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Prophylactic chemotherapy for primary and recurrent superficial bladder cancer: preliminary results*

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Summary. A multicenter trial for postoperative prophylaxis of the recurrence of superficial Ta-T1, G1-G2 bladder cancer was performed. Eligible patients with primary or recurrent superficial bladder cancer were randomized into four groups. For the primary cases, intravesical instillation of drugs [group A, 20 mg Adriamycin (ADM) + 200 mg cytosine arabinoside (CA) in 30 ml physiological saline; group B, 10 mg peplomycin (PEP) + 200 mg CA in 30 ml physiological saline; group C, 2 mg neocarzinostatin (NCS) + 200 mg CA in 30 ml physiological saline; and group D, control] was carried out once a week for 2 weeks, once every 2 weeks for 14 weeks, once monthly for 8 months, and, finally, once every 3 months for 1 year. For the recurrent cases, intravesical instillation of 20 mg ADM + 200 mg CA in 30 ml physiological saline as described above and daily oral administration of another drug [group E, 300 mg/day UFT; group F, 200 mg 5-fluorouracil (5-FU)/day; group G, 30 mg ubenimex/day; and group H, no oral drug] was performed. The postoperative follow-up period was 3–36 months. A total of 193 primary cases and 121 recurrent cases of superficial bladder cancer were evaluated.

The cumulative 12-month nonrecurrence rates for the primary cases were 86.2% in group A, 78.1% in group B, 82.1% in group C, and 68.4% in group D. The cumulative nonrecurrence rate obtained using ADM+CA (group A) was significantly higher than the control value. On the other hand, no significant difference was found in the cumulative nonrecurrence rates calculated for the recurrent cases, regardless of the oral drug given. Intravesical instillation of ADM+CA for primary superficial bladder cancer was considered to be useful, but the long-term effect of intravesical instillation remains to be elucidated. Further refinement of this regimen is necessary for effective prophylaxis of the recurrence of superficial bladder cancer.

Introduction

The major problem in the treatment of superficial bladder cancer is the high incidence of recurrence after initial management [12–14], which is primarily due to the multifocal growth of the tumor. Another contributing factor might be implantation of tumor cells liberated during transurethral resection (TUR) [14, 17, 18]. Among many prophylactic treatment modalities, intravesical chemotherapy with a single agent [thiotepa, mitomycin C, doxorubicin, or bacille Calmette Guérin (BCG)] has been proven to be effective in preventing the recurrence of bladder cancer [1, 3, 5–7, 10, 13, 14, 17]. However, there are few reports concerning the use of combination chemotherapy for prophylaxis of the recurrence of bladder cancer [2, 4, 8, 9, 11].

The present study was undertaken to assess which combination of drugs is most effective in preventing the recurrence of tumors in primary cases. An attempt was also made to evaluate whether the additional oral administration of an antineoplastic drug would be effective in recurrent cases. The study was a prospective randomized trial that was conducted jointly by Hokkaido University Hospital and 21 affiliated clinics (Table 1).

Materials and methods

Patients who had been diagnosed as having superficial bladder cancer were registered in this trial. Included in the study were cases of Ta, T1 and G1, G2 superficial bladder cancer. The eligible patients with superficial bladder cancer were stratified into primary or recurrent cases and then randomized into four groups each; i.e., groups A–D for primary cases and groups E–H for recurrent cases (Fig. 1).

The intravesical instillation regimens for the four groups of primary cases were as follows: 20 mg Adriamycin (ADM) and 200 mg cytosine arabinoside (CA) for group A, 10 mg peplomycin (PEP) and 200 mg CA

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Table 2. Characteristics of patients with primary superficial bladder cancer

	Group				Statistical difference
	A	B	C	D	
Number registered	71	63	64	54	
Number evaluated	54	50	51	38	
Average age (years)	62.9	62.4	65.3	66.0	NS
Sex:					
M	41	39	41	30	NS
F	13	11	10	8	
Size of largest tumor:					
<1 cm	21	19	23	18	NS
1–3 cm	24	25	21	19	
>3 cm	9	6	7	1	
Number of tumors:					
Solitary	35	33	30	30	NS
Multiple	19	17	21	8	
Growth pattern:					
Papillary, pedunculate	42	41	35	36	NS
Nonpapillary, pedunculate	1	2	8	2	
Papillary, sessile	10	5	8	0	
Nonpapillary, sessile	1	2	0	0	
Histological grade:					
G1	24	20	23	20	NS
G2	30	28	27	18	
Gx	0	2	0	0	
Pathological stage:					
Ta	27	18	22	20	NS
T1	26	29	28	18	
Tx	1	3	1	0	

