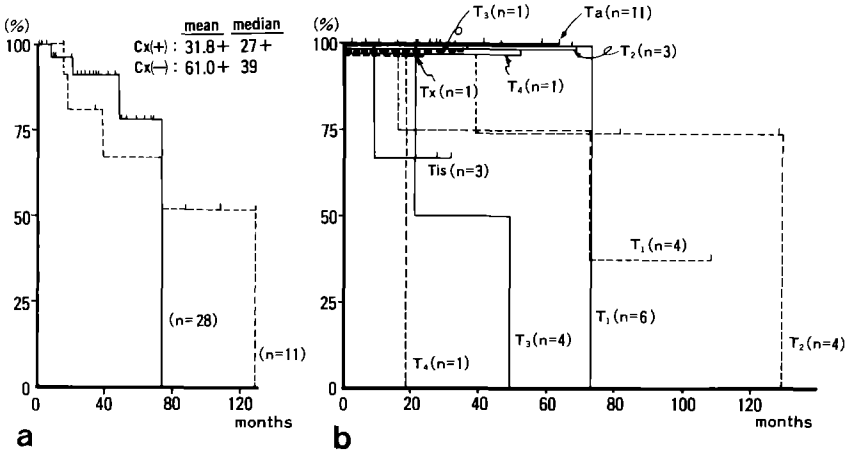

Fig. 3. Effect of adjuvant chemotherapy on survival rate of patients with upper urinary tract tumor. **a** All cases; **b** by T category

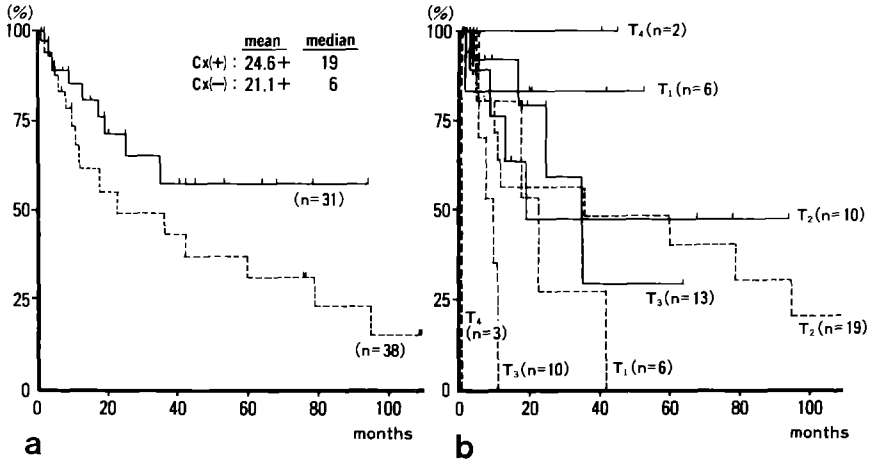

Fig. 4. Effect of adjuvant chemotherapy on duration of remission in patients with invasive bladder tumor. **a** All cases; **b** by T category

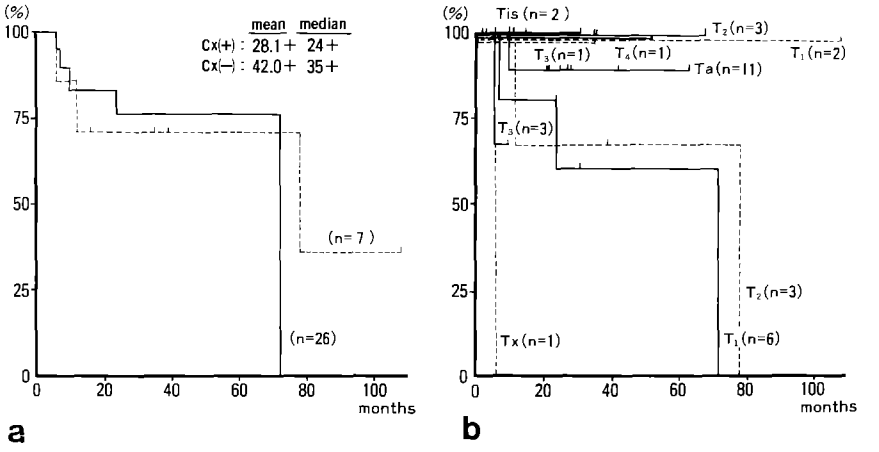

Fig. 5. Effect of adjuvant chemotherapy on duration of remission in patients with upper urinary tract tumor. **a** All cases ($n=33$); **b** by T category

