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Intravesical instillation of Adriamycin in the presence or absence of verapamil for the treatment of superficial bladder cancer: preliminary report of a collaborative study*

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Summary. A case-controlled collaborative study on the intravesical administration of Adriamycin in the presence or absence of verapamil, a calcium-channel blocker, as chemotherapy of superficial bladder cancer was carried out at two universities, Okayama and Kagoshima, and their affiliated hospitals. Although little is known about the expression of P-glycoprotein in superficial bladder cancer, it may be a cause of multidrug resistance (MDR). Verapamil was used as an inhibitor of P-glycoprotein. Arm A consisted of Adriamycin given at 50 mg/50 ml saline, and arm B constituted Adriamycin given at 50 mg/40 ml saline plus 5 ampules (10 ml) of injectable verapamil. The drugs were instilled into the bladder for 3 consecutive days in each of 3 consecutive weeks for a total of 9 instillations. No significant difference in antitumor effects was observed between arm A and arm B. Recurrent tumors responded better than did primary tumors to both arm-A and arm-B treatments ($P = 0.012$). In both treatment arms, significant differences ($P = 0.031$) in the response rate were found between tumors with diameters of <1 cm and those measuring 1–3 cm in diameter. Although the number of evaluable patients was limited, recurrent subjects who had previously received Adriamycin instillations responded in both treatment arms.

Introduction

Since the first report of Niijima et al. [6] in 1975, intravesical Adriamycin instillation has been clinically accepted as treatment of superficial bladder cancer [7–10, 13]. Intravesical chemotherapy has been given to patients with superficial bladder cancer not only as preoperative treatment [7] but also for prevention of recurrence [1]. The antitumor efficacy of intravesical Adriamycin correlates with the concentration of the drug [7]. It has been shown that Adriamycin penetrates into the tumor tissue after its administration into rat bladders bearing *N*-butyl-*N*-butanolnitrosamine (BBN)-induced tumors [4].

Tumor-cell resistance to cytotoxic agents is considered to be one of the major causes of failure of clinical chemotherapy [2]. It is also well known that a complete response is not always obtained by intravesical chemotherapy of superficial bladder cancer. Expression of a high-molecular-weight plasma-membrane glycoprotein (P-glycoprotein) has been shown to correlate with multidrug resistance (MDR) in cancer cells [2, 3, 11]. In an in vitro experiment using an MDR cell line of bladder-cancer origin, Long et al. [3] demonstrated that the cytotoxicity of Adriamycin was enhanced by its combination with verapamil, a calcium-channel blocker. Yoshimoto et al. [13] performed combination intravesical instillation of Adriamycin and verapamil in 8 patients with recurrent superficial bladder cancer and obtained a good response (86%). To confirm that finding, we gave Adriamycin intravesically to patients with superficial bladder cancer in the presence or absence of verapamil. The present study is being collaboratively performed at two universities and their affiliated hospitals and is being conducted by a controller. Although the data are preliminary, we tried to evaluate the clinical usefulness of verapamil in combination with Adriamycin.

Patients and methods

The subjects of the present study were patients with primary superficial bladder cancer, including those with recurrent tumors who had been given Adriamycin not only as treatment but also as prophylaxis. Cases of recurrence following transurethral resection (TUR) or partial cystectomy and primary cases were also included. This study was started in January

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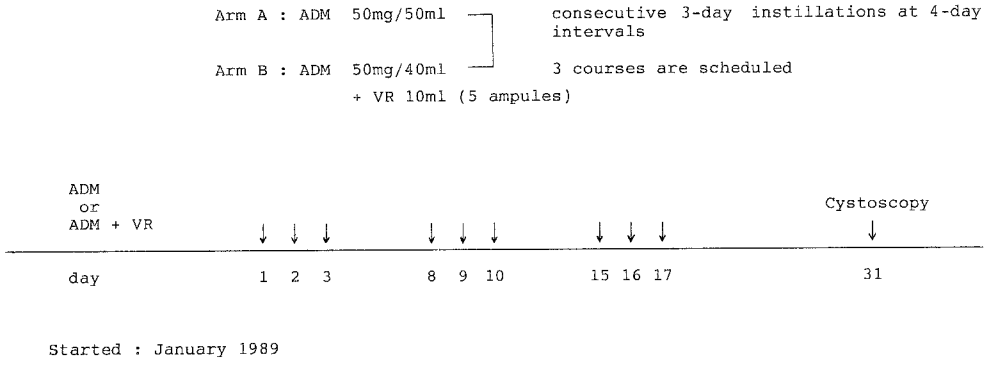

