Cancer Chemother Pharmacol (1992) 30 (Suppl): S 31–S 36

Cancer Chemotherapy and Pharmacology

Adjuvant chemotherapy with early intravesical instillation of Adriamycin and long-term oral administration of 5-fluorouracil in superficial bladder cancer*

Toyofumi Ueda[1], Seiji Naito[1], Atsushi Iguchi[2], Kazuyuki Sagiyama[3], Yukio Osada[4], Asami Ariyoshi[5], Tetsuo Omoto[6], Joichi Kumazawa[1], and the Kyushu University Urological Oncology Group

[1] Department of Urology, Faculty of Medicine, Kyushu University, Fukuoka, Japan
[2] Division of Urology, Department of Surgery, Saga Medical School, Saga, Japan
[3] Department of Urology, Sanshinkai Hara General Hospital, Fukuoka, Japan
[4] Department of Urology, Miyazaki Medical College, Miyazaki, Japan
[5] Department of Urology, Fukuoka University School of Medicine, Fukuoka, Japan
[6] Department of Urology, Kyushu Kosei-Nenkin Hospital, Kitakyushu, Japan

Summary. A randomized controlled trial was performed to study the efficiency of adjuvant chemotherapy with early intravesical instillation of Adriamycin and long-term oral administration of 5-fluorouracil in 275 patients with superficial bladder cancer. All of the patients were randomized into four groups. Group A received early (immediately and 2 days after transurethral resection) instillation of Adriamycin alone; Group B received early instillation of Adriamycin with oral administration of 5-fluorouracil; Group C received delayed (7 days after transurethral resection) instillation of Adriamycin alone; and group D received delayed instillation of Adriamycin with oral administration of 5-fluorouracil. All patients subsequently received instillations weekly for 2 weeks and then every 2 weeks for a further 14 weeks. After 4 months, they received monthly instillations for 8 months. 5-Fluorouracil (groups B and D) was given daily p.o. for 1 year. Evaluation was possible in 187 patients. The postoperative follow-up period for determination of non-recurrence rates was 36 months, during which no significant difference was detected among the four groups. Moreover, no statistically significant difference was found between the early- and delayed-instillation groups. However, the non-recurrence rates obtained in the groups undergoing early instillation were higher than those determined in the delayed-instillation groups during the 36-month follow-up period, and this difference was especially significant at 4 and 5 months. In addition, the early-instillation groups showed significantly higher non-recurrence rates than did the delayed-instillation groups in terms of primary cases ($P < 0.01$), tumor size of <1 cm ($P < 0.05$), multiple tumors ($P < 0.01$), pathological stage pTa ($P < 0.01$), and histological grades G1 and G2 ($P < 0.05$). Groups B and D, which were treated by intravesical instillation of Adriamycin with oral administration of 5-fluorouracil, showed no significant prophylaxis of recurrence during the 36-month follow-up as compared with groups A and C, which received intravesical instillations alone. The main side effect, which required discontinuation of the treatment, was bladder irritation. However, no significant difference in its incidence was found between the early- and delayed-instillation groups. No severe systemic side effect was encountered in this study. These results suggest that early as well as repeated intravesical instillation of Adriamycin is clinically tolerable and may be effective in preventing the recurrence of superficial bladder cancer.

Introduction

The recurrence of tumors after transurethral resection (TUR) is one of the important problems encountered in the treatment of superficial bladder cancer. The high incidence of recurrence is primarily due to the multifocal nature of bladder tumors, but liberation and implantation of tumor cells during surgical manipulation may be a contributing factor [7, 9, 10]. Those who favor the implantation theory advocate the early instillation into the bladder of drugs to which transitional-cell carcinoma is sensitive so as to destroy any liberated neoplastic cells remaining. On the other hand, long-term oral administration of anticancer drugs with the intention of achieving a relatively high concentration in the urine may also have a cytotoxic effect on areas of unstable urothelium and may prevent new tumor formation at a later time.

Thus, we designed a prospective randomized study to address these concepts concerning chemoprophylaxis of superficial bladder cancer. Preliminary findings have been reported elsewhere [11], and this report presents the final results of this study.

