Cancer Chemother Pharmacol (1987) 20 (Suppl): S 85–S 90

Cancer Chemotherapy and Pharmacology

Prophylactic treatment for superficial bladder cancer following transurethral resection

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Summary. A total of 130 primary cases with superficial bladder cancer were entered in the prospective randomized group study. The prophylactic treatments compared consisted in intravesical instillation of adriamycin (20 mg/-40 ml or 30 mg/30 ml), mitomycin C (20 mg/40 ml) or thio-TEPA (30 mg/30 ml), and noninstillation treatments with etretinate or tegafur; control patients were also studied. All agents were administered for 2 years. Recurrences were significantly suppressed in the instillation groups compared with control and non-instillation groups. Significant suppression of recurrence was observed in stage 1 or grade 2 disease treated with prophylactic instillation administered over the first 24 months of a 48-month observation period. These results may indicate the clinical usefulness of prophylactic instillation, but the long-term effect of intravesical instillation is still uncertain. A long-term follow-up study is therefore necessary.

Introduction

Despite the relatively high incidence of recurrence, the prognosis of superficial bladder cancer is generally good. The main factors affecting frequent tumor recurrence are the multifocal origin of superficial bladder cancer and the seeding of cancer cells following transurethral electroresection (TUR-Bt) [9]. It is well known that multifocal precancerous lesions have frequently already developed by the time TUR-Bt is performed for the visible tumor, and effective prophylactic treatment has therefore been sought in many institutions [1, 3, 11, 12]. Among many prophylactic treatment modalities, intravesical instillations of anticancer agents have proved to be effective; efficacy of many agents has been reported in the last 20 years [2, 4, 6, 8].

In the present study, the prophylactic effect of intravesical instillation of adriamycin, mitomycin, or thio-TEPA was investigated and compared with that of non-instillation prophylactic treatments with etretinate or tegafur. The study was a prospective randomized study conducted jointly by Nara Medical University Hospital and six affiliated clinics.

Patients and methods

Between April 1981 and October 1985, 130 patients with histologically proven superficial (T_a and T_1) transitional cell carcinoma of any grade (1–3) were found to be eligible for the study. Patients with a history of previous treatment were excluded from this study (Table 1). All visible tumor had to be resected completely, with a 1-cm margin of mucosa all round. Multiple cold-cup biopsies were also

Table 1. Characteristics of patients

Group	No. of case	Mean age	Sex		Grade			Stage		Multi	
			M	F	1	2	3	Ta	T1	S	M
Control	27	61.3	24	3	17	9	1	13	14	17	10
FT-207	23	60.1	21	2	11	11	1	5	18	15	8
ETR	20	59.1	15	5	8	11	1	8	12	12	8
T-TEPA	18	65.8	12	6	8	9	1	4	14	11	7
ADM-20	12	66.4	5	7	4	6	2	2	10	8	4
ADM-30	16	64.4	14	2	7	6	3	6	10	7	9
MMC	14	62.4	10	4	3	10	1	7	7	7	7
Total	130	61.9	101	29	58	62	10	45	85	77	53

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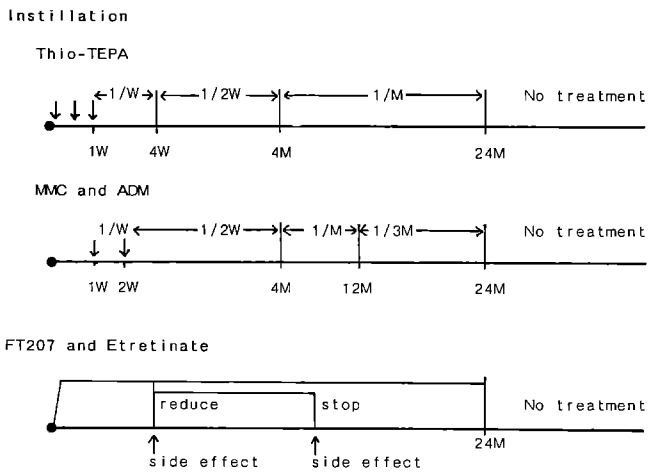

Fig. 1. Protocol of prophylactic treatment following TUR-Bt

performed at a minimum of six sites (trigone, posterior, dome, anterior and both lateral walls). All specimens were examined histopathologically (H&E stain). Patients with pathological evidence of muscle invasion after TUR-Bt were considered ineligible for the study. The patients eligible for the study were randomized to receive prophylactic treatment according to the protocol immediately after TUR-Bt (Fig. 1).

