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SESSION III

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Prophylactic intravesical chemotherapy with Adriamycin plus verapamil for primary superficial bladder cancer: preliminary results*

Abstract A prospective randomized trial was conducted to compare the prophylactic effect of intravesical instillation of Adriamycin (ADM) plus verapamil (VR) with that of ADM alone for recurrence of superficial bladder cancer. A total of 226 patients were enrolled and randomized into 2 groups. Group A received intravesical instillation of ADM (30 mg/30 ml physiological saline) on 19 occasions during a 1-year period after transurethral resection, whereas group B received intravesical instillation of ADM (30 mg/24 ml physiological saline) plus VR (15 mg/6 ml saline) according to the same schedule used for group A. Evaluation was possible in 157 of the 226 registered patients (group A, 76; group B, 81). There was no significant difference in the patients' characteristics between the two groups, and there was no significant difference in the overall nonrecurrence rate determined over a 24-month follow-up period. However, group B showed a significantly higher nonrecurrence rate than did group A for tumors measuring less than 1 cm in diameter ($P < 0.05$) and for histological grade 2 tumors ($P < 0.01$) in spite of there being no significant difference in the other characteristics of each subgroup of patients. The incidence and severity of side effects were similar in both groups, and VR caused no significant systemic toxicity. Although further follow-up is necessary, these results suggest that intravesical instillation of ADM plus VR is clinically safe and may be more effective than instillation of ADM alone in preventing the postoperative recurrence of superficial bladder cancer (less than 1 cm in diameter, histological grade 2).

Key words Multidrug resistance · Superficial bladder cancer · Intravesical chemotherapy

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Introduction

The high incidence of tumor recurrence following transurethral resection (TUR) is one of the important problems encountered in the treatment of superficial bladder cancer. To prevent local recurrence, intravesical instillation chemotherapy with various anticancer agents, especially Adriamycin (ADM), is widely performed as an adjuvant to surgery. In spite of such prophylactic intravesical chemotherapy, however, recurrent tumors develop in many patients.

It has been demonstrated that when tumor cells acquire resistance to naturally occurring anticancer drugs such as anthracyclines, they generally show cross-resistance to a wide range of structurally and functionally unrelated drugs [1, 9]. Such acquired-multidrug-resistant (MDR) tumor cells have an enhanced drug-efflux function, and the mechanism of the drug resistance is closely related to overexpression of P-glycoprotein encoded by the mdr 1

gene [3, 4]. In addition to such acquired MDR, intrinsic MDR associated with increased expression of P-glycoprotein is also observed in some untreated carcinomas, including bladder cancer [8]. Thus, overcoming MDR, whether acquired or intrinsic, may be a key to improving the prophylactic effect of ADM on the recurrence of superficial bladder cancer.

Recently, verapamil (VR), a calcium-channel blocker has been demonstrated not only to enhance the efficacy of anticancer agents in chemosensitive tumor cells but also to overcome MDR [11, 12]. In the field of bladder cancer, Simpson et al. [10] demonstrated that VR enhanced the chemotherapeutic response of T24 human bladder cancer cells to ADM. Kimiya et al. [5] reported that VR enhanced the ADM sensitivity of an ADM-resistant human bladder-cancer cell line, KK47/ADM, although complete overcoming of the resistance could not be obtained. Furthermore, Naito et al. [7] performed a pilot study involving intravesical therapy with ADM plus VR in patients with superficial bladder cancer, and they reported that it was safe and effective for the treatment not only of untreated but also of recurrent chemoresistant superficial bladder cancer.

Thus, the present prospective randomized study was conducted to compare the effect of intravesical instillation of ADM plus VR with that of ADM alone in the prevention of recurrence of superficial bladder cancer.

Patients and methods

From July 1989 through June 1991, a total of 226 patients with superficial bladder cancer (Ta and T1) were enrolled in this study at 21 collaborating hospitals. The eligibility and exclusion criteria are shown in Table 1. Since VR has a possibility to induce adverse reactions of the cardiovascular system, the absence of severe heart disease, particularly severe bradycardia, sinus-atrial (S-A) block, and second- or third-degree atrioventricular (A-V) block, were included in the eligibility criteria. Recurrence within the 1st postoperative month was considered to be a residual tumor, and such patients were judged to be ineligible. Prior to enrollment, informed consent was obtained from all patients. Before undergoing TUR, the patients were randomized into the following two groups:

1. Group A: the first and second intravesical instillations of ADM were performed immediately and a few 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.