* Presented at the 4th International Conference on Treatment of Urinary Tract Tumors with Adriamycin/Farmorubicin, 16–17 November 1990, Osaka Japan

Correspondence to: T. Ueda, Department of Urology, Faculty of Medicine, Kyushu University, 3-1-1-, Maidashi, Higashi-ku, Fukuoka, 812, Japan

Table 1. Classification of patients

Group	Number of patients entered	Number of patients eligible	Number of patients evaluable
A	68	50	40
B	67	55	44
C	70	58	53
D	70	61	50
Totals	275	224	187

Patients and methods

From November 1984 through December 1986, a total of 275 patients with superficial bladder cancer of pathological stages Ta and T1 were entered in this study at 21 collaborating hospitals. Before undergoing TUR, the patients were randomized into the following four groups, and the drug treatments were started after TUR.

Group A. The first and second intravesical instillations of Adriamycin (ADM) were performed immediately and 2 days after TUR. Instillations were subsequently given weekly for 2 weeks and then every 2 weeks for a further 14 weeks. After 4 months, one instillation per month was given for 8 months. Thus, a total of 19 instillations were given over a period of 1 year.

Group B. Intravesical instillation of ADM was performed in the same manner as for group A, and 5-fluorouracil (5-FU) was also given p. o. at 200 mg/day for 1 year beginning at 1 week after TUR.

Group C. Intravesical instillation of ADM was first carried out at 7 days after TUR. Thereafter, the same instillation schedule used for group A was followed. A total of 17 instillations were given in 1 year.

Group D. Intravesical instillation of ADM was performed in the same manner as for group C, and the same 5-FU dose used for group B was also given p. o. for 1 year.

ADM (30 mg) dissolved in 30 ml physiological saline was instilled into the bladder through a sterile catheter. The patients were instructed to refrain from urinating for 2 h after each instillation.

The criteria for exclusion from this study were a high-stage tumor (stage, >pT2), a histology other than transitional-cell carcinoma, or a high probability of there being residual tumor tissue due to incomplete resection along with recurrence within the 1st postoperative month. The pathological findings were classified according to the International Union Against Cancer (UICC) system [12].

Control cystoscopy, blood chemistry (SGOT and SGPT), and WBC counts were performed at 4 weeks after TUR and every 3 months thereafter. Patients were checked for local and systemic side effects during and after each instillation. The follow-up period ranged from 1 to 60 months (mean, 31 months). Non-recurrence rates during the 36-month follow-up period were calculated by the Kaplan-Meier method. Statistical analyses were performed using the chi-square test, the Z-test, the U-test, and the generalized Wilcoxon test.

Results

Of the 275 patients entered in this study, 51 (18.5%) were ineligible because of protocol violations and 37 (13.5%) were unevaluable due to inadequate follow-up (Table 1). Thus, 187 patients were evaluable, and no significant difference was found among the 4 groups in terms of age, tumor history, or the growth pattern, size, number, stage, or grade of tumors (Table 2). Moreover, no significant difference was detected between the early- and delayed-instillation groups or between groups receiving instillations in the presence versus the absence of 5-FU administration in terms of the same background characteristics (Tables 3, 4).

Table 2. Clinical and pathological characteristics of 187 evaluable patients

Background factor		Group				χ^2 test
		A	B	C	D	
Mean age (years)		63.8	65.5	63.2	60.1	NS[a]
Sex						
	M	29	36	44	39	NS
	F	11	8	9	11	
History:						
	Primary	28	34	40	35	NS
	Recurrent	12	10	13	15	
Tumor-growth pattern:						
	Papillary, pedunculated	30	31	44	34	NS
	Non-papillary, pedunculated	1	2	2	0	
	Papillary, sessile	11	11	13	16	
	Non-papillary, sessile	3	4	3	6	
Tumor size (cm):						
	<1	16	17	21	27	NS
	1–3	21	23	29	16	
	3–5	3	3	3	6	
	>5	0	1	0	1	
Number of tumors:						
	Solitary	21	21	30	24	NS
	2–4	17	20	20	22	
	⩾5	2	3	3	4	
Pathological stage:						
	pTa	22	22	25	34	NS
	pT1	16	15	21	14	
	pTx[b]	2	7	7	2	
Histological grade:						
	G1	14	15	12	21	NS
	G2	22	23	33	20	
	G3	4	6	8	9	

[a] Student's *t*-test
[b] Definitive classification as pTa or pT1 was impossible
NS, Not significant

