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Early intravesical instillation of adriamycin with oral administration of 5-fluorouracil after transurethral resection for superficial bladder cancer: preliminary results

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Summary. In all, 199 patients were entered in this study by 21 collaborating hospitals. Patients with superficial transitional cell carcinoma of the bladder were randomized postoperatively into four groups. Group A received early (immediately and 2 days after transurethral resection) instillation of adriamycin (30 mg/30 mg); group B received early instillation of adriamycin with oral administration of 5-fluorouracil (200 mg/day); group C received delayed (7 days after transurethral resection) instillation of adriamycin (30 mg/30 ml); and group D received delayed instillation of adriamycin with oral administration of 5-fluorouracil (200 mg/day). All patients subsequently received instillations weekly for 2 more weeks, and then every 2 weeks for a further 14 weeks. After 4 months, they received one instillation per month for 8 months. 5-Fluorouracil was administered p. o. for 1 year. The postoperative follow-up period was 12 months. After 3 and 6 months there were significant differences in the non-recurrence rates between groups B and C. After 12 months the overall non-recurrence rates were 87.9% in group A, 83.5% in group B, 89.2% in group C, and 82,8% in group D, and there were no significant differences among the four groups. The number of patients entered and the follow-up period are not adequate for firm conclusions, and further studies are necessary. The main side effect was bladder irritation, which was observed in 38.8% of patients in the early instillation groups and in 26.3% of those in the delayed instillation groups. No severe systemic side effects were observed in this study.

Introduction

One of the most important problems encountered in surgical treatment of superficiial bladder cancer is the high recurrence rate even after complete resection of tumors [9, 11]. The high incidence of recurrence is primarily due to the multifocal growth of this tumor. Another possibility may be related to tumor cell seeding during transurethral resection (TUR) [9, 11, 12].

Early intravesical chemotherapy may be able to reduce the true incidence of recurrence, by destroying viable tumor cells remaining in contact with the urothelium after TUR. Long-term oral administration of an anticancer drug with the intention of achieving a relatively high concentration in the bladder may also have a cytotoxic effect on areas of unstable urothelium and prevent new tumor recurrence at a later time. Thus, we designed a prospective randomized study to answer the following two questions concerning chemoprophylaxis of superficial bladder cancer: (1) what is the best time for the initiation of instillation? and (2) is the oral administration of an anticancer drug effective? This report describes the preliminary results of this study.

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Patients and methods

From November 1984 to March 1986, in all 199 patients with superficial transitional cell carcinoma of the bladder (T_a and T_1) were entered in this study by 21 collaborating hospitals. Patients were randomized after TUR into four groups and the treatment was started.

Group A. The first and second intravesical instillations of adriamycin (ADM) were performed immediately and 2 days after TUR. Instillations were subsequently performed weekly for 2 more 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 was 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 administered p. o. for 1 year in addition.

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

Group D. The intravesical instillation of ADM was performed in the same manner as for group C and 5-FU was administered p. o. for 1 year in addition.

ADM (30 mg) dissolved in 30 ml physiologic saline was instilled into the bladder through a sterile catheter. The patients were instructed to refrain from voiding for 2 h after each instillation. 5-FU (100 mg) was administered p. o. twice a day.

Patients in whom residual tumor was highly probable, on the grounds of incomplete resection, omission of histological examination, or recurrence within the 1st postoperative month, were excluded from this study. Pathological findings were classified according to the UICC classification [13].

Control cystoscopy, blood chemistry, and blood counts were performed at 4 weeks and every 3 months thereafter. Local and systemic side effects were observed during and after each instillation.

Non-recurrence rates were calculated by the Kaplan-Meier method. Statistical analyses were made by the Chi-square test, Z-test, U-test, and the generalized Wilcoxon test.

Results

Of the 199 patients entered in this study, 36 (18.1%) were inelgible because of protocol violations and 11 (5.5%) were inevaluable as they were lost to follow-up (Table 1). A total of 152 patients were evaluable, and the patients were well randomized in the four groups. There were no significant differences in age, sex, tumor history, growth pattern, size, or number, stage, and grade of tumors (Tables 2–4).

Recurrences were analyzed in the 152 evaluable patients after follow-up periods ranging from 1 to 12 months, but only 45 patients have so far been followed up for 12 months (Table 5). During 6 months of follow-up no recurrences were observed in group B. After 3 and 6 months there were significant differences between groups B and C ($P<0.05$). After 12 months the overall non-recurrence rates were 87.9% in group A, 83.5% in group B, 89.2% in group C, and 82.8% in group D, and there were no statistically significant differences among the four groups (Fig. 1). The groups of patients with large, multiple and high-grade tumors had high recurrence rates according to the clinico-pathological features, but there were no significant differences specific to any one category (Fig. 2).

