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A prospective randomized study of prophylaxis of tumor recurrence following transurethral resection of superficial bladder cancer – intravesical thio-TEPA versus oral UFT*

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Summary. The long-term prophylactic effect of chemotherapy following transurethral electroresection of bladder tumors (TUR-Bt) was investigated using three different modalities: no prophylactic treatment (group C); oral UFT given at 1296 mg/day for 2 years (group U); and intravesical thio-TEPA at 30 mg/30 ml physiological saline, instilled 32 times over 2 years (group T). Patients newly diagnosed as having superficial bladder cancer (stage, ≦pTlb; grade, ≦G2) who had undergone TUR-Bt at Nara Medical University and its affiliated hospitals between November 1986 and March 1990 were allocated to one of the three groups by the envelope method. The initial treatment was maintained until the third recurrence or disease progression, except for TUR-Bt which was performed at the time of recurrence. The registered cases included 51 patients in group C, 50 in group U, and 52 in group T, and the number of evaluable cases in each group were 48, 47, and 45, respectively. The non-recurrence rates at 3 years were 54% in group C, 67% in group U, and 85% in group T, and the difference between groups T and C was significant. In terms of the tumor grade and stage, No significant difference was observed among the groups in the category of G1 or Ta tumors, but the non-recurrence rates determined in group T for G2 or T1 tumors were significantly higher than those obtained in group C. Moreover, no significant difference was found among the groups in relation to solitary tumors, but the non-recurrence rate obtained in group T for multiple tumors was significantly higher than that determined in group C. The overall cumulative recurrence rate in each group was 3.07 in group C, 1.95 in group U, and 0.70 in group T, and that determined according to tumor grade, stage, and multiplicity was also highest in group C, followed by group U and group T. The main adverse effects encountered were upper gastrointestinal (GI) symptoms (8.5%) in group U and irritable bladder (11.1%) in group T. Intravesical instillation of thio-TEPA tended to produce greater preventive efficacy than did oral UFT during the early postoperative period, but the prophylactic efficacy of thio-TEPA and UFT should be elucidated over a longer observation period.

Introduction

Although the prognosis of superficial bladder cancer is favorable, prophylaxis of its frequent recurrence and early detection of disease progression are current problems. Various anticancer agents used for intravesical instillation either therapeutically or prophylactically have yielded favorable clinical results in large collaborative studies, and the efficacy of intravesical instillation of chemotherapeutic agents has been established [1, 3, 6, 9, 13, 14].

UFT is a 4:1 mixture of uracil and tegafur [a 5-fluorouracil (5-FU) prodrug], and its use produces a higher concentration of 5-FU in cancer tissues than in normal tissues. Oral administration of UFT has resulted in significant suppression of the development of rat bladder tumors induced by *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine (BBN) [2]. Therefore, UFT seems to be potentially useful for the chemoprophylaxis of superficial bladder cancer.

In the present study, the long-term prophylactic effect of chemotherapy following transurethral resection of bladder tumors (TUR-Bt) was investigated using the following three modalities: no prophylactic therapy, oral treatment with UFT, and periodic intravesical instillation of thio-TEPA for 2 years.

Patients and methods

Patients newly diagnosed as having superficial bladder cancer (stage, ≦pTlb; grade, ≦G2) who had undergone TUR-Bt at Nara Medical

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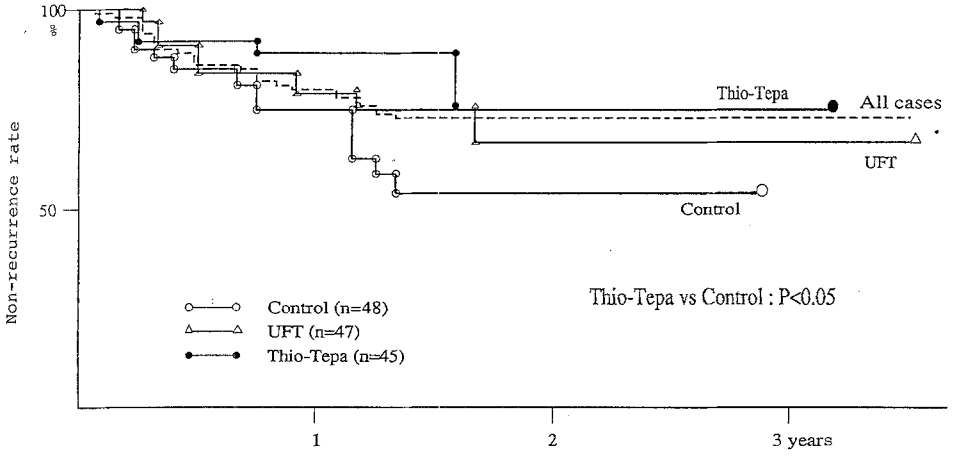