After 36 months, the overall non-recurrence rates were 79.4% in group A, 73.7% in group B, 67.6% in group C, and 63.1% in group D (Fig. 1). No significant difference was observed among the four groups during the 36-month follow-up period, although significant differences were detected between groups B and C at 3–6 months ($P < 0.05$). No significant difference was detected between the early- and delayed-instillation groups during the 36-month follow-up period, but the non-recurrence rates obtained in the early-instillation group were higher than those determined in the delayed-instillation group, and these differences were significant at 4 and 5 months ($P < 0.05$; Fig. 2). A comparison of the non-recurrence rates between the early- and delayed-instillation groups revealed significant differences in terms of primary cases ($P < 0.01$), tumor size of <1 cm ($P < 0.05$), multiple tumors ($P < 0.01$), pathological stage pTa ($P < 0.01$), and histological grades 1 and 2 ($P < 0.05$) during the 36-month follow-up period (Figs. 3–8). No significant difference was found between

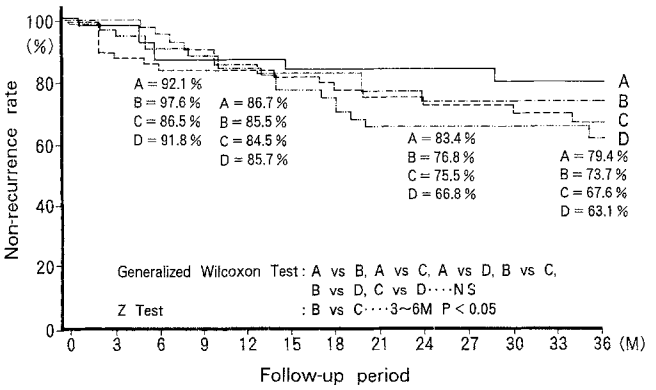

Fig. 1. Comparison of overall non-recurrence rates among the four groups. *NS*, Not significant; *M*, months

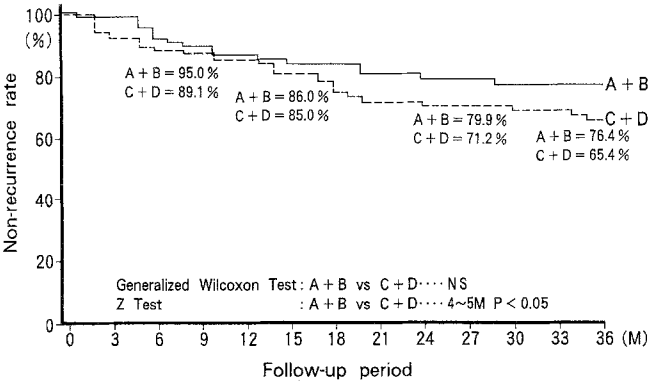

Fig. 2. Comparison of non-recurrence rates between groups receiving early (*A+B*) and delayed (*C+D*) intravesical instillation of ADM. *NS*, Not significant; *M*, months

Table 3. Comparison of clinical and pathological characteristics between groups receiving early and delayed instillations of ADM

Background factor		Group		χ^2 test
		Early	Delayed	
Mean age (years)		64.7	61.9	NS[a]
Sex:				
	M	65	83	NS
	F	19	20	
History:				
	Primary	62	75	NS
	Recurrent	22	28	
Tumor-growth pattern:				
	Papillary, pedunculated	61	78	
	Non-papillary, pedunculated	3	2	NS
	Papillary, sessile	22	29	
	Non-papillary, sessile	7	9	
Tumor size (cm):				
	<1	33	48	
	1–3	44	45	NS
	3–5	6	9	
	>5	1	1	
Number of tumors:				
	Solitary	42	54	
	2–4	37	42	NS
	⩾5	5	7	
Pathological stage				
	pTa	44	59	
	pT1	31	35	NS
	pTx[b]	9	9	
Histological grade:				
	G1	29	33	
	G2	45	53	NS
	G3	10	17	

[a] Student's *t*-test
[b] Definitive classification as pTa or pT1 was impossible
NS, Not significant

Table 4. Comparison of clinical and pathological characteristics between groups receiving ADM instillations in the presence or absence of 5-FU