Fig. 1. Treatment protocol used in the present study

Table 1. Patients' characteristics

	All cases		⩾ Instillations	
	A ($n = 30$)	B ($n = 28$)	A ($n = 25$)	B ($n = 25$)
Sex:				
M	24	21	21	18
F	6	7	4	7
Age (years):				
⩽49	4	2	3	1
50–59	2	6	2	6
60–69	4	9	4	9
⩾70	20	11	16	9
Type of disease:				
Primary	11	9	9	8
Recurrent	19	19	16	17
Recurrent cases:				
Number of recurrences/patient	2.9	3.2	2.6	3.4
Observation period (months)	39	43	31	47
Tumor morphology:				
Pedunculated	16	12	14	10
Broad based	14	15	11	14
Tumor size:				
<1 cm	23	23	19	20
1–3 cm	6	5	5	5
3–5 cm	1	0	1	0
>5 cm	0	0	0	0
Number of tumors:				
2–4	20	13	17	12
⩾5	10	15	8	13
Almost confluent	0	0	0	0
Pathological stage:				
Ta	20	19	15	17
T1	8	8	8	7
Histological grade:				
G1	17	13	13	10
G2	11	13	10	13

of 1989, and 58 patients were enrolled. The patients were registered with a controller by telephone and were assigned to one of the treatment arms described below.

Arm A consisted of Adriamycin given at 50 mg/50 ml saline, and arm B constituted Adriamycin given at 50 mg/40 ml saline plus 5 ampules of injectable verapamil. The drugs were instilled into the bladder for 3 consecutive days in each of 3 consecutive weeks for a total of 9 instillations (Fig. 1). Cystoscopic examination was performed at 2 weeks after the last treatment.

Results

Of the 58 patients enrolled in the study, 50 were given >6 instillations, but 8 received <5 instillations because of adverse reactions. We evaluated the clinical effectiveness of the treatment in patients who received >6 instillations. The patients' characteristics are shown in Table 1. The two treatment groups showed no significant difference in sex, age, primary tumor, recurrent tumor, time of recurrence, observation period, tumor size, number of tumors, pathological stage, or histological grade. In all, 24 patients in arm A and 25 in arm B were evaluable for response. A complete response (CR) was defined as the complete disappearance of the tumor as determined either cystoscopically or pathologically, a partial response (PR) consisted of a reduction of >50% in the size of the tumor, no change (NC) represented a decrease of <50% or an increase of <25% in the size of the lesion, and progressive disease (PD) was defined as an increase of >25% in the size of the tumor.

Of the 24 arm-A cases evaluated, 15 (62.5%) showed a response (CR+PR), whereas 12 (48.2%) of the 25 cases in arm B responded (Table 2). However, the difference in these response rates was not significant. In arm A, the response rate in patients with primary tumors was 33.3%, whereas it was 75.0% in those with recurrent tumors ($P = 0.012$, Table 3). Arm B showed the same tendency toward a better response by recurrent tumors as compared with primary lesions (Table 4). No statistically significant difference was found between arms A and B in the response of primary (Table 5) or recurrent tumors (Table 6). In addition, no significant difference was noted in the response rates determined according to tumor morphology (pedunculated versus broad-based; Tables 7, 8). Both regimens showed a significant difference ($P = 0.031$) between the response rates determined for tumors with a diameter of <1 cm as compared with those measuring 1–3 cm in diameter (Tables 9, 10). The correlation between the patients' episodes and the response to the treatment is reviewed in Table 11. Although the number of evaluable patients was small, the responses obtained in recurrent cases following Adriamycin instillation were encouraging. As for adverse reactions to the intravesical chemotherapy, local inflammatory symptoms such as urinary frequency, micturition pain, hematuria, difficulty in urinating, and urinary turbidity were recorded by the physicians in charge and are listed in Table 12. No significant difference was found between arms A and B.