Fig. 1. Non-recurrence rates for each prophylactic treatment

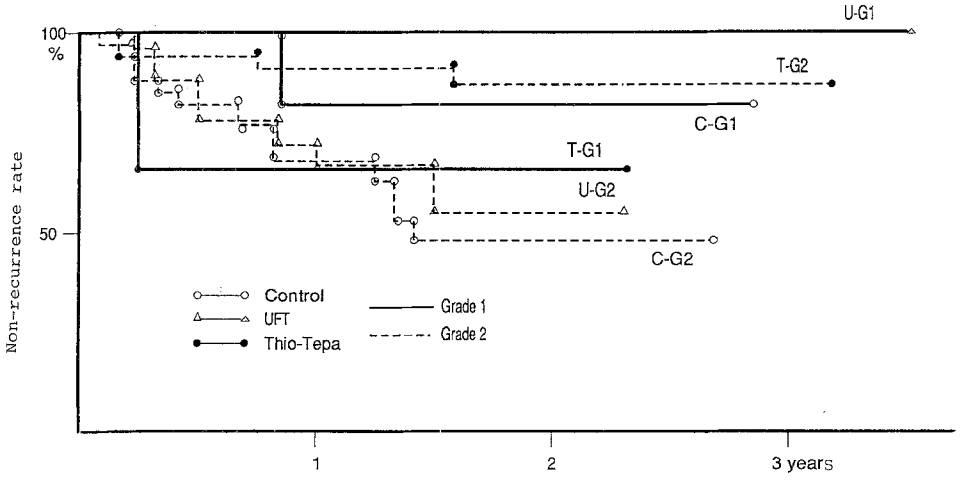

Fig. 2. Non-recurrence rates for each prophylactic treatment and histological grade

University and its affiliated hospitals between November 1, 1986, and March 30, 1990, were allocated to one of three groups by the envelope method. The treatment arms included TUR-Bt alone (group C), TUR-Bt followed by oral administration of UFT at 4 Cap. (1296 mg)/day for 2 years (group U), and TUR-Bt followed by intravesical instillation of thio-TEPA at 30 mg/30 ml physiological saline for a total of 32 periodic instillations over a 2-year period (group T). Cases in which muscle invasion or a grade 3 cancer was detected by postoperative pathological examination were excluded from the study. The initial treatment was maintained until the third recurrence or disease progression, except for TUR-Bt which was performed at the time of recurrence. Cystoscopic examination and urinary cytology were carried out every 3 months for 3 years and at 6-month intervals thereafter until at least 5 years had elapsed. The prophylactic efficacy of the treatment was evaluated by the Kaplan-Meier method on the basis of the non-recurrence rates and the cumulative recurrence rates obtained during the observation period. The total number of cases entered in this study as of the end of May 1990 was 153, including 51 patients in group C, 50 in group U, and 52 in group T. The number of evaluable cases in each group were 48, 47, and 45, respectively. No significant difference was found among the groups in terms of any of the background factors except the lower mean age of the patients in group T (Table 1).

Table 1. Characteristics of the patients

Characteristic	Treatment groups		
	Control	UFT	thio-TEPA
Entered patients	51	50	52
Evaluable patients	48	47	45
Mean age (years)	64.2 ± 12.2	65.4 ± 13.8	59.1 ± 12.9
Sex (M/F)	39/9	39/8	38/7
T category (Ta/T1)	20/28	17/30	14/31
Histological grade (G1/G2)	11/37	11/36	4/41
Multiplicity (solitary/multiple)	15/33	15/32	16/29
Mean observation period (months)	14.9 ± 10.7 (range, 1–42)	14.1 ± 12.0 (range, 1–39)	19.6 ± 10.8 (range, 1–38)

Results

The non-recurrence rates determined in each group at 3 years were 54% in group C, 67% in group U, and 85% in group T (Fig. 1). Intravesical instillation of thio-TEPA significantly suppressed the recurrence as compared with TUR-Bt alone. The non-recurrence rates found for each group were analyzed on the basis of tumor grade, stage, and multiplicity.