There were three major study groups (instillation, non-instillation, and control). The anticancer agents and doses used for instillation in this study were adriamycin (ADM) 20 mg/40 ml or 30 mg/30 ml, mitomycin C (MMC) 20 mg/40 ml, and thio-TEPA (t-TEPA) 30 mg/30 ml. All agents were dissolved in physiological saline solution. The instillation of ADM or MMC was carried out under the aegis of the Japanese Urological Cancer Research Group for Adriamycin [6], in a regimen of long-term prophylactic intravesical chemotherapy, and t-TEPA was instilled according to the schedule previously established for use in our department (Fig. 1). The patients were instructed to abstain from excess fluid intake before instillation and to retain the agent for about 2 h. For prophylactic treatment without instillation, etretinate (ETR), a retinoid derivative, was administered at 10 mg/day p.o. for 2 years as part of a group study conducted by Prof. Yoshida of Kyoto University. Tegafur (FT-207), a masked compound of 5-FU, was administered at 1000 mg/day p.o. or as a suppository. The control group was treated with TUR-Bt alone.

Reevaluation with cystoscopy and urinary cytology was performed every 3 months for 3 years after initiation of therapy and at 6-month intervals thereafter. The patients were considered to have a recurrence when any visible tumor was diagnosed histopathologically. If a tumor recurred without evidence of progression, the follow-up study was continued with no change in the regimen until the 3rd recurrence. On the 2nd recurrence, however, the patients could be removed from the study on the decision of the attending physician. Progression was defined as advancement to grade 3 or invasion of the muscular layer at the time of recurrence. Cases showing progression were withdrawn from the study and underwent other treatment.

Recurrence was evaluated statistically by the Kaplan-Meier method and by the Cox-Mantel test. The cumulative recurrence rate was presented as the number of recurrences per 100 patient-months. A difference was considered to be statistically significant when the *P*-value was smaller than 0.05.

Results

Recurrence was evaluated separately by regimens of prophylactic treatment, treatment modality, and factor affecting bladder tumor recurrence (grade and stage of tumor and whether multiple or solitary). Some variables of selected characteristics of patients in each group were not evenly distributed because of the relatively small groups. However, comparison of the instillation group and non-instillation group, including controls, reveals that the ranges of differences were well within the range of chance variation.

The non-recurrence rates in each instillation group were between 85.9% and 92.3% at 48 months, and did not differ significantly among the groups. The non-recurrence rates in the ETR and FT-207 groups were 68.8% and 56.0% at 48 months, resepctively, and did not significantly differ from the 57.6% of control group (Fig. 2). The non-recurrence rate in all the instillation groups was 90.4%, in the group treated with ETR or FT-207, 62.0%, and in the controls, 57.6%. There were significant differences in non-recurrence rates between the instillation group plus the

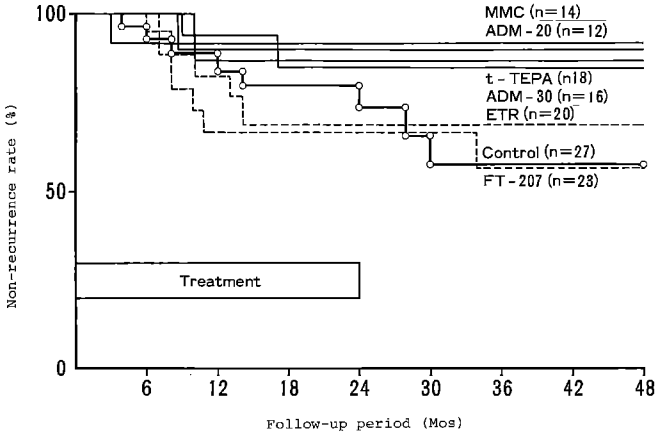

Fig. 2. Non-recurrence rate obtained with prophylactic treatment in primary cases of superficial bladder cancer