NS, Not significant

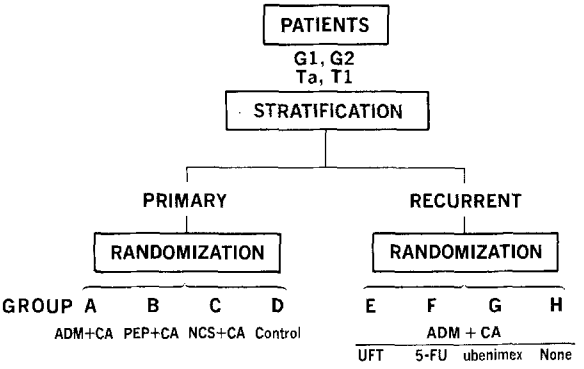

Fig. 1. Design of the study protocol

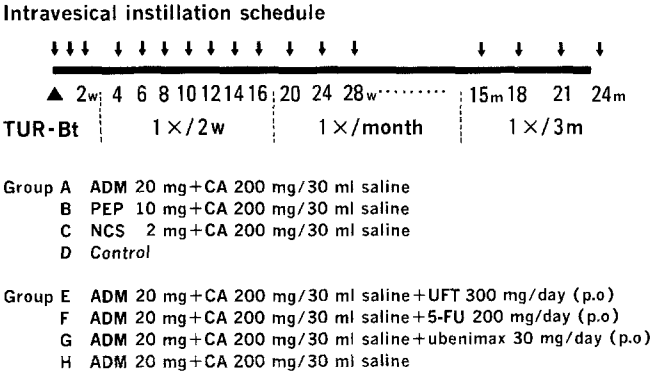

Fig. 2. Protocol for prophylactic treatments following TUR-Bt. *w*, Weeks; *m*, months

for group B, and 2 mg neocarzinostatin (NCS) and 200 mg CA for group C. The patients in group D served as nontreated controls. The drugs were dissolved in 30 ml physiological saline. All recurrent cases received intravesical instillation of 20 mg ADM and 200 mg CA in 30 ml physiological saline. Additionally, an oral antineoplastic drug was given to these patients daily as follows: 300 mg UFT for group E, 200 mg 5-fluorouracil (5-FU) for group F, and 30 mg ubenimex (an immunostimulant) for group G. The patients in group H received no oral drug.

In all of the treatment groups, intravesical instillation was started immediately after TUR of the tumors and was performed once a week for 2 weeks, once every 2 weeks for 14 weeks, once monthly for 8 months, and, finally, once every 3 months for 1 year. The oral drugs were given daily for 2 years (Fig. 2).

For evaluation, cystoscopy and urinary cytology were repeated at 3-month intervals during the study period. The results were evaluated on the basis of the nonrecurrence rates. The disease-free interval was defined as the interval between the operation and the date of the first positive pathological findings. Nonrecurrence rates were calculated by the Kaplan-Meier method. Statistical analyses were carried out using the chi-square test or the generalized Wilcoxon test.

Results

From June 1987 to May 1989, 252 patients with primary superficial bladder cancer and 144 patients with recurrent superficial bladder cancer were registered. Of these 396 subjects, 193 with primary cancer and 121 with recurrent cancer were evaluable; the remaining 82 patients were ex-