In terms of tumor grade, the recurrence of disease in each group was low in cases of G1 cancer, and no significant difference was observed in the presence versus the absence of prophylaxis. However, in cases of G2 cancer, the non-recurrence rate obtained in group T was signifi-

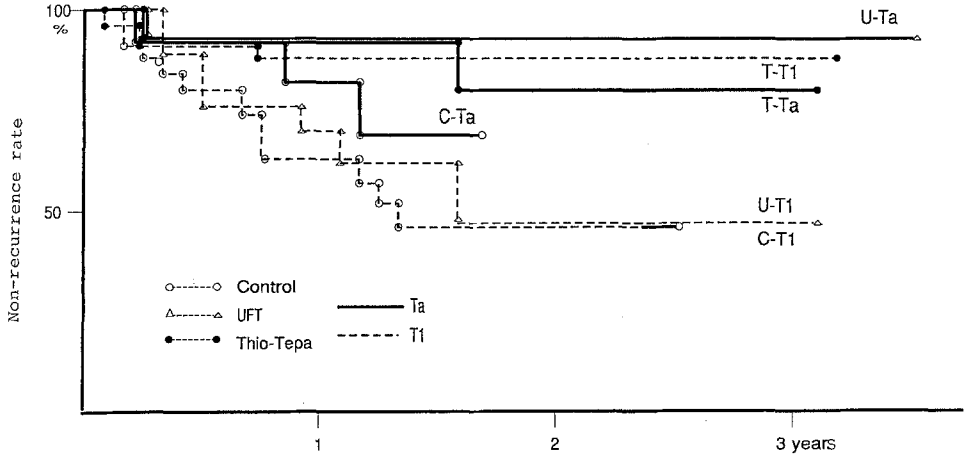

Fig. 3. Non-recurrence rates for each prophylactic treatment and pathological stage

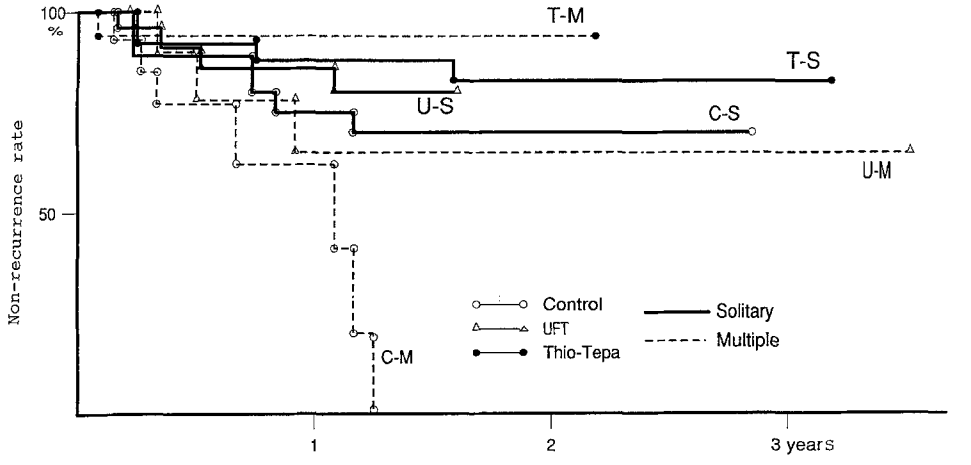

Fig. 4. Non-recurrence rates for each prophylactic treatment and tumor multiplicity

Table 2. CRR values obtained following prophylactic treatment of patients with superficial bladder cancer

Characteristic	Treatment group		
	Control	UFT	thio-TEPA
All cases	3.07 (48)	1.95 (47)	0.70 (45)
T category:			
Ta	2.03 (20)	1.04 (17)	0.97 (14)
T1	3.80 (28)	2.66 (30)	0.55 (31)
Histological grade:			
G1	1.92 (11)	0.0 (11)	1.33 (4)
G2	3.99 (37)	2.70 (36)	0.64 (41)
Multiplicity:			
Solitary	2.44 (33)	2.04 (32)	0.77 (29)
Multiple	4.86 (15)	1.79 (15)	0.48 (16)

Values in parentheses represent the number of cases involved

cantly higher than that determined in group C (Fig. 2). In terms of tumor stage, no significant difference in the non-recurrence rates was observed among the groups in cases of Ta tumors. However, in cases of T1 tumors, the non-recurrence rate obtained in group T was significantly higher than that determined in group C (Fig. 3). In terms of tumor multiplicity, no significant difference in the non-recurrence rates was found among the groups in patients presenting with solitary tumors. However, in cases of multiple tumors, the non-recurrence rate determined in group T was significantly higher than that obtained in group C (Fig. 4).

Because superficial bladder cancer is characterized by frequent recurrence, the prophylactic effect was then evaluated by the cumulative recurrence rate (CRR), calculated as $100\times$ the total number of recurrences/the total follow-up period in months. The CRR calculated for all cases in each group was 3.07 in group C, 1.95 in group U, and 0.70 in group T, and the CRR score determined according to tumor grade, stage, and multiplicity was also highest in group C, followed by group U and group T (Table 2).