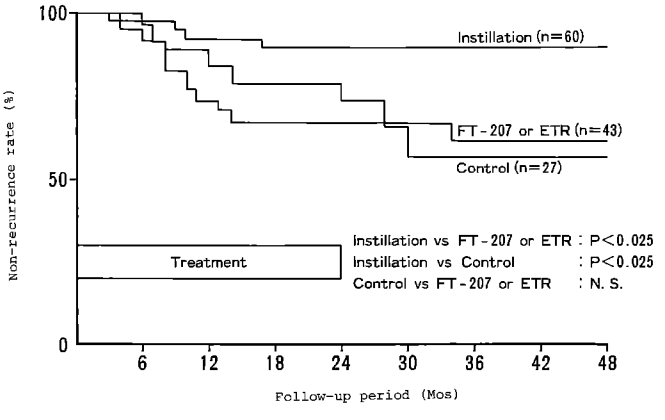

Fig. 3. Non-recurrence rate according to treatment modality in primary cases of superficial bladder cancer (instillation vs non-instillation)

group with ETR or FT-207 and the controls ($P < 0.025$). However, there was no significant difference between the group with ETR or FT-207 and controls (Fig. 3). The non-recurrence rates in the instillation group were compared with those in the ETR or FT-207 group plus the control group (non-instillation group). Concerning the pathological status, prophylactic instillation suppressed bladder cancer recurrence significantly both in grade 2 (96.7% vs 38.6% $P < 0.001$) and in stage T_1 (92.3% vs 47.7%, $P < 0.005$), but did not suppress it significantly in grade 1 (88.7% vs 71.0%) and stage T_a (84.7% vs 76.2%) compared with the non-instillation groups (Figs. 4 and 5). When the number of tumor sited was considered, prophylactic instillation was found to suppress recurrence significantly in both solitary (96.7% vs 72.1%, $P < 0.05$) and multiple tumors (82.8% vs 29.3%, $P < 0.025$) compared with the non-instillation group (Fig. 6). There was no significant difference in non-recurrence rates in the instillation group according to the range of grade, stage, and multifocal solitary tumor. The non-recurrence rates in the non-instillation group decreased with increasing risk factors [grade (G_1; 71.0% vs G_2; 38.6%) and stage (T_a; 76.2% vs T_1; 47.7%)], but there was no statistically significant difference. The non-recurrence rate in the non-instillation group was significantly lower in patients with multiple tumors (29.3%) than in those with solitary tumors (72.1%) ($P < 0.025$).

The incidence of recurrence in this study was also evaluated in terms of the cumulative recurrence rate, because frequent recurrence is commonly observed in patients with superficial bladder cancer. Evaluation of the effects of instillation on the recurrence of bladder cancer with reference to the factors affecting the recurrence revealed that the recurrence rates were lower in each instillation group than in the ETR, FT-207, and control groups for all variables (Table 2). In the groups not receiving instillation treatment, the recurrence rates increased with the risk factors, from grade 1 to grade 2, from stage T_a to T_1, and from solitary to multiple tumor (Table 3).

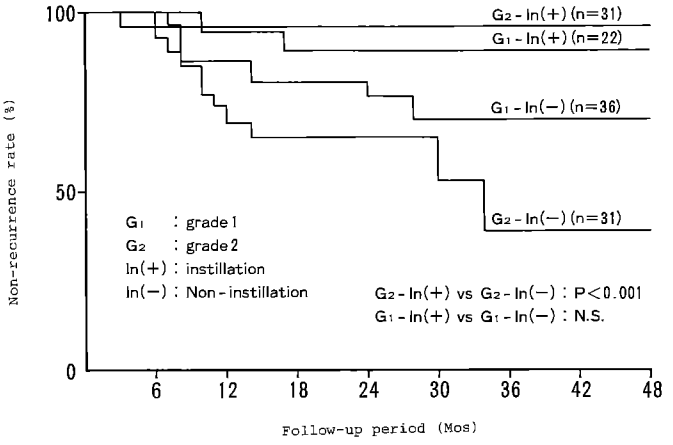

Fig. 4. Non-recurrence rate according to pathological grade in primary cases of superficial bladder cancer (instillation vs non-instillation)

