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Intravesical instillation of Adriamycin for bladder tumors*

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Summary. In the present series of trials, Adriamycin (ADM) intravesical instillation therapy was found to be effective against tumors of papillary morphology measuring <10 mm in diameter that were of low pathological stage and low histological grade. The rate of complete disappearance increased in proportion to the concentration of ADM and the duration of retention of the drug, although the efficacy rates were almost the same in each trial. On the other hand, side effects on the bladder were reduced when the instilled solution was lower in concentration and the retention time was short.

Introduction

It is well known that intravesical instillation of ADM is ablative against bladder tumors. However, the resultant side effects increase in proportion to the treatment's effectiveness. In the present report, an ideal ablative ADM-instillation regimen for the treatment of bladder tumors is discussed.

Materials and methods

In our department, topical ADM instillation therapy for bladder tumors was first studied in 1979 in group 1, comprising 20 cases (Table 1) [1]. In that study, 40 mg ADM dissolved in 20 ml sterilized distilled water was instilled into the bladder. The drug was retained in the bladder as long as possible, usually for about 3 h. This procedure was performed daily for 2 weeks.

Next, the administration of two instillation regimens to groups 2 and 3, respectively, were tested in the second study, which was performed up to the date of this writing. In group 2, 50 mg ADM in 30 ml saline solution was used in 17 cases, and in group 3, 50 mg ADM in 50 ml saline solution was instilled in 34 cases. On these schedules, ADM was retained in the bladder for 1 h. These regimens were repeated 3 times weekly for 3 weeks.

Table 1. Regimens for ADM instillation therapy

First study (1979):	
Group 1	
ADM, 40 mg/20 ml distilled water	
20 cases	
3 h, every day for 2 weeks	
Second study:	
Group 2	
ADM, 50 mg/30 ml saline solution	
17 cases	
Group 3	
ADM, 50 mg/50 ml saline solution	
34 cases	
1 h, 3 times weekly for 3 weeks	
Preliminary study:	
Group 4	
ADM derivatives, 30 mg/50 ml saline solution	
3 cases (epirubicin, one case; pirarubicin, two cases)	
10 min, 3 times weekly for 2 weeks	

In a preliminary study in group 4, a brief instillation period of 10 min was used for the administration of two ADM derivatives in the treatment of three cases of low-grade and low-stage superficial bladder tumors (epirubicin, one case; pirarubicin, two cases; Table 1).

The effects of ADM instillation on bladder tumors were evaluated by cystoscopy and sonography after the final instillation of the drug. For interpretation of the results, "complete disappearance" indicated that disappearance of the bladder tumor was confirmed macroscopically by cystoscopic examination. "Partial disappearance" was defined as a reduction of >50% in the diameter of the bladder tumor in cases of a single tumor or a decrease of >50% in the number of tumors in cases of multiple tumors. "No effect" indicated that the reduction in the size of the tumor amounted to <50%; this category included tumors that either did not diminish in size or showed enlargement in spite of the therapy.

Results

Overall results

The overall results of ADM instillation therapy for bladder tumors are shown in Table 2. In the first study involving

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Table 2. Results of ADM intravesical instillation therapy

Regimen[a]	Cases (*n*)	Complete disappearance of tumors	Partial disappearance of tumors	No effect	Efficacy rate
Group 1 (40 mg/20 ml)	20	8 (40.0%)	5 (25.0%)	7 (35.0%)	65.0%
Group 2 (50 mg/30 ml)	17	2 (11.8%)	9 (52.9%)	6 (35.3%)	64.7%
Group 3 (50 mg/50 ml)	34	4 (11.8%)	17 (50.0%)	13 (38.2%)	61.8%
Group 4 (30 mg/50 ml)	3	2 (66.7%)	0	1 (33.3%)	66.7%
Epirubicin	1	1 (100%)	0	0	100%
Pirarubicin	2	1 (50.0%)	0	1 (50.0%)	50.0%

[a] Drug doses are expressed as milligrams of ADM (or derivatives, group 4) per 20, 30, or 50 ml liquid solution