The main side effects in 163 patients eligible for the study are shown in Table 6. Bladder irritation was recorded in 38.8% of patients in the early instillation groups and in 26.5% of those in the delayed instillation groups. There was a significant difference between the early and delayed instillation groups ($P<0.01$). Gastrointestinal symptoms occurred in 13.4% of the patients receiving 5-FU p. o. Increased GOT and GPT were observed in only 2 patients receiving 5-FU p. o. Nineteen (11.7%) patients withdrew from the study because of side effects (Table 7). The most frequent reason for dropping out was bladder irritation. However, there was no significant difference between the early and the delayed instillation groups in this. There were no life-threating severe systemic side effects.

Table 1. Classification of patients

Group	No. of patients entered	No. of patients eligible	No. of patients evaluable
A	49	38	34
B	48	42	37
C	53	43	42
D	49	40	39
Total	199	163	152

Table 2. Clinical characteristics of 152 evaluable patients

Categories	Group				*df*
	A	B	C	D	
Age (mean)	65	67	64	60	N.S
Sex					
Male	25	29	33	29	N.S
Female	9	8	9	10	
History					
Primary	22	27	32	25	N.S
Recurrent	12	10	10	14	

Table 3. Endoscopic characteristics of 152 evaluable patients

Categories	Group				*df*
	A	B	C	D	
Growth pattern					
Papillary pedunculate	25	26	32	27	N.S
Non-papillary pedunculate	0	1	1	0	
Papillary sessile	8	8	7	12	
Non-papillary sessile	1	2	2	4	
Size (cm)					
<1	13	18	17	21	N.S
1–3	19	15	23	13	
3–5	2	3	2	5	
5<	0	1	0	0	
Number					
Solitary	20	15	26	20	N.S
2–4	13	15	12	15	
5<	1	7	4	4	

Table 4. Pathological characteristics of 152 evaluable patients

Categories	Group				*df*
	A	B	C	D	
Stage					
pT_a	17	17	20	26	N.S
pT_1	10	16	14	8	
pT_x	7	4	8	5	
Grade					
G_1	12	11	11	14	N.S
G_2	18	22	24	18	
G_3	4	4	7	7	

Table 5. Number of 152 evaluable patients followed-up

Period of follow-up (month)	Group				Total
	A	B	C	D	
1	34	37	42	39	152
3	28	37	37	38	140
6	25	28	26	31	110
9	20	18	20	24	82
12	11	8	10	16	45