Table 2. Response rate of patients who received ≧6 instillations

Arm	Number of patients	Response				Response rate	
		CR	PR	NC	PD		
A	24	8 (33.3%) (P-4, C-1)	7 (29.2%)	6 (25.0%)	3 (12.5%)	15 (62.5%)	NS
B	25	5 (20.0%) (P-2, C-0)	7 (28.0%)	12 (48.0%)	1 (4.0%)	12 (48.0%)	

P, Pathological; C, clinical; NS, not significant

Table 3. Response rate of patients in arm A who received ≧6 instillations as determined

Type of disease	Number of patients	CR + PR		NC + PD
Primary	9	3 (33.3%)	$P = 0.012$	6 (66.7%)
Recurrent	16	12 (75.0%)		4 (25.0%)

Table 4. Response rate of patients in arm B who received ≧6 instillations as determined according to type of disease

Type of disease	Number of patients	CR + PR		NC + PD
Primary	8	2 (25.0%)	$P = 0.012$	6 (75.0%)
Recurrent	16	10 (58.8%)		7 (41.2%)

Table 5. Response rate of patients with primary tumors who received ≧6 instillations as determined according to treatment arm

Arm	Number of patients	CR + PR		NC + PD
A	9	3 (33.3%)	NS	6 (66.7%)
B	8	2 (25.0%)		6 (75.0%)

Table 6. Response rate of patients with recurrent tumors who received ≧6 instillations as determined according to treatment arm

Arm	Number of patients	CR + PR		NC + PD
A	16	12 (75.0%)	NS	4 (25.0%)
B	16	10 (58.8%)		7 (41.2%)

NS, Not significant

Table 7. Response rate of patients in arm A who received ≧6 instillations as determined according to tumor morphology

Tumor morphology	Number of patients	CR + PR		NC + PD
Pedunculated	14	10 (71.4%)	NS	4 (28.6%)
Broad based	11	5 (45.5%)		6 (54.5%)

NS, Not significant

Table 8. Response rate of patients in arm B who received ≧6 instillations as determined according to tumor morphology

Tumor morphology	Number of patients	CR + PR		NC + PD
Pedunculated	10	6 (60.0%)	NS	4 (40.0%)
Broad based	14	5 (35.7%)		9 (64.2%)

NS, Not significant

Table 9. Response rate of patients in arm A who received ≧6 instillations as determined according to tumor size

Tumor diameter	Number of patients	CR + PR		NC + PD
<1 cm	19	13 (68.4%)	$P = 0.031$	6 (31.6%)
1–3 cm	5	2 (40.0%)		3 (60.0%)
3–5 cm	1	0		1 (100%)

Table 10. Response rate of patients in arm B who received ≧6 instillations as determined according to tumor size

Tumor diameter	Number of patients	CR + PR		NC + PD
<1 cm	20	11 (55.0%)	$P = 0.031$	9 (45.0%)
1–3 cm	5	1 (20.0%)		4 (80.0%)
3–5 cm	0	0		0

Discussion

Intravesical instillation of antitumor agents, especially Adriamycin, has been widely accepted in the treatment and prophylaxis of superficial bladder cancer [1, 6–10, 13]. To evaluate the efficacy of intravesical chemotherapy in superficial bladder cancer, urologists carry out urinary cytology, cystoscopy, and cold-punch biopsy. The efficacy of topical Adriamycin chemotherapy has been excellent [6–10, 13]. However, the reason why some superficial bladder cancers never respond remains obscure. Because of its relatively high molecular weight (580 kDa), Adriamycin's penetration into tumors of the bladder does not extent to the muscle layer [4, 8]. The optimal dose and methods for local application of Adriamycin remain to be defined [8]. The dose- and time-dependent cytotoxicity of Adriamycin has been demonstrated in an in vitro testing system [12].