2. Group B: intravesical instillation of ADM plus VR was performed according to the schedule used for group B.

ADM (30 mg) dissolved in 30 ml physiological saline or ADM (30 mg) dissolved in 24 ml physiological saline plus VR (15 mg/6 ml saline) was instilled into the bladder through a sterile catheter. The patients were instructed to refrain from urinating for 2 h after each instillation.

Cytologic examination of urine samples, endoscopy, and routine laboratory tests (hematology tests, biochemistry tests, and urinalysis) were performed at 4 weeks after TUR and every 3 months thereafter. Bladder biopsy was performed when necessary. Patients were checked for local and systemic side effects, including the blood pressure and heart rate, during and after each instillation.

The follow-up period ranged from 2 to 46 months (median, 24 months). Nonrecurrence rates over the 24-month follow-up period were calculated by the Kaplan-Meier method. Statistical analyses were performed using the chi-square test and the generalized Wilcoxon test.

Table 1 Eligibility and exclusion criteria

Eligibility criteria – patients with primary superficial bladder cancer had to satisfy the following criteria:

1. Transitional-cell carcinoma
2. Primary cancer
3. Stage pTa – pT1
4. Absence of residual tumors due to incomplete resection
5. Absence of any other active malignancy
6. Absence of any serious complication, especially severe impairment of hepatic or hematopoietic function
7. Absence of severe heart disease, especially severe bradycardia, S-A block, and second- or third-degree A-V block

Exclusion criteria:

1. Recurrence within the 1st postoperative month
2. Unavailability for periodic follow-up
3. Any other reason for exclusion on the basis of the judgment of the attending physician

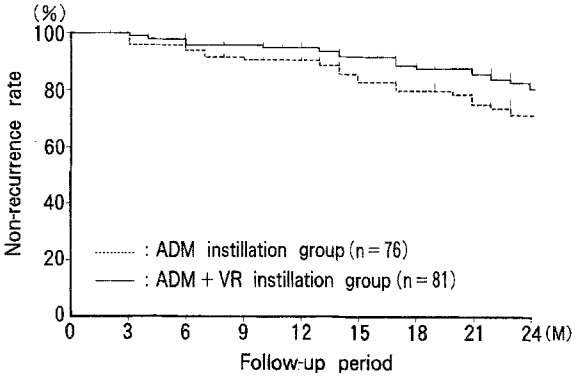

Fig. 1 Comparison of overall nonrecurrence rates determined for the ADM-only instillation group versus the ADM plus VR instillation group

Table 2 Disposition of the subjects

	Group A	Group B	Total (%)
Enrolled patients	113	113	226 (100)
Eligible patients	92	94	186 (82.3)
Evaluable patients	76	81	157 (69.5)

Results

Table 2 presents the status of patient entry. Of the 226 patients enrolled in this study, 40 (17.7%) were considered to be ineligible based on the entry criteria: 10 patients had an invasive (>pT2) tumor, 10 were considered to have residual lesions, 9 had benign tumors, 7 had not primary but recurrent tumors, 3 were impossible to diagnose histologically, and 1 had active hepatocellular carcinoma. In all, 29 patients (12.8%) were unevaluable: 18

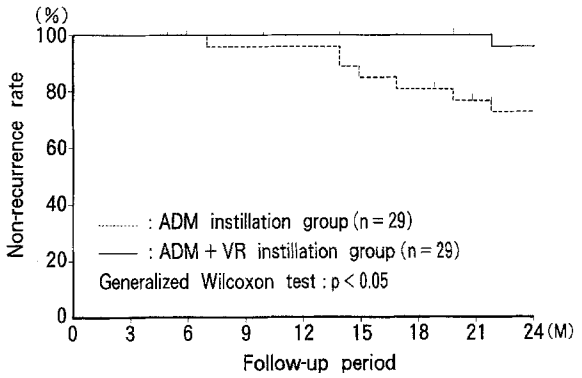

Fig. 2 Comparison of nonrecurrence rates determined for the ADM-only instillation group versus the ADM plus VR instillation group in terms of tumors measuring less than 1 cm in diameter