Table 3. Tumor size and effect

Group	Tumor	Cases (*n*)	Complete disappearance of tumors	Partial disappearance of tumors	No effect	Efficacy rate
1	< 1 cm	10	7 (70%)	2 (20%)	1 (10%)	90%
	≧1 cm	10	1 (10%)	3 (30%)	6 (60%)	40%
2	< 1 cm	7	2 (29%)	2 (29%)	3 (43%)	57%
	≧1 cm	14	0	7 (50%)	3 (21%)	50%
3	< 1 cm	17	3 (18%)	5 (29%)	9 (53%)	47%
	≧1 cm	16	1 (6%)	12 (75%)	4 (25%)	81%
4	< 1 cm	3	2 (67%)	0	1 (33%)	67%

Table 4. Tumor number and effect

Group	Number of tumors	Cases (*n*)	Complete disappearance of tumors	Partial disappearance of tumors	No effect	Efficacy rate
1	Single	9	4 (44%)	3 (33%)	2 (22%)	78%
	Multiple	11	4 (36%)	2 (18%)	5 (45%)	55%
2	Single	8	2 (25%)	4 (50%)	2 (25%)	75%
	Multiple	9	0	5 (56%)	4 (44%)	56%
3	Single	21	2 (10%)	9 (43%)	10 (48%)	52%
	Multiple	13	2 (15%)	8 (62%)	3 (23%)	77%
4	Single	2	2 (100%)	0	0	100%
	Multiple	1	0	0	1	0

group 1, the tumors disappeared completely in 8 of 20 cases (40%). Partial disappearance was achieved in 5 cases (25%), and the result was rated as no effect in 7 cases (35%). Accordingly, the efficacy rate of this therapy for bladder tumors was 65% (13/20). In the second study, the rate of complete tumor disappearance was the same in groups 2 and 3, i.e., 11.8%. The partial disappearance rates were 52.9% in group 2 and 50.0% in group 3. No effect was observed in 35.3% of cases in group 2 and in 38.2% of cases in group 3. The efficacy rates were 64.7% in group 2 and 61.8% in group 3. In Group 4, complete disappearance was observed in 2 cases (66.7%). These results were analyzed with reference to the size, number, morphology, grade, and stage of the bladder tumors prior to the instillation therapy.

Tumor size and effect. In all treatment groups, the complete disappearance rate was higher for tumors with a diameter of <10 mm than in those that measured >10 mm in diameter (Table 3).

Tumor number and effect. Complete disappearance was achieved in a greater number of cases involving a single

Table 5. Tumor morphology and effect

Group	Tumor morphology	Cases (*n*)	Complete disappearance of tumors	Partial disappearance of tumors	No effect	Efficacy rate
1	Papillary, pedunculated	12	7 (58%)	2 (17%)	3 (25%)	75%
	Papillary, sessile	6	1 (17%)	3 (50%)	4 (67%)	50%
2	Papillary, pedunculated	11	1 (9%)	7 (64%)	3 (27%)	73%
	Papillary, sessile	6	1 (17%)	2 (33%)	3 (50%)	50%
3	Papillary, pedunculated	30	2 (7%)	16 (53%)	12 (40%)	60%
	Papillary, sessile	3	2 (67%)	1 (33%)	0	100%
4	Papillary, pedunculated	2	2 (100%)	0	0	100%
	Papillary, sessile	1	0	0	1	0

Table 6. Tumor grade and effect

Group	Tumor grade	Cases (*n*)	Complete disappearance of tumors	Partial disappearance of tumors	No effect	Efficacy rate
1	G1 and G2	10	3 (30%)	4 (40%)	3 (30%)	70%
	≧ G3	2	0	0	2 (100%)	0
	Unknown	8	5 (63%)	1 (13%)	2 (25%)	75%
2	G1 and G2	15	2 (13%)	8 (53%)	5 (33%)	67%
	G3	2	0	1 (50%)	1 (50%)	50%
3	G1 and G2	33	4 (12%)	16 (48%)	13 (39%)	61%
	G3	1	0	1	0	100%
4	G1	3	2 (67%)	0	1 (33%)	67%