apy group, compared with 6 months in the nonchemotherapy group. According to stage, these values were 20+ vs 10+ months in G_3 of T_1 cases, 13 vs 10 months in T_2, 17 vs 6 months in T_3, and 40+ vs 0+ months in T_4, showing that a longer disease-free interval was observed in every stage. Also in upper urinary tract tumors, there was such tendency observed in bladder tumor, but the difference was not statistically significant (Fig. 5). The 1-, 3-, and 5-year disease-free rates were 86.7%, 80.5%, and 80.5% in the chemotherapy group and 71.4%, 71.4%, and 71.4% in the nonchemotherapy group. The median disease-free intervals for the entire series were 19 vs 35+ months in the two groups. In terms of T categories, disease-free intervals of 24 vs 16+ months in T_1, 35+ vs 39+ months in T_2, and 6+ vs 35+ months in T_3 were observed. However, the frequency of recurrence, regardless of the time of recurrence on follow up, showed a marked difference even in patients with upper UT tumors (Table 5). In the non-chemotherapy group, recurrence was recognized in almost two-thirds of patients, whereas, the rate of recurrence was 25% in the chemotherapy group; this difference was statistically significant according to the X^2-test ($P < 0.001$).

Table 5. Effect of adjuvant chemotherapy on recurrence after complete tumor resection in invasive bladder tumor and upper urinary tumor

Group	Adjuvant chemotherapy	No. of cases	Recurrences No. (%)	x^2-test	Type of recurrence			
					Same site		Other uroepithelial side	Distant metastasis
					Same stage	Stage more advanced		
Bladder tumor	Yes	31	9 (29)	0.0024	5	3	0	1
	No	38	25 (66)		14	6	2	3
Upper UT tumor	Yes	28	6 (21)	0.0119	0	0	4	2
	No	11	7 (64)		0	0	3	4
Total	Yes	59	15 (25)	0.0001	5	3	4	3
	No	49	32 (65)		14	6	5	7

Discussion

This report describes the effects of adjuvant chemotherapy in uroepithelial transitional cell carcinoma with reference to prolongation of the disease-free interval and of survival time. A preliminary report on a study of tegafur + vincristine (VCR) + mitomycin C (MMC) and bleomycin (BLM) has already been published [2].

The control of invasive bladder tumor is one of the targets of clinical investigations concerning the management of patients with this disease [11]. For this purpose, various combined-modality therapies have been introduced, such as radiotherapy combined with chemotherapy [1]. Published data give 5-year survival rates in invasive bladder tumor of 39% (T_2 or T_3 and N_0M_0) [1], 40% (stage B_2 or C) [4], 20.8% ($\geqq T_2$) [7], and less than 40%–50% [9]. These low survival rates are thought to be due to micrometastases, which are usually present at the time of first presentation [9]. The present series showed a 76.3% 5-year survival rate in the chemotherapy group. Though this rate is influenced by other various factors, such as cell differentiation, growth pattern of the tumor, presence or absence of infiltrating tendency, and method of surgery, it is still relatively satisfactory. One reason is thought to be the use of antineoplastic agents confirmed to be effective for the treatment or prophylaxis of bladder cancer [1, 3, 8]. Long-term oral 5-FU might be effective in providing protection against recurrence or metastasis. In the tumors originating from the upper urinary tract, a 74.4% 3-year survival rate has been reported after complete tumor resection in our area [6]. Our 3-year survival of 91.2% in the chemotherapy group is also good. However, there was no statistically significant difference according to the generalized Wilcoxon test compared with the non-chemotherapy group. This is thought to be due to the fact that the non-chemotherapy group has been followed up for a relatively longer time, and some patients have survived longer than the follow-up duration in chemotherapy group. Examination of more cases and longer follow-up periods will result in a clearer evaluation of this adjuvant chemotherapy.

Another aim of adjuvant chemotherapy is prolongation of the disease-free interval, which will also extend the survival time of the patients, and improvement of the patients' quality of life. A cooperative study in our area revealed that recurrence rates for all stages of bladder tumor during a 4-year follow up were 31.4% in patients who underwent TUR or segmental resection ($n=895$) and 25.3% in those who underwent cystectomy ($n=320$) [5]. Our study showed a statistical difference between chemotherapy and non-chemotherapy groups with bladder tumor, but this phenomenon was not observed in groups with upper UT tumor. However, the recurrence rate, regardless of the time it occurred, was significantly higher in the non-chemotherapy group in both lower and upper UT tumors. Moreover, a further advance in the stage and occurrence of distant metastases, which are directly related to patients' survival were observed in 6 of 59 cases (5.1%) in the chemotherapy group and 13 of 49 patients (26.5%) in the non-chemotherapy group.

In conclusion, adjuvant chemotherapy in patients with invasive bladder tumor or upper urinary tract tumor, may be useful after complete tumor resection, as it seems to extend survival time and bring about a marked protraction of the disease-free interval, especially in cases of advanced bladder tumor.

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