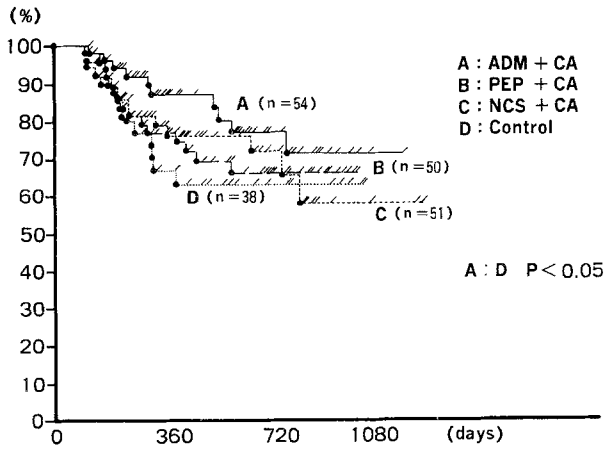

Fig. 3. Nonrecurrence rates in primary cases of superficial bladder cancer

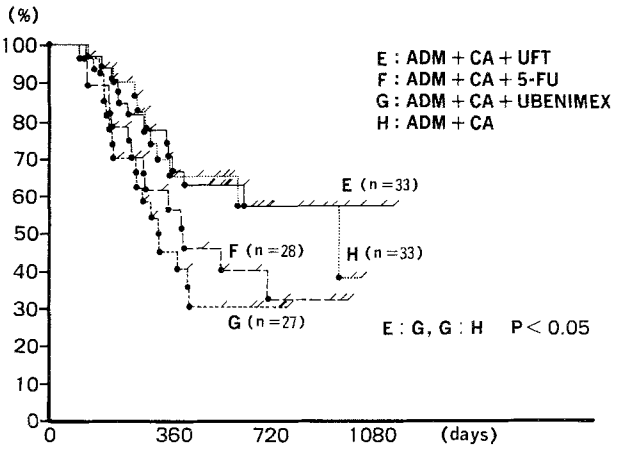

Fig. 4. Nonrecurrence rates in recurrent cases of superficial bladder cancer

Table 3. Period of follow-up in 193 evaluable patients with primary tumors

Period of follow-up (months)	Group				Totals
	A	B	C	D	
3	54	50	51	38	193
6	50	43	44	35	172
12	29	32	28	19	108
24	14	11	9	8	42
36	1	0	2	0	3

Table 4. Relationships between background factors and the prophylactic effect

Background factor	Group		
	A	B	C
Size of largest tumor:			
<1 cm	–	–	–
1–3 cm	0	–	0
>3 cm	–	–	–
Number of tumors:			
Solitary	–	–	–
Multiple	0	–	0
Histological grade:			
G1	–	–	–
G2	0	–	–
Pathological stage:			
Ta	0	–	–
T1	–	–	–

0, Statistically significant effect as compared with the control group; –, difference from control values not statistically significant

cluded on the basis of being an unqualified candidate or due to inadequate follow-up.

For the primary cases, no intergroup difference in age, sex, tumor-growth pattern, largest tumor size, number of tumors, histological grade, or pathological stage was found (Table 2). Recurrence was analyzed in the 193 evaluable patients after follow-up periods ranging from 3 to 36 months. The mean follow-up period was 467 days (Table 3). After a follow-up of 12 months, the nonrecurrence rates were 86.2% in group A, 78.1% in group B, 82.1% in group C, and 68.4% in group D, whereas the rates determined at 24 months were 73.0%, 67.5%, 67.5%, and 64.9%, respectively (Fig. 3). The nonrecurrence rate found for group A was significantly higher than that obtained in group D (P <0.05). However, the values determined for groups B and C did not differ significantly from that found for group D.

The relationships between various background factors and the prophylactic effect of the therapy are summarized in Table 4. Each group was compared with group D by the generalized Wilcoxon test. A significant prophylactic effect of the instillation of ADM+CA (group A) was observed in patients whose tumors were intermediate in size (1–3 cm), occurred as multiple lesions, and were graded histologically as G2 or staged pathologically as Ta. Furthermore, a prophylactic effect for NCS+CA (group C) was observed in patients bearing medium-sized or multiple tumors.

Analysis of the 121 evaluable recurrent cases did not reveal any significant difference in any of the clinicopathological features except the growth pattern of the tumor (Table 5). Recurrence was evaluated after a follow-up period ranging from 3 to 36 months. The mean follow-up period was 420 days in these recurrent cases (Table 6). After a follow-up of 12 months, the nonrecurrence rates were 72.7% in group E, 61.5% in group F, 45.0% in group G, and 70.6% in group H. The rates determined at 24 months were 57.0%, 32.6%, 30.5%, and 57.0%, respectively (Fig. 4). Thus, no increase in the recurrence-inhibiting effect was obtained using any of the oral drugs given. Conversely, the ubenimex group (group G) showed a nonrecurrence rate significantly lower than that of groups E or H.