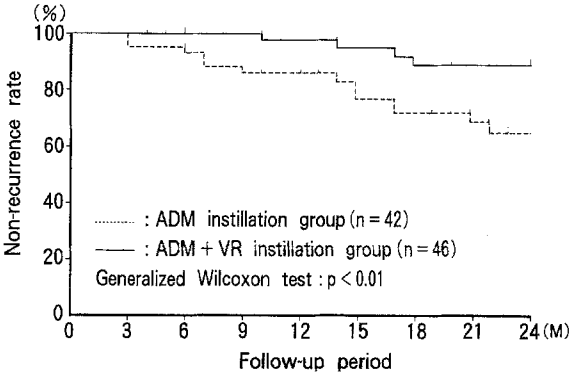

Fig. 3 Comparison of nonrecurrence rates determined for the ADM-only instillation group versus the ADM plus VR instillation group in terms of histological grade 2 tumors

were lost to follow-up with inadequate treatment (less than 13 instillations), 3 withdrew due to side effects, and 8 had other protocol violations. Thus, 157 patients (69.5%) were evaluable, and no significant difference was found between the two groups in terms of age or sex or the number, growth pattern, size, stage, or histological grade of the tumors (Table 3).

After 24 months, the overall nonrecurrence rate was 72.1% in group A and 80.8% in group B, respectively (Fig. 1). Although the nonrecurrence rates obtained in group B were always higher than those determined for group A, the difference was not significant during the 24-month follow-up period. However, group B showed significantly higher nonrecurrence rates than did group A in terms of tumors measuring less than 1 cm in diameter

Table 3 Characteristics of the evaluable patients (*NS* Not significant)

Background factor	All patients			Patients with tumor <1 cm in diameter			Patients with grade 2 tumor		
	Group A (n = 76)	Group B (n = 81)	χ^2 test	Group A (n = 29)	Group B (n = 29)	χ^2 test	Group A (n = 42)	Group B (n = 46)	χ^2 test
Age:									
<60 years	28	26	NS	11	12	NS	14	11	NS
≧60 years	48	55		18	17		28	35	
Sex:									
M	54	67	NS	21	22	NS	32	31	NS
F	22	14		8	7		10	15	
Tumor growth pattern:			NS			NS			NS
Papillary, pedunculated	56	60		20	25		27	32	
Papillary, sessile	17	19		7	4		12	13	
Nonpapillary, pedunculated	0	1		0	0		0	1	
Nonpapillary, sessile	3	1		2	0		3	0	
Tumor size (cm):			NS			NS			NS
<1	29	29		–	–		15	19	
1–3	40	41		–	–		21	21	
3–5	7	9		–	–		6	5	
≧5	0	2		–	–		0	1	
Number of tumors:			NS			NS			NS
1	56	48		20	20		32	27	
2–4	14	23		7	7		5	15	
≧5	6	10		2	2		5	4	
Pathological stage:			NS			NS			NS
pTa	52	53		22	21		26	34	
pT1	24	28		7	8		16	12	
Histological grade:			NS			NS			NS
G1	28	26		12	10		–	–	
G2	42	46		15	19		–	–	
G3	6	9		2	0		–	–	

Table 4 Incidence and severity of side effects

Side effect	Group A (n = 108) (%)	Group B (n = 110) (%)	χ^2 test
Pollakisuria[a]:			NS
–	92 (85.2)	89 (80.9)	
+	9 (8.3)	7 (6.4)	
++	7 (6.5)	11 (10.0)	
+++	0	3 (2.7)	
Pain on urination[a]:			NS
–	91 (84.3)	93 (84.5)	
+	8 (7.4)	7 (6.4)	
++	9 (8.3)	7 (6.4)	
+++	0	3 (2.7)	
Urethral discomfort or pain[a]:			NS
–	107 (99.1)	105 (95.5)	
+	1 (0.9)	3 (2.7)	
++	0	2 (1.8)	
+++	0	0	
Bladder calculi:			NS
–	85 (78.7)	90 (81.8)	
+	23 (21.3)	20 (18.2)	

[a] –, None; +, mild (treatment could be completed without any treatment); ++, moderate (treatment could be completed with appropriate treatment); +++, severe (treatment was discontinued)

($P < 0.05$) and histological grade 2 tumors ($P < 0.01$) in spite of there being no significant difference in the other characteristics (Figs. 2, 3; Table 3). No significant difference in the nonrecurrence rates was observed between the two treatment groups in terms of any of the other parameters evaluated.