Background factor		Group		χ^2 test
		5-FU (–)	5-FU (+)	
Mean age (years)		63.5	62.8	NS[a]
Sex:				
	M	73	75	NS
	F	20	19	
History:				
	Primary	68	69	NS
	Recurrent	25	25	
Tumor-growth pattern:				
	Papillary, pedunculated	74	65	
	Non-papillary, pedunculated	3	2	NS
	Papillary, sessile	24	27	
	Non-papillary, sessile	6	10	
Tumor size (cm):				
	<1	37	44	
	1–3	50	39	NS
	3–5	6	9	
	>5	0	2	
Number of tumors:				
	Solitary	51	45	
	2–4	37	42	NS
	⩾5	5	7	
Pathological stage:				
	pTa	47	56	
	pT1	37	29	NS
	pTx[b]	9	9	
Histological grade:				
	G1	26	36	
	G2	55	43	NS
	G3	12	15	

[a] Student's *t*-test
[b] Definitive classification as pTa or pT1 was impossible
NS, Not significant

groups receiving instillations in the presence versus the absence of 5-FU administration during the 36-month follow-up period (Fig. 9). Moreover, no significant difference was observed between these two groups in terms of any of the parameters evaluated.

The main side effects encountered in 224 eligible patients are shown in Table 5. As a local side effect, bladder irritation was recorded in 54 (51.4%) of 105 patients in the early-instillation groups and in 31 (26.1%) of 119 subjects in the delayed-instillation groups, and the difference

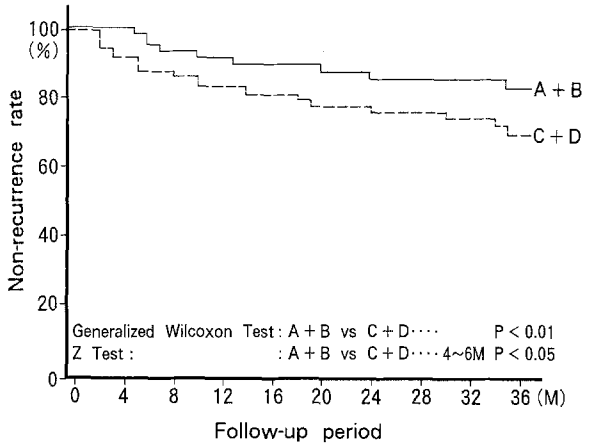

Fig. 3. Comparison of non-recurrence rates between groups receiving early (*A+B*) and delayed (*C+D*) intravesical instillation of ADM for primary tumor cases. *M*, Months

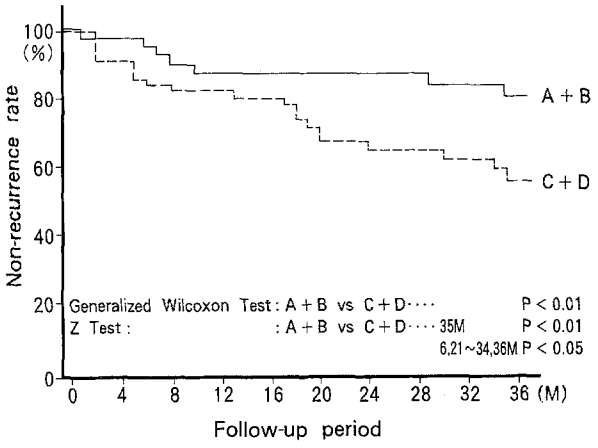

Fig. 6. Comparison of non-recurrence rates between groups receiving early (*A+B*) and delayed (*C+D*) intravesical instillation of ADM for cases involving pTa tumors. *M*, Months

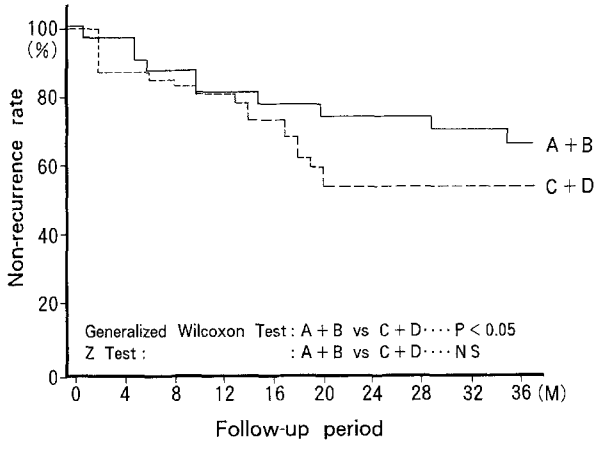

Fig. 4. Comparison of non-recurrence rates between groups receiving early (*A+B*) and delayed (*C+D*) intravesical instillation of ADM for cases involving a tumor measuring <1 cm in diameter. *NS*, Not significant; *M*, months