Table 11. Distribution of the response to treatment of selected patients who received ≥6 instillations according to disease status

Disease status	Response			
	CR + PR		NC + PD	
	A	B	A	B
(1) Recurred after ADM instillation; CR or PR	1	1	0	0
(2) Recurred after ADM instillation; NC or PD	0	0	0	2
(3) Recurred after or during ADM prophylaxis	4	2	1	0
(4) Recurred after treatment other than ADM instillation	5	2	2	1
(5) Recurred after TUR or partial cystectomy	2	3	1	2
(6) Primary tumor	3	2	5	6
(7) 1 + 4	0	0	0	1
(8) 3 + 5	0	1	0	0
(9) 1 + 2	0	1	0	0
(10) 4 + 5	0	0	0	1

The concept of multidrug resistance (MDR) in cancer cells is a new problem to be solved [2, 3, 11]. One mechanism of MDR has been considered to involve the expression of P-glycoprotein by the cancer cells, and calcium-channel blockers are now thought to act by binding with P-glycoprotein [11]. Whether P-glycoprotein is expressed in superficial bladder cancer remains unclear. In our laboratory, Nishiyama (unpublished data) has demonstrated the expression of P-glycoprotein in two of nine bladder cancers.

Of the 49 cases finally evaluated in the present study, efficacy rates (CR+PR) of 62.5% and 48.0% were obtained in arms A and B, respectively. Adriamycin (30 mg/30 ml saline) has been used for prophylaxis of the recurrence of superficial bladder cancer in Japan [1]. The dose-dependent cytotoxicity of Adriamycin might limit its efficacy in patients with recurrent superficial bladder cancer who have received previous therapeutic or prophylactic treatment with this drug. The drug sensitivity or resistance of the primary or recurrent tumor should be meticulously investigated. Although no significant difference has been found in the efficacy of Adriamycin following its instillation at various doses [10], the drug sensitivity of each tumor should none the less be checked. Of course, the investigation of P-glycoprotein expression in transitional-cell carcinoma is desirable. These biological and biochemical analyses as well as genetic studies should be carried out before the initiation of treatment.

It is evident that verapamil binds to P-glycoprotein, but its binding potential and function are not necessarily complete [11]. However, the safety of intravesical application of this calcium-channel blocker has been confirmed [5]. The clinical efficacy found for the intravesical instillation of Adriamycin in combination with verapamil in the present study was in sufficient as compared with the experimental results reported by Long et al. [3]. Further study of a greater number of patients is needed. Causes of MDR other than P-glycoprotein are also under investigation [2]. From the viewpoints of tumor recurrence and multiplicity, we must focus not only on invasive or advanced bladder carcinoma but also on superficial bladder cancer.

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Table 12. Incidence of local adverse reactions to therapy

Side effect	Arm	Severity of reactions			
		–	+	++	+++
Urinary frequency	A	13 (43.3%)	6 (20.0%)	6 (20.0%)	5 (16.7%)
	B	11 (39.3%)	5 (17.9%)	6 (21.4%)	6 (21.4%)
Micturition pain	A	14 (46.7%)	10 (33.3%)	4 (13.3%)	2 (6.7%)
	B	12 (42.9%)	7 (25.0%)	5 (17.9%)	4 (14.3%)
Hematuria	A	24 (80.0%)	4 (13.3%)	1 (3.3%)	1 (3.3%)
	B	20 (71.4%)	4 (14.3%)	3 (10.7%)	1 (3.6%)
Difficulty in urinating	A	27 (90.0%)	2 (6.7%)	0	1 (3.3%)
	B	26 (92.9%)	1 (3.6%)	0	1 (3.6%)
Urinary turbidity	A	26 (86.7%)	3 (10.0%)	1 (3.3%)	0
	B	21 (75.0%)	5 (17.9%)	0	2 (7.1%)

–, non; +, slight; ++, moderate; +++, severe

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