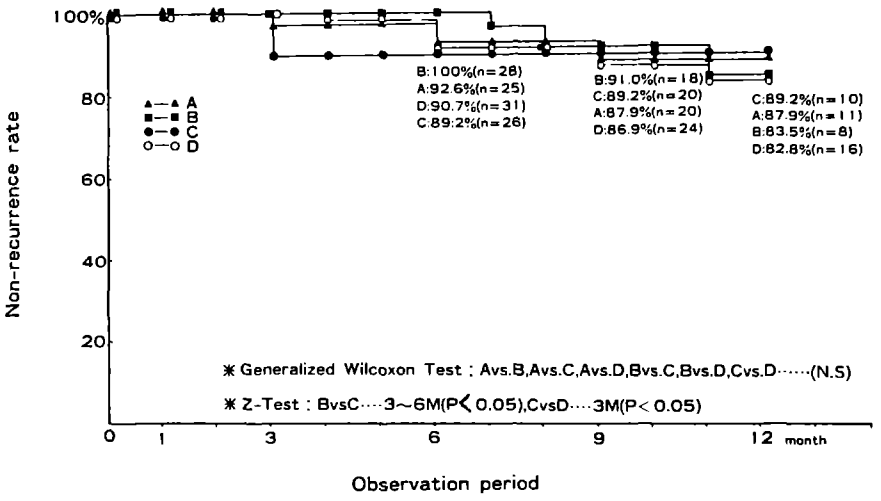

Fig. 1. Comparison of overall – non-recurrence curves among four groups

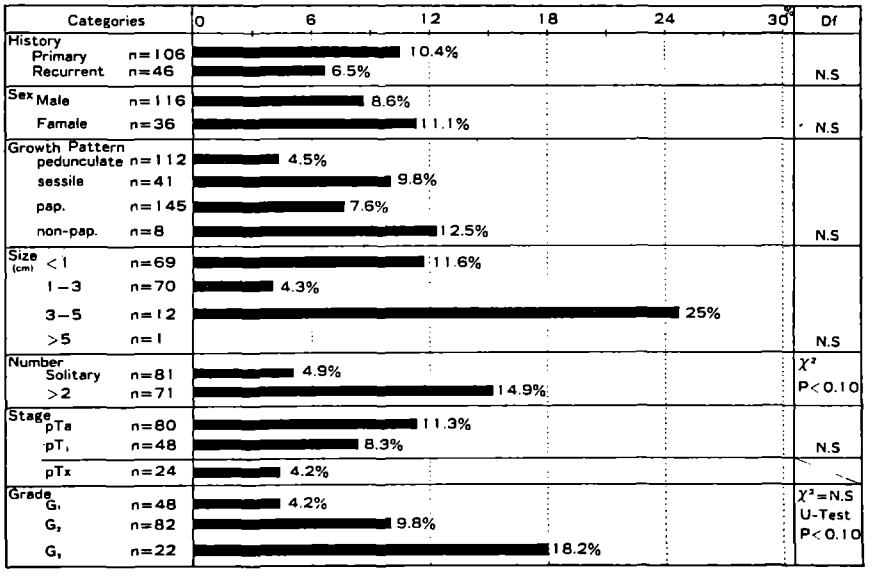

Fig. 2. Recurrence rates and clinico-pathological features

Table 6. Frequency of side effects in 163 eligible patients

Side effects	Early instillation group		Delayed instillation group	
	A (38)	B (42)	C (43)	D (40)
Bladder irritation	14 (36.8%)	17 (40.5%)	12 (27.9%)	10 (25.0%)
Gastrointestinal	1 (2.6%)	5 (11.9%)	2 (4.7%)	6 (15.0%)
Allergic reaction	1 (2.6%)	4 (9.5%)	0	1 (2.5%)
Leukopenia	0	0	0	0
Increased GOT, GPT	0	1 (2.4%)	0	1 (2.5%)

Table 7. Withdrawals due to side effects

Side effects	Early instillation group		Delayed instillation group	
	A (38)	B (42)	C (43)	D (40)
Bladder irritation	3	4	2	2
Gastrointestinal	0	3	0	1
Allergic reaction	1	2	0	0
Hematuria and bladder calculi	0	0	0	1
Total	4 (10.5%)	9 (21.4%)	2 (4.7%)	4 (10.0%)

Discussion

It is commonly recognized that postoperative intravesical chemotherapy is effective in preventing recurrence of superficial bladder cancer [4, 7]. However, there are still numerous questions concerning chemoprophylaxis. With the aim of improving the prevention of recurrence, we designed a prospective randomized study, using early and late repeated intravesical instillation of ADM, with or without oral chemoprophylaxis, after TUR in patients with superficial transitional cell carcinoma of the bladder.

ADM has recently been used intravesically for the chemoprophylaxis of bladder tumors, with no evidence of severe systemic toxic effects of ADM [2, 6]. Moreover, the efficacy of early intravesical instillation of ADM after TUR in superficial bladder cancer has recently been reported [10, 15]. On the other hand, systemic chemotherapy with 5-FU either alone or in combination with other cytotoxic agents, has been performed for patients with advanced bladder cancer [1, 3]. It was reported that when 5-FU was administered p. o. high concentrations were noted in the urine [5]. Moreover, long-term oral administration of tegafur, which is derived from 5-FU, had a good prophylactic effect against recurrence of bladder tumos [14].

After 12 months the non-recurrence rates obtained in this study were higher than those recorded in other reports [6, 10]. However, these high non-recurrence rates may decline as the numbers of long-term follow-up patients increase. During a 6-month follow-up, the non-recurrence rate in the group with early instillatiion of ADM and administration of 5-FU p. o. was significantly higher than that in the group with delayed instillation of ADM alone. However, there were no significant differences among the four groups after 12 months of follow-up. It may be that the numbers of patients entered and the follow-up period are insufficient. Further studies are necessary to obtain definitive results. On the other hand, in terms of tumor characteristics, it was suggested that the presence of multiple tumors and high histological grade were important prognostic factors in superficial bladder cancer. These facts have also been recognized in earlier studies [6, 8].

It is reported that 48.1% of patients presented with local side effects, essentially chemical cystitis; 21.8% of the patients in a study of early intravesical instillation of ADM withdrew [10]. Our data showed that early intravesical instillation of ADM also leads to a significant incidence of local side effects in the form of bladder irritation, but in most cases this is tolerable. Moreover, no severe systemic side effects were recorded in this study. Thus, the protocol designed for this study was clinically tolerable.

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