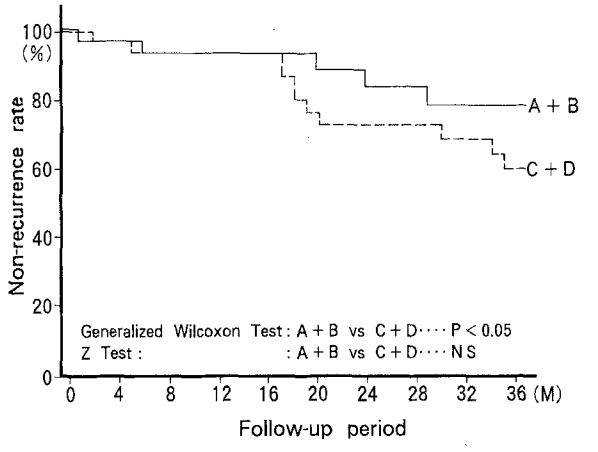

Fig. 7. Comparison of non-recurrence rates between groups receiving early (*A+B*) and delayed (*C+D*) intravesical instillation of ADM for cases involving G1 tumors. *NS*, Not significant; *M*, months

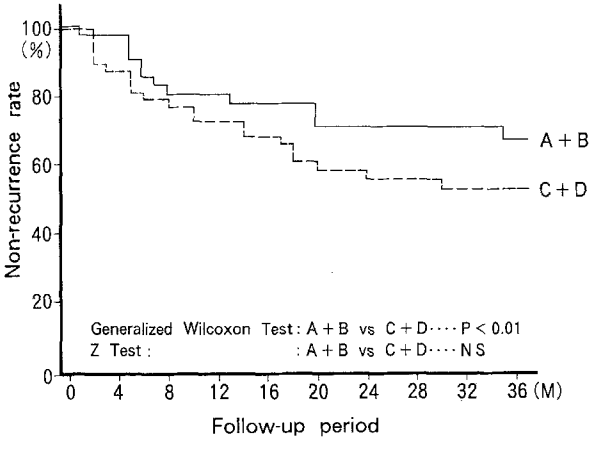

Fig. 5. Comparison of non-recurrence rates between groups receiving early (*A+B*) and delayed (*C+D*) intravesical instillation of ADM for cases involving multiple tumors. *NS*, Not significant; *M*, months

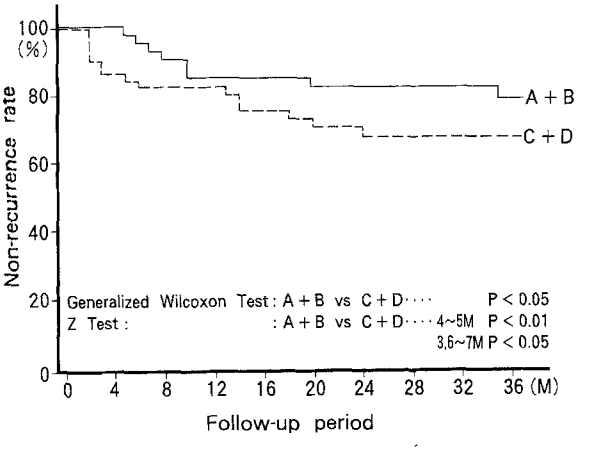

Fig. 8. Comparison of non-recurrence rates between groups receiving early (*A+B*) and delayed (*C+D*) intravesical instillation of ADM for cases involving G2 tumors. *M*, Months

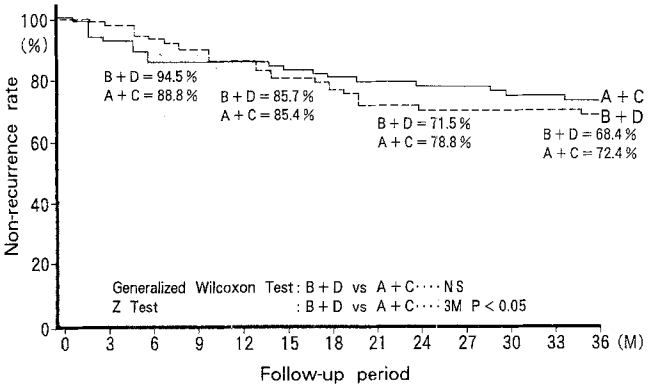

Fig. 9. Comparison of non-recurrence rates between groups receiving ADM instillations in the presence (*B+D*) and absence (*A+C*) of oral administration of 5-FU. *NS*, Not significant; *M*, months

