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Intravesical Adriamycin chemotherapy in bladder cancer

Yosuke Matsumura, Yujiro Ozaki, Hiroyuki Ohmori, and Okayama Urological Cancer Collaborative Group (OUCCG)

Department of Urology, Okayama University, Medical School, 2–5–1 Shikata-cho, Okayama 700, Japan

Summary. *In an experimental study undertaken to elucidate the mechanism whereby Adriamycin (ADM) instilled into the bladder produces its side-effects, the time course of ADM concentration in blood, urine, and tissues of various organs, and also histopathological changes in the bladder mucosa were investigated in normal adult dogs that had undergone bilateral ureterostomy and then received intravesically instilled ADM. Clinically, ADM was used in the treatment of superficial bladder tumors in an attempt to facilitate the transurethral operative procedure. A total of 261 patients were included in this trial. ADM was instilled into the bladder at the following dosages: 1,000 μg/ml (30 mg ADM per 30 ml physiological saline), 1,600 μg/ml (50 mg ADM per 30 ml physiological saline), and 2,000 μg/ml (60 mg ADM per 30 ml physiological saline). The rate of effectiveness was 32%, 66%, and 60%, respectively. The incidence of side-effects was 29%, 20%, and 45%, respectively. The systemic uptake of the drug was small and the side-effects were pain an micturition, pollakiuria, and urgency. From the aspects of efficacy and toxicity, 1,600 μg/ml was found to be the optimal dosage.*

Introduction

Various therapies are available for low-grade, low-stage bladder cancer, but there is no consensus as to their use. Among these modalities, intravesical instillation of anticancer agents is considered significant, as adequate cytocidal effects can be obtained in a short time with no need for any special devices or techniques.

We selected Adriamycin (ADM) both because it is considered suitable for intravesical injection and because it has the following characteristics: (1) transitional cell carcinoma is sensitive to this drug; (2) its effect is dose-dependent; (3) its tissue affinity is strong; and (4) transfer of this drug into the blood is minimal.

On the other hand, the drug has shortcomings in terms of bladder mucosal irritation and cost. Therefore, careful selection of indications is required, in addition to consideration of the exact nature of the regimen.

We carried out experimental and clinical studies on intravesical ADM chemotherapy in bladder cancer. This report summarizes the results of these studies.

Reprint requests should be addressed to Y. Matsumura

Experimental study

Methods and results

The effect of ADM on the bladder mucosa, and transfer into blood, urine, and various organs were studied using normal adult dogs ranging in weight from 8.5 to 15 kg, with surgically altered urinary tracts as reported previously [11].

a Transfer into the blood, urine and tissue. ADM was instilled into the bladders of the animals at the following four different concentrations:

Group 1, 10 mg ADM/10 ml physiological saline (1,000 μg/ml);

Group 2, 20 mg ADM/10 ml physiological saline (2,000 μg/ml);

Group 3, 100 mg ADM/10 ml physiological saline (10,000 μg/ml);

Group 4, 20 mg ADM/10 ml physiological saline (2,000 μg/ml), preceded by a 100 mg/kg IV dose of cyclophosphamide given 48 h before surgical treatment (ureterostomy). Concentrations of ADM were measured by determining the intensity of fluorescence.

The transfer rate to the blood was very low, and the transfer of the drug into other organs from the bladder was similar to that observed following IV administration of the drug. Urinary levels of the drug were somewhat higher than blood levels. Concerning tissue levels of Adriamycin in the bladder, the level in mucosa is higher than that in the muscular layer. Levels of ADM in tissues other than bladder tissues became higher as the duration of exposure to the drug became longer.

b Effects on bladder mucosa. Almost no effects were recognized after 6 h of exposure of the mucosa to 1,000 μg/ml of ADM; however, after 2,000 μg/ml mild inflammation was noted, and after 10,000 μg/ml marked changes, such as exfoliation of the epithelium and submucosal edema, were observed.

c Autoradiography. Tumor tissue was obtained from bladder cancer patients admitted to the Urology Department of Okayama University. Materials were obtained under sterile conditions at surgery, cut into 1–2 mm^3 blocks, and cultured with stirring for 30 min to 2 h in culture medium to which ^{3}H-thymidine (^{3}H-TdR) or ^{3}H-ADM had been added. ^{3}H-TdR had a specific activity of 5 Ci/m*M* and was purchased from the Radiochemical Centre, Amersham through the Japan Isotope

Institute. ^{3}H-ADM was labeled with tritium gas and provided by the research laboratory of Farmitalia. The radiochemical purity was over 96% on paper chromatography and the specific activity was 27.479 μCi/mg. The culture medium was Eagle's MEM containing 10% fetal calf serum, and culture was performed at 37° C under 5% CO_2 and 95% air. After culture, the tumor tissue was fixed in 10% formalin; paraffin sections were made and used for the autoradiogram.

Autoradiograms were made by the dipping method, using Sakura NR-M2 emulsion at 4° C, with exposure for 2–3 weeks in a dark room. After exposure autoradiograms were developed using Rendol (Fuji Film) and H.E. staining for microscopy was performed.

In autoradiograms using surgical material nearly 100% uptake of ^{3}H-ADM was observed regardless of the grade of the tumor.

The autoradiogram was prepared using cultured cells derived from the rat transitional cell carcinoma. Uptake of ^{3}H-TdR was reduced markedly after treatment with ADM.

Clinical study

Patients and methods

Patients' characteristics. We have evaluated this therapy modality in a total of 261 patients since 1974, including those treated at affiliated hospitals. The patients' characteristics are summarized in Table 1. There were 211 male and 50 female patients; 162 primary cases and 99 cases of recurrence; 66 cases of single and 195 cases of multiple lesions; 221 low-grade cases and 40 high-grade cases.