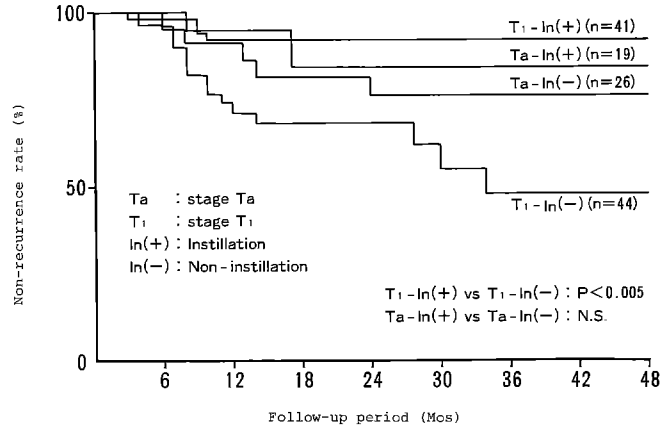

Fig. 5. Non-recurrence rate according to pathological stage in primary cases of superficial bladder cancer (instillation vs non-instillation)

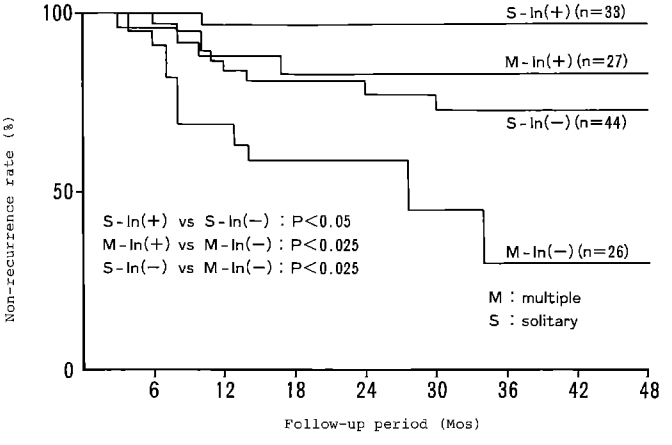

Fig. 6. Non-recurrence rate according to number of tumor foci in primary superficial bladder cancer (instillation vs non-instillation)

Table 2. Cumulative recurrence rates in prophylactic treatment groups

Group	No. of pts	Total follow-up (months)	Mean follow-up (months)	Recurrence		Rate/ 100 pt-months
				Pts.	No.	
Control	27	784	29.0	8	13	1.66
FT-207	23	612	26.6	8	11	1.80
ETR	20	512	25.6	5	8	1.56
t-TEPA	18	343	19.1	2	2	0.58
MMC	14	332	23.7	1	2	0.60
ADM-30	16	333	20.8	2	3	0.90
ADM-20	12	287	23.9	1	2	0.70

A total of 10 patients with grade 3 superficial bladder cancer were entered in this study and carefully observed (Table 4). Recurrence was observed in 4 patients (40%), 1 in the non-instillation group and 3 in the instillation group. The treatment regimen had to be changed for 2 patients, because of frequent recurrences in 1 and progression in the other. The cumulative recurrence rates, in both the instillation group and the non-instillation groups, were much higher than those of grades 1 and 2 (Table 3 and 4).

Eight patients with more advanced grade and/or stage at recurrence were observed in this study (Table 5). More advanced grade at the time of recurrence was observed in