Table 5. Incidence of side effects in 224 eligible patients

Side effect	Early instillation group		Delayed instillation group	
	A (50)	B (55)	C (58)	D (61)
Bladder irritation	24 (48%)	30 (55%)	15 (26%)	16 (26%)
Gastrointestinal symptoms	0	11 (20%)	0	8 (13%)
Allergic reaction	1 (2%)	8 (15%)	0	2 (3%)
Leukopenia	0	0	0	0
Increased SGOT, SGPT	0	1 (2%)	0	1 (2%)

Table 6. Treatment withdrawals due to side effects

Side effect	Early instillation group		Delayed instillation group	
	A (50)	B (55)	C (58)	D (61)
Bladder irritation	4 (8%)	3 (5%)	1 (2%)	2 (3%)
Gastrointestinal symptoms	0	3 (5%)	0	2 (3%)
Allergic reaction	0	1 (2%)	0	0
Hematuria and bladder calculi	0	0	0	1 (2%)
Totals	4 (8%)	7 (12%)	1 (2%)	5 (8%)

was significant ($P < 0.01$). An allergic reaction was observed in only 1 patient receiving ADM instillation alone. Gastrointestinal symptoms and allergic reactions occurred in 19 (16.4%) and 10 (8.6%), respectively, of the 116 patients undergoing ADM instillations in combination with the oral administration of 5-FU. Increased levels of SGOT and SGPT were detected in only 2 patients receiving 5-FU p.o. Of the 224 eligible patients, 10 (4.5%) withdrew from the treatment because of bladder irritation; 6 (2.7%), due to gastrointestinal symptoms and allergic reactions; and 1 (0.4%), because of hematuria together with bladder calculi (Table 6). The most frequent reason for dropping out was thus bladder irritation, involving 7 (6.7%) patients in the early-instillation groups and 3 (2.5%) in the delayed-instillation groups. No significant difference was found between the two groups. We encountered no severe systemic side effects.

Discussion

It is commonly recognized that postoperative intravesical chemotherapy is effective in preventing recurrence of superficial bladder cancer [5, 6]. However, numerous questions remain concerning the best time for the first instillation, the duration of repeated instillations, and the choice of anticancer drugs and their concentrations. It is also unclear whether combined oral administration of an anticancer drug further improves the non-recurrence rate. Our present study was thus initiated to determine whether the early instillation of ADM after TUR would yield better results than delayed instillation and whether the simultaneous oral administration of 5-FU would provide better results than the instillation of ADM alone.

ADM has recently been used intravesically for the chemoprophylaxis of recurrence of bladder cancers, with no severe systemic toxic effects being encountered [5]. Early intravesical instillation of ADM after TUR of superficial bladder cancers has been reported to be efficacious [8, 14]. It has been noted that further prospective randomized studies comparing early chemotherapy with delayed instillations are needed, since the beneficial effect of ADM is obvious [8]. Studies are being performed by the European Organization for Research and Treatment of Cancer (EORTC) to assess the prophylactic value of immediate versus delayed administration of mitomycin C and ADM, but the follow-up period is thus for too short to permit any statistical conclusions [2]. The non-recurrence rates obtained in the present study revealed no significant difference between the early- and delayed-instillation groups during the 36-month follow-up. However, patients receiving early instillations showed non-recurrence rates higher than those determined in groups receiving delayed instillations, and significant differences in recurrence rates were found between the two groups as a function of the following background factors: primary tumor, multiple tumors, tumor size of <1 cm, pathological stage pTa, and histological grades G1 and G2. These results suggest that early instillation of ADM after TUR is effective in preventing disease recurrence in the majority of patients with superficial bladder cancer.

Systemic chemotherapy with 5-FU given alone or in combination with other cytotoxic agents has yielded good results in patients with advanced bladder cancer [1, 3]. When 5-FU was given p.o., a high drug concentration was noted in the urine [4]. Moreover, long-term oral administration of tegafur, which is derived from 5-FU, resulted in a good prophylactic effect against the recurrence of superficial bladder cancer [13]. In the present study, the simul-

taneous administration of oral 5-FU with ADM instillation failed to provide results better than those obtained using ADM instillation alone over the 36-month follow-up period. To assess the effectiveness of oral 5-FU administration in preventing the recurrence of superficial bladder cancer, it will be necessary to compare the efficacy of administration of 5-FU after TUR with that of TUR alone.