Toxicity was evaluated in 218 patients (96.9%), excluding 8 who received either no instillation or less than 3 instillations. As a local side effect, symptoms of bladder irritation (pollakisuria and/or pain on urination) were observed in about 20% of the patients in each group (Table 4). In all, 3 patients (2.7%) in group B withdrew from the study because of severe pollakisuria and pain on urination after the 6th, 9th, and 10th instillations, respectively. However, there was no significant difference in the incidence and severity of pollakisuria or pain on urination between the two treatment groups. There was also no significant difference in the incidence of bladder calculi, which affected 23 of 108 patients (21.3%) in group A and 20 of 110 patients (18.2%) in group B. There was no evidence of systemic toxicity or hematological side effects in either treatment group.

Discussion

The present prospective randomized multicenter trial was conducted to examine whether intravesical instillation of VR can enhance the prophylactic effect of ADM on recurrence of superficial bladder cancer. During a 2-year period, 226 patients were enrolled in this study. Since in our previous study [13], early instillation of ADM after TUR was more effective than delayed instillation of ADM in preventing disease recurrence in patients with superficial bladder cancer, the instillation chemotherapy in this study was also started immediately after TUR. Therefore, patients were registered without any information about the histology of the TUR specimens. Consequently, quite a few patients were found to be ineligible after registration, and the prophylactic effect of ADM in the presence and absence of VR was evaluated in 157 (69.5%) patients. However, there was no significant difference in the patients' characteristics between the ADM plus VR instillation group and the ADM-only instillation group.

The dose of VR used in this study was 15 mg (in 6 ml saline), which is the maximal clinical dose for intravenous bolus injection, and it was instilled together with 30 mg ADM dissolved in 24 ml physiological saline. In this condition, the VR concentration is considered to be more than 500 times higher than that needed to enhance the drug sensitivity or overcome the drug resistance of malignant tumors [10–12]. Nevertheless, the nonrecurrence rates obtained for the 24-month follow-up period revealed no significant difference between the ADM plus VR instillation group and the ADM-only instillation group. Although the follow-up period was not long enough to enable conclusions to be drawn, the following explanations may be suggested as possible reasons why no enhanced prophylactic effect could be demonstrated with the combination of VR with ADM.

First, the high concentration of ADM obtained by intravesical instillation may be enough in itself to overcome the MDR of bladder cancer in humans. Second, the subjects in this study were patients with primary superficial bladder cancer, and those with recurrent tumors and previous intravesical chemotherapy were excluded. The MDR phenotype with expression of P-glycoprotein is not always present in primary superficial bladder cancer. Naito et al. [7] demonstrated that only about one-third of primary bladder cancers showed the MDR phenotype with expression of P-glycoprotein. Other biological changes such as increased intracellular glutathione values [2] or decreased levels of cellular enzymes [6] may play important roles in MDR tumors that do not express P-glycoprotein. In such tumors, VR may not contribute to enhancing ADM's effects. However, the ADM plus VR instillation group showed significantly higher nonrecurrence rates than did the ADM-only instillation group in the subgroup of patients with tumors that were less than 1 cm in diameter or of histological grade 2. Expression of intrinsic MDR may be frequent in these types of superficial bladder cancer.

The absorption of VR into the systemic circulation was shown to be minimal when 15 mg VR was instilled into the bladder therapeutically [7]. In the present study, no patient developed systemic toxicity, in agreement with a previous pilot study [7] involving therapeutic instillation of ADM plus VR. The incidence and severity of symptoms of bladder irritation also did not differ significantly between the ADM plus VR instillation group and the ADM-only instillation group. These findings indicate that prophylactic intravesical instillation of ADM plus VR is safe, even when the instillation is started immediately after TUR.

In conclusion, prophylactic intravesical instillation of ADM plus VR is clinically tolerable. Although further follow-up is necessary, this combination may be more effective than ADM alone in preventing the postoperative recurrence of superficial bladder cancer in terms of tumors that measure less than 1 cm in diameter or are of histological grade 2. We are now examining the prophylactic effect of this combination of ADM and VR in relation to the recurrence of superficial bladder cancer for which a conventional intravesical instillation chemotherapy has not been effective.

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