Table 3. Cumulative recurrence rates by tumor characteristics

Characteristics	Group	No. of pts	Total follow-up (months)	Mean follow-up (months)	Recurrence		Rate/ 100 pt-months
					Pts.	No.	
Grade							
G_1	Control	17	559	32.9	4	6	1.07
	ETR-FT	11	529	48.1	5	8	1.51
	Inst.	22	561	25.5	3	3	0.55
G_2	Control	9	184	20.4	3	4	2.17
	ETR-FT	22	534	24.3	8	11	2.06
	Inst.	31	694	22.4	1	2	0.29
Stage							
T_a	Control	13	446	34.3	3	5	1.12
	ETR-FT	13	378	29.1	2	5	1.32
	Inst.	19	459	24.2	2	4	0.87
T_1	Control	14	344	24.6	5	8	2.24
	ETR-FT	30	751	25.0	11	14	1.86
	Inst.	41	966	23.6	4	5	0.52
Solitary/multiple							
Solitary	Control	17	574	32.2	4	5	0.87
	ETR-FT	27	700	25.9	6	10	1.43
	Inst.	33	775	23.5	1	1	0.13
Multiple	Control	10	216	21.6	4	8	3.70
	ETR-FT	16	429	26.8	7	9	2.10
	Inst.	27	662	24.5	5	8	1.21

Table 4. Prognosis for grade 3 superficial bladder cancer treated with prophylactic treatment

Group	No. of case	Recurrent case	No. of recurrence	Total follow-up (months)	Mean follow-up (months)	Recurrences/ 100 pt-months
All	10	4	7	251	25.1	2.79
ETR-FT	3	1	3	69	23.0	4.35
Inst.	7	3	4	182	26.0	2.19

Table 5. Cases with advanced grade and/or stage at recurrence

Age of pt (years)	Original regimen	Primary tumor (months)	Recurrent tumor			Subsequent treatment	Prognosis
			1st (months)	2nd (months)	3rd		
60	Control	G_2-T_a (6)	G_2-T_1 (4)	G_1-T_a (12)	–	Nephrectomy[a]	7M CD[a]
46	ETR	G_1-T_a (14)	G_1-T_a (21)	G_2-T_1	–	–	2M Rec (–)
67	ETR	G_1-T_1 (14)	G_2-T_1 (5)	G_1-T_1	–	ADM-20	16M Rec (+) 8M Rec (–)
73	ETR	G_2-T_a (13)	G_2-T_1 (24)	G_2-T_1	–	t-TEPA	7M Rec (–)
60	FT-207	G_1-T_a (8)	G_1-T_1 (43)	G_1-T_1 (17)	G_1-T_a	–	7M Rec (–)
73	t-TEPA	G_3-T_1 (9)	G_2-T_1<	–	–	t-TEPA + Chemo.	7M Rec (–)
70	FT-207	G_2-T_1 (11)	G_3-T_1 (6)	G_3-T_2	–	RAD + Chemo.	14M Rec (–)
64	MMC	G_2-T_1 (3)	G_2-T_x	Contracted bladder (19 months)	–	Total cystectomy (G_3–T_2)	3M Alive

(Mos), months between transurethral section and recurrence

[a] Subsequent upper urinary tract tumor developed during follow-up period postoperative

Table 6. Complications

Control		0
Etretinate	Lip dryness	3
	Angular stomatitis	2
	Anorexia	2
	Skin desquamation	1
FT-207	Anorexia	3
Thio-TEPA	Mild leukopenia	1
	Irritable bladder	2
MMC	Irritable bladder	1
	Contracted bladder	1
ADM	Irritable bladder	1

4 patients (3.1% of all patients and 14.8% of all with recurrence) and increased stage in 7 patients (5.4% of all patients and 25.9% of all with recurrence). The treatment regimen had to be changed for 5 of these patients. In the ETR group 2 patients had tumors that were still superficial at the time of recurrence, and these 2 crossed over to prophylactic instillation. Three patients were found to have progression (2.3% of all patients and 11.1% of all with recurrence). A grade 3 T_1 transitional cell carcinoma observed in 1 patient was thought to be highly indicative of muscle invasion at the first recurrence, and the patient continued to receive t-TEPA instillation in addition to UFT (1:4 mixture of FT-207 and uracil). One patient with progression to G_3/T_2 disease received radiation therapy combined with systemic chemotherapy, and another patient was found to have G_3/T_2 cancer at the time of total cystectomy necessitated irreversible contraction of the bladder following intravesical instillation of MMC.

Only 1 patient in this study had severe complications. The patient complained of irritable bladder symptoms after 15 MMC instillations following TUR-Bt for G_2 T_1 transitional cell carcinoma. During the observation period, G_2 T_x tumor recurred 3 months after the initial treatment. Further instillation was prescribed, but the effective bladder capacity decreased daily in spite of various treatments, including steroid therapy and intravesical DMSO. The final bladder capacity was 5 ml at 22 months after surgery, and total cystectomy was necessary. Other complications in this study were mild and reversible (Table 6).