Early and repeated instillations of ADM seem to cause more side effects in the form of bladder irritation than do delayed and repeated instillations. In fact, early instillations resulted in a significantly higher incidence of bladder irritation than did delayed instillations in our study. In the EORTC study of early and repeated instillations of ADM, however, chemical cystitis requiring a delay or discontinuation of treatment occurred in only 4% of the patients [2]. That incidence is similar to our result. In addition, the present results demonstrate that there was no significant difference between early and delayed instillations in the incidence of patient withdrawal due to bladder irritation. Moreover, no severe systemic side effects were encountered in this study. Thus, it seems that early and repeated intravesical instillations of ADM are clinically tolerable.

References

1. Cross RJ, Glashan RW, Humphrey CS, Robinson MRG, Smith PH, Williams RE (1976) Treatment of advanced bladder cancer with Adriamycin and 5-fluorouracil. Br J Urol 48: 609
2. Denis L, Bouffioux C, Kurth KH, Debruyne F, Sylvester R, De Pauw M, Members of the EORTC Urological Group (1987) Current status of intravesical chemotherapy trials in the EORTC Urological Group. An overview. Cancer Chemother Pharmacol 20 [Suppl]: S67
3. Fosså SD, Gudmundsen TE (1981) Single drug chemotherapy with 5-FU and Adriamycin in metastatic bladder carcinoma. Br J Urol 53: 320
4. Leissner KH, Gustavsson B (1982) Oral administration of 5-fluorouracil: renal clearance and urinary concentration in man. J Urol 128: 697
5. Niijima T, Koiso K, Akaza H, the Japanese Urological Cancer Research Group for Adriamycin (1983) Randomized clinical trial on chemoprophylaxis of recurrence in cases of superficial bladder cancer. Cancer Chemother Pharmacol 11 [Suppl]: S79
6. Omoto T, Masaki Z, Kano M, Morita I, Ariyoshi A, Ishizawa N, Momose S (1982) Postoperative prophylactic intravesical instillation of cytosine arabinoside and mitomycin C in superficial bladder tumor: follow-up study. Urology 20: 510
7. Schulman CC, Robinson M, Denis L, Smith P, Viggiano G, De Pauw M, Dalesio O, Sylvester R, Members of the EORTC Genito-Urinary Tract Cancer Cooperative Group (1982) Prophylactic chemotherapy of superficial transitional cell bladder carcinoma: an EORTC randomized trial comparing thiotepa, an epipodophyllotoxin (VM 26) and TUR alone. Eur Urol 8: 207
8. Schulman CC, Denis LJ, Oosterlinck W, De Sy W, Chatrie M, Bouffioux C, Van Caugh PJ, Van Erps P (1983) Early adjuvant Adriamycin in superficial bladder carcinoma. World J Urol 1: 86
9. Soloway MS (1980) Rationale for intensive intravesical chemotherapy for superficial bladder cancer. J Urol 123: 461
10. Soloway MS, Martino CC (1976) Prophylaxis of bladder tumor implantation: intravesical and systemic chemotherapy. Urology 7: 29
11. Ueda T, Iguchi A, Sagiyama K, Osada Y, Ariyoshi A, Omoto T, Kumazawa J, the Kyushu University Urological Oncology Group (1987) Early intravesical instillation of Adriamycin with oral administration of 5-fluorouracil after transurethral resection for superficial bladder cancer: preliminary results. Cancer Chemother Pharmacol 20 [Suppl]: S81
12. UICC (1978) Bladder. In: Harmer MH (ed) TNM classification of malignant tumours, 3rd edn. UICC, Geneva, p 113
13. Uyama T, Yamamoto A, Aga Y, Sumiyoshi Y, Yonezawa M, Fujita J (1984) Prophylactic long-term treatment of bladder tumors with oral chemotherapy (tegafur). Urology 23: 367
14. Zincke H, Utz DC, Taylor WF, Myers RP, Leary FJ (1982) Influence of thiotepa and doxorubicin instillation at time of transurethral surgical treatment of bladder cancer on tumor recurrence: a prospective, randomized, double-blind, controlled trial. J Urol 129: 505