As judged from the non-recurrence rates and CRRs obtained in the present study, bladder-cancer patients bearing solitary tumors categorized as Ta and G1 show a low recurrence rate, and no significant difference was observed among the groups in the presence versus the absence of prophylaxis.

The adverse effects encountered in this study included GI symptoms (8.5%) in group U and irritable bladder (11.1%) in group T. Leukopenia (WBC, $<2000/mm^3$) was observed in only patient in group T (2.2%). Most of the patients could continue the prophylactic treatment for 2 years (Table 3). As a severe adverse effect, contracted bladder developed in one patient who had undergone extensive TUR for multiple lesions and subsequent thio-

Table 3. Adverse effects and disease progression observed in this study

Adverse effects:	
UFT:	
GI symptoms	4 cases (8.5%)
Dermatitis	1 case (2.1%)
thio-TEPA:	
Irritable bladder	4 cases (8.9%)
Contracted bladder	1 case (2.2%)
Leukopenia	1 case (2.2%)
Determatitis	1 case (2.2%)
Disease progression:	
Controls	1 case (T1b · G2→CIS · G3) →BCG
UFT	1 case (T1b · G2→T4 · G3) →Cystectomy
thio-TEPA	1 case (Ta · G2→CIS · G3) →BCG

TEPA instillation. She underwent cystectomy and urinary diversion, showing no evidence of tumor recurrence.

Progression was observed in three patients in each group. One group U case required cystectomy, and the other two patients with CIS underwent intravesical bacille Calmette-Guérin (BCG) treatment (Table 3).

Discussion

Superficial bladder cancer has a good prognosis, but it also recurs frequently. Since the first report of intravesical chemotherapy using thio-TEPA by Jones and Swinney in 1961 [5], many anticancer agents have been used for intravesical instillation. The clinical usefulness of thio-TEPA, mitomycin C (MMC), and Adriamycin (ADM) has been demonstrated in multicenter, prospective, randomized studies [1, 7, 9, 10, 11, 14].

From the viewpoint of the objective of prophylaxis, the long-term effectiveness of prophylactic treatment should be considered as well as the resultant adverse effects and the economic burden. Most studies reporting favorable results have been based on relatively short observation periods. The results of our retrospective analysis of superficial bladder cancer patients that have been treated at Nara Medical University since 1963 reveal that prophylactic instillation of anticancer agents for 2 years following TUR-Bt significantly suppressed recurrence during the treatment, but the late recurrence rate calculated for these patients at 5–10 years after the first TUR-Bt did not significantly differ from that found for those who did not receive prophylactic treatment. The CRR value determined for patients who received prophylaxis was slightly higher than that found for the control groups. Moreover, the carcinogenic effects of these agents should be considered. Experimental studies using Wistar rats have revealed that intravesical anticancer agents such as ADM, MMC, and cisplatin induce epithelial proliferation and bladder tumors [8]. A higher incidence of disease progression has also been observed in patients who have undergone intravesical instillation of anticancer agents [9].

Various prophylactic treatments other than intravesical chemotherapy have been attempted using a β-glucuronidase inhibitor [4], a retinoid derivative [3, 12], and oral administration of 5-FU [13] and its prodrugs [3]. We have examined various prodrugs of 5-FU, e.g., tegafur, UFT, and HCFU, for their suppressive effects on the development of bladder cancer induced by BBN in rats. Oral administration of UFT or HCFU at 100 mg/kg daily resulted in significant prevention of tumor development [2]. To elucidate the clinical usefulness of these drugs, we chose oral UFT as the prophylactic agent for the present study. Although the non-recurrence rates and CRRs determined in group U did not significantly differ from those obtained in groups T and C, the CRR values found for group U lay just between those calculated for groups C and T. Because one purpose of this study was to elucidate the long-term prophylactic effect, a longer observation period is necessary to clarify the usefulness of UFT in prophylaxis of the recurrence of bladder cancer.

At present, the indication for prophylaxis of superficial bladder cancer has not been well established. In group C, the recurrence rates calculated for grade 1, stage Ta, and solitary tumor groups (low-risk groups) were significantly lower than those found for grade 2, stage T1, and multiple-tumor groups (high-risk groups). Significant suppression of recurrence was not observed in the low-risk groups despite the prophylactic treatment used. However, prophylactic effects were quite evident in the high-risk groups. Considering the lower malignant potential and the lower recurrence rates of grade 1 bladder cancer, low-risk groups could be excluded from randomized studies together with patients bearing grade 3 superficial bladder cancers, which need more intensive treatment. The indication for prophylaxis should be based on information regarding the biological malignant potential and the results of chemosensitivity tests on the individual bladder cancer, but various problems remain to be solved.

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