Discussion

The frequently recurring nature of superficial transitional cell carcinoma of the urinary bladder after TUR-Bt requires effective prophylactic treatment to suppress the incidence of subsequent tumor [9]. Although intravesical instillation of anticancer agents is considered to have significant prophylactic effects in reducing or delaying recurrence, however, many reports have been based on relatively limited short-term experience [2, 4, 8]. The long-term effect of intravesical chemotherapy is still uncertain.

From the results of a retrospective analysis of superficial bladder cancers experienced in our clinics since 1963, the prophylactic instillation of anticancer agents for 2 years significantly suppressed the recurrence of superficial bladder cancer during the period of postoperative prophylactic treatment; however, the late recurrence rate 5–10 years after the operation was not significantly different from that of controls. When analyzed with cumulative recurrence rate in patients followed up over 5 years, the recurrence rate in the instillation group was slightly higher than that in the non-instillation group. However, since these results were based on a retrospective study using historical controls, a prospective randomized study was essential.

In this study, the initial results of a prospective randomized group study using ADM, MMC, and t-TEPA, each at two doses, for prophylactic instillations, and ETR or FT-207 for non-instillation prophylaxis are reported. The agents used for instillation in this study have been reported to be effective for prophylactic instillation following TUR-Bt [2, 9]. Both agents used for non-instillation prophylaxis, ETR, a derivative of 13-*cis*-retinoic acid, and FT-207, a masked compound of 5-FU, proved to have suppressive effects on tumor growth in a rat bladder tumor model induced with *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine [5, 7, 10]. Some clinical trials on prophylaxis using these agents have been reported [11], but comparison of these different modalities for chemoprophylaxis of recurrence of superficial bladder cancer has not previously been reported.

Concerning the prophylactic effects observed in this study, ETR and FT-207 demonstrated less suppressive effects on the recurrence of superficial bladder cancer after TUR-Bt in this study. However, it seems too early to define the suppressive effect of these agents on recurrence at present, because they may demonstrate efficacy after long-term administration. Regardless of the agents, the recurrence rates in the instillation groups were significantly lower than those in the non-instillation groups during the 48-month period after TUR-Bt. These results indicate that prophylactic instillation has suppressive effects against tumor recurrence. These excellent suppressive results observed for prophylactic instillation may be connected with the fact that none of the patients in this study had had any previous treatment and also with the frequent instillation schedule, which is more like a therapy schedule than a prophylaxis schedule. However, when evaluation was carried out separately for different variables affecting bladder tumor recurrence, there was found to be a significant difference in G_2 T_1 or multifocal tumors between the instillation and non-instillation groups. On the other hand, there was no significant difference between the instillation group and non-instillation group in stage T_a or G_1 tumors. In the non-instillation group the recurrence rates were higher in G_2 T_1 or multiple tumors. This may reflect the nature of recurrence of superficial bladder tumor. These results may indicate that a patient with solitary G_1 T_a bladder cancer has less chance of recurrence, so that these patients might not be candidates for expensive prophylactic treatment. On the other hand, multiple G_2 T_1 bladder cancer cases have a higher possibility of recurrence and need effective prophylactic treatment.

The recurrence rate is much higher for G_3 cancer than for G_1 and G_2 cancer. Prophylactic instillation may reduce the recurrence, but the recurrence rate of G_3 tumors was still high. Even if G_3 superficial bladder cancers could be managed by TUR-Bt and prophylactic treatment, the high frequency of recurrence and progression must be borne in mind as it makes close follow-up studies essential. It may be necessary to perform more aggressive surgical treat-

ment rather than preserving the bladder, even in cases of superficial lesions.

The results reported in this paper, which are still preliminary as the observation period is still relatively short, indicate that prophylactic instillation is useful to suppress the recurrence of superficial bladder cancer after TUR-Bt; however, a long-term follow-up study is necessary to evaluate its overall clinical usefulness.

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