Table 7. Tumor stage and effect

Group	Tumor stage	Cases (*n*)	Complete disappearance of tumors	Partial disappearance of tumors	No effect	Efficacy rate
1	≦T1	13	8 (62%)	3 (23%)	2 (15%)	85%
	≧ T2	7	0	2 (29%)	5 (71%)	29%
2	Ta	6	2 (33%)	2 (33%)	2 (33%)	67%
	T1	11	0	7 (64%)	4 (36%)	64%
3	Ta	33	4 (12%)	16 (47%)	13 (39%)	61%
	T1	1	0	1 (100%)	0	100%
4	Ta	2	2 (100%)	0	0	100%
	T1	1	0	0	1	0

tumor than in those bearing multiple tumors in groups 1 and 2 (Table 4).

Tumor morphology and effect. In the first study (group 1), the efficacy rate was higher for the pedunculated type than for the sessile type, especially in terms of the complete disappearance rate (Table 5). In the second study (groups 2 and 3), this point was not analyzed clearly. In group 2 the complete disappearance rate was almost the same, regardless of the tumor morphology; however, in group 3 it was higher for sessile tumors than for pedunculated tumors.

Tumor grade and effect. Complete disappearance was marked for low-grade tumors (grades G1 and G2) in all groups (Table 6).

Tumor stage and effect. In the first study, all cases of complete tumor disappearance involved lesions staged as

Table 8. Local side effects encountered

Group	Cases (*n*)	Frequent and painful urination	Interruption of therapy
1 (40 mg/20 ml)	20	20 (100%)	2 (10%)
2 (50 mg/30 ml)	17	13 (76%)	5 (29%)
3 (50 mg/50 ml)	34	8 (24%)	2 (6%)
4 (30 mg/50 ml)	3	0	0

<T2. However, details of their related categories of Ta and T1 were not analyzed. There was no case of complete disappearance of T2 tumors (Table 7). In the second study, which compared tumors staged as Ta and T1, complete disappearance was observed only for stage Ta tumors.

Local side effects

Finally, the local side effects of the instillation regimens were analyzed (Table 8). In the first study (group 1), local bladder reactions such as urinary frequency, painful urination, and urethral pain were noted in all cases and required interruption of the therapy in two cases. In the second study (groups 2 and 3), bladder symptoms were observed in 13 cases (76%) in group 2 and in 8 cases (24%) in group 3. The therapy was interrupted in 5 cases (29%) in group 2 and in 2 cases (6%) in group 3. The incidence of side effects was lower in group 3, although the effect of the treatment itself was the same in both groups. In the preliminary study (group 4), no local side effect was encountered.

Discussion

The analysis of the present series of instillation regimens confirmed that ADM intravesical instillation therapy is effective against tumors of papillary form morphology measuring <10 mm in diameter that are of low pathological stage and low histological grade [1, 4]. The complete disappearance rate was highest in the first study, probably due to the high frequency of administration, the long period of the drug retention, and the high drug concentration in the instillation solution. On the other hand, no difference in the complete disappearance rate (11.8%) was found between group 2 and group 3 in the second study, in which the drug concentrations differed but the frequency of administration and the duration of drug retention were the same for both schedules. Although the partial disappearance rate was slightly higher in group 2 than in group 3, there seemed to be no significant difference in the efficacy of the two regimens.

Throughout the present series of trials, tumors that were not affected by the ADM instillation therapy were detected at the same rate in the first and second studies, although the drug concentration, the frequency of administration, and the duration of the instillations were quite different. Therefore, the efficacy rate in each study was around 65%.

In the ablative use of intravesical instillation therapy for bladder tumors, complete disappearance of the lesion is significant. Even if partial disappearance of a tumor is achieved by the chemotherapy, additional transurethral resection of the tumor cannot be avoided. Accordingly, the significance of the instillation therapy is invalidated in cases of merely partial tumor disappearance.