Although the main side effect encountered in the treatment groups was bladder irritability, all patients except one tolerated the therapy well. The only case requiring treat-

Table 5. Characteristics of patients with recurrent bladder cancer

	Group				Statistical difference
	E	F	G	H	
Number registered	38	33	34	37	
Number evaluated	33	28	27	33	
Average age (years)	65.0	65.2	65.8	67.1	NS
Sex:					
M	25	24	19	20	NS
F	8	4	8	13	
Size of largest tumor:					
<1 cm	28	20	22	30	NS
1–3 cm	3	5	5	2	
>3 cm	0	1	0	0	
Number of tumors:					
Solitary	17	9	16	14	NS
Multiple	15	18	11	18	
Growth pattern:					
Papillary, pedunculate	30	21	15	28	$P<0.05$
Nonpapillary, pedunculate	1	0	2	0	
Papillary, sessile	1	3	7	2	(E:G, G:H)
Nonpapillary, sessile	0	3	3	2	
Histological grade:					
G1	16	13	10	20	NS
G2	15	15	15	13	
Gx	2	0	2	0	
Pathological stage:					
Ta	22	14	14	20	NS
T1	9	14	12	11	
Tx	2	0	1	2	

NS, Not significant

Table 6. Period of follow-up in 121 evaluable patients with recurrent tumors

Period of follow-up (months)	Group				Totals
	E	F	G	H	
3	33	28	27	33	121
6	31	25	22	28	106
12	22	13	10	17	62
24	6	4	3	5	18
36	2	0	0	0	2

ment discontinuation involved a patient who developed recurrent bladder cancer after 8 months of instillation of ADM and CA. No life-threatening, severe systemic side effect was observed in any of the treatment groups.

Discussion

The major problem in the treatment of superficial bladder cancer (pathological stages Ta and T1) is the high incidence of recurrence after TUR. This high recurrence rate is attributable to many factors, including the continuous exposure of the bladder epithelium to carcinogens, the multifocal growth of bladder cancer, the implantation of tumor cells liberated during TUR, and incomplete tumor resection. For these reasons, prophylactic instillation of antineoplastic agents has been attempted to prevent disease recurrence, and this approach has been proven to be effective [1, 3, 5–11, 13, 14–18]. However, the recurrence-inhibiting effect obtained using a single drug is not fully satisfactory. Therefore, we applied the principle of combination chemotherapy to intravesical chemoprophylaxis so as to broaden the spectrum of antitumor activity.

Patients with multifocal bladder cancer or a history of bladder cancer have an increased risk of developing a subsequent tumor. Zincke et al. [18] emphasized the importance of stratification before randomization, particularly for variables known to contribute to a higher rate of tumor recurrence. Therefore, we divided the patients into two groups on the basis of their history of bladder cancer and then randomized them into various treatment subgroups.

Various drugs such as thiotepa [3, 13, 17, 18], mitomycin C (MMC) [3, 7, 18], ADM [1, 5, 7, 10, 17], bleomycin [8], NCS [16], and CA [11] have been used in prophylactic instillation therapy. CA, an antimetabolite, is more effective when used in combination with other agents. Beneficial effects have been obtained using CA together with MMC for the treatment of superficial bladder cancer [9, 11]. In the present study, we randomized primary cases into three treatment groups for intravesical instillation of ADM+CA, PEP+CA, and NCS+CA, respectively. Although the intravesical route has been conventionally used, the administration of drugs designed to affect superficial bladder cancer in combination with oral agents has been suggested. Long-term oral administration of tegafur, which is derived from 5-FU, has been effective in preventing the recurrence of bladder cancer [15]. Thus, we added the oral administration of UFT, 5-FU, or ubenimex to the intravesical instillation of ADM+CA for our patients with recurrent bladder cancer.

As a single agent, ADM has been reported to be effective for prophylactic instillation following TUR [1, 5, 7, 10]. In the present study, the intravesical instillation of ADM+CA was effective in preventing the recurrence of bladder cancer in patients with primary disease. On the other hand, no recurrence-inhibiting effect was observed in patients with recurrent bladder cancer, regardless of the oral drug given. Conversely, the ubenimex group (group G) showed a high recurrence rate, which might have been caused by a difference in the patients' background factors.

The results reported herein must be considered as preliminary, since the observation period was relatively short. Further refinement of this treatment regimen is necessary for effective prophylaxis of the recurrence of superficial bladder cancer.

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