In a sense, the treatment effect obtained in our first study, in which the complete disappearance rate was 40.0%, should be satisfactory. However, local side effects occurred in all cases. According to our results, the local side effects caused by ADM instillation seemed to be de-

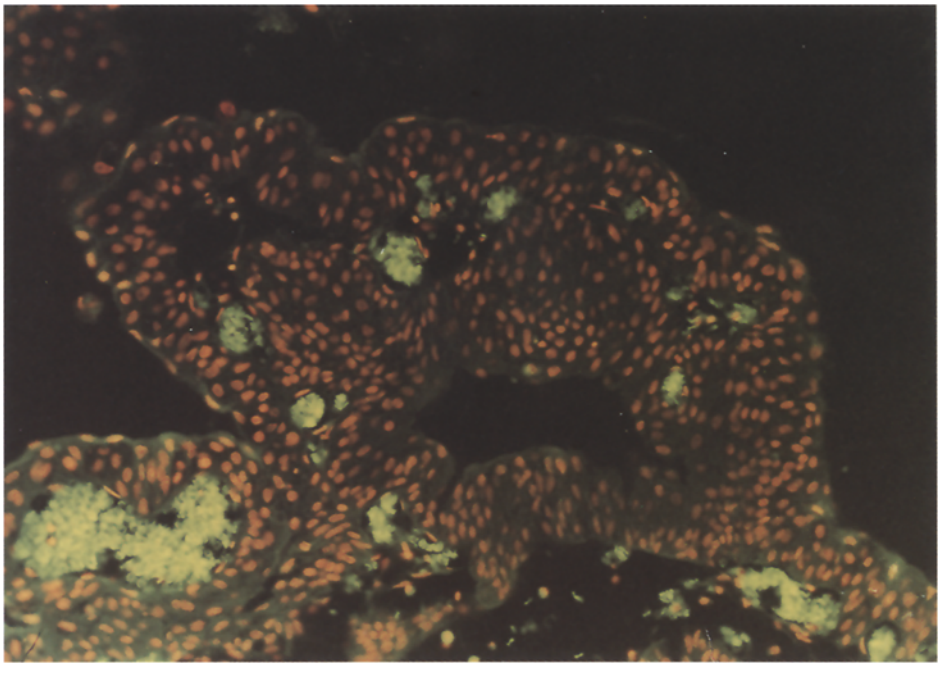

Fig. 1. Fluorescence micrograph of a bladder tumor obtained at 5 min after the instillation of ADM, showing that orange fluorescence corresponding to ADM has permeated into all of the bladder tumor cells within 5 min. ×160

pendent on both the drug concentration and the duration of drug retention. Therefore, the incidence of such side effects may be lowered by drug dilution and transient instillation without diminishing the efficacy rate; however, the complete disappearance rate might decrease.

From the present clinical studies, it is clear that a more practical and useful instillation therapy needs to be established that will keep the local side effects of the drug to a minimum. We have experimentally investigated the absorption and disappearance of ADM in the normal rat bladder and in *N*-butyl-*N*-butanolnitrosamine (BBN)-induced rat-bladder tumors using a histological method along with fluorescence microscopy [2, 3]. The results of this experimental study confirm that ADM permeates into the lamina propria and the inner layer of the muscle within 15 min after instillation. Thereafter, it is confined mostly to the bladder epithelium and gradually disappears over 48 h. In the case of papillary bladder tumors, ADM permeated into all of the tumor cells within 5 min (Fig. 1).

From this study, it seemed that the duration of drug retention might be shortened to prevent local side effects without reducing the effect of the treatment on the tumor cells. According to this idea, a brief instillation of 10 min using ADM derivatives was attempted in group 4 as a preliminary study. During this trial, the observed effects on bladder tumors were the same as those obtained using ADM instillation therapy (groups 1–3), and no local side effects were encountered.

Although further research is clearly needed, we hope that an ideal instillation therapy that is effective against bladder-tumor cells and produces no side effects, such as brief instillation therapy using ADM derivatives, can be realized in the near future.

References

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