Treatment schedule. After a pilot study [7] the clinical protocol shown in Fig. 1 was established.

ADM was dissolved in 30 ml physiological saline solution for instillation in the bladder with retention for at least 2 h, during which period the patient is forbidden to urinate and is required to change position at 15-min intervals. Six instillations are given, one a day for two 3-day periods, with an interval of 4 days. One week after the final dose, therapeutic effectiveness is determined cystoscopically. When the shrinkage in size of the tumor after therapy was more than 50% compared with its initial size the drug was considered to be effective. When the shrinkage was more than 90% it was judged as remarkably effective. When no shrinkage or less than 50% shrinkage was observed, it was categorized as ineffective. If effectiveness with no side-effects was recognized, additional instillations were given as appropriate [10].

Clinical results

Results according to ADM concentration

The results obtained in the three groups receiving 1,000 μg/ml, 1,600 μg/ml, and 2,000 μg/ml are shown in Table 2. Even though this was not a randomized study, there was a significant difference between the 1,000 μg/ml and 1,600 μg/ml groups ($P < 0.01$); however, there was no significant difference between the 1,600 μg/ml and 2,000 μg/ml groups.

On the other hand, no significant difference in toxicity was noted between the 1,000 μg/ml and 1,600 μg/ml groups, but significant differences were observed between the 1,600 μg/ml and 2,000 μg/ml groups ($P < 0.001$). In terms of maximal efficacy with low toxicity, 1,600 μg/ml was found to be the optimal dosage.

Rate of efficacy, single lesion versus multiple lesions

The rates of efficacy in 156 cases of single or multiple lesions treated by the Okayama University group were compared, since sufficient follow-up was possible in these patients. It was shown that the therapy was more effective in multiple lesion

Table 1. Patient characteristics

	No. of cases
Male	211
Female	50
Primary	162
Recurrent	99
Solitary	66
Multiple	195
Low grade	221
High grade	40
Total	261

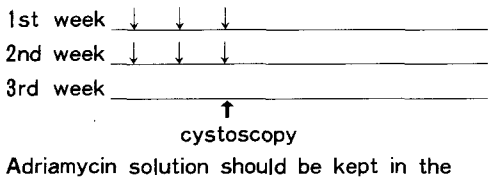

Fig. 1. Treatment schedule. ADM 1,600 μg/ml (30 ml) daily for two 3-day periods separated by an interval of 4 days.

Table 2. Rate of effectiveness and incidence of side effects

EFFECTIVE RATE and INCIDENCE of SIDE-EFFECTS	Remarkably effective		Effective	Ineffective	(side-effects)
1,000 μg/ml group $n = 28$	2 1	32%[a]	7 3	19 4	8 (29%)
1,600 μm/ml group $n = 94$	23 6	66%[a]	39 8	32 5	19 (20%)[b]
2,000 μg/ml group $n = 139$	33 14	60%	51 30	55 18	62 (45%)[b]
Total 261	58	59% (40%)	97	106 25%)	(34%)

[a] $P < 0.01$ [b] $P < 0.001$

Table 3. Rate of efficacy by multiplicity and grade

	Effective		Ineffective	Total
Solitary	16	41%[a]	18	34
Multiple	87	71%[a]	35	122
Low grade	87	67% N.S	39	126
High grade	16	53%	14	30
Total	103	66%	53	156

[a] $P < 0.02$

cases; that is, it was effective in 47% of the single lesion group, as against 71% of the multiple-lesion group ($P < 0.05$) (Table 3).

Rate of efficacy according to grades

There was no significant difference in the rate of efficacy according to grade (Table 3).

Multiple-lesion cases showing favorable clinical courses after ADM instillation

As shown in Table 3, intravesical instillation of the drug was considered most effective for patients with multiple lesions; therefore, cases showing favorable and unfavorable clinical courses are illustrated in Fig. 2.

In these cases, instillation of ADM following TUR was repeated to achieve tumor-free conditions with minimal damage to the bladder and preservation of bladder function.

Case 1: 75-year-old male, TCC, G2, papillary, multiple. ADM 1,600 μg/ml × 10, followed by TUR. He is alive 2 years postoperatively, and is disease-free.

Case 2: 56-year-old female, TCC, G2. ADM 1,600 μg/ml × 8, followed by TUR. She is alive 3 years postoperatively, and is disease-free.

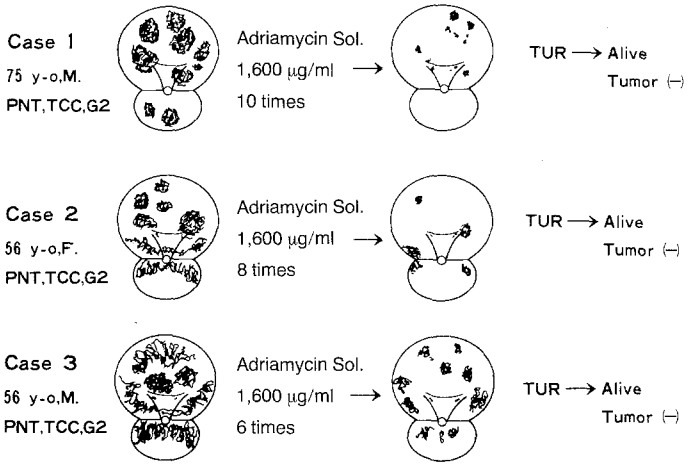

Fig. 2. Favorable clinical courses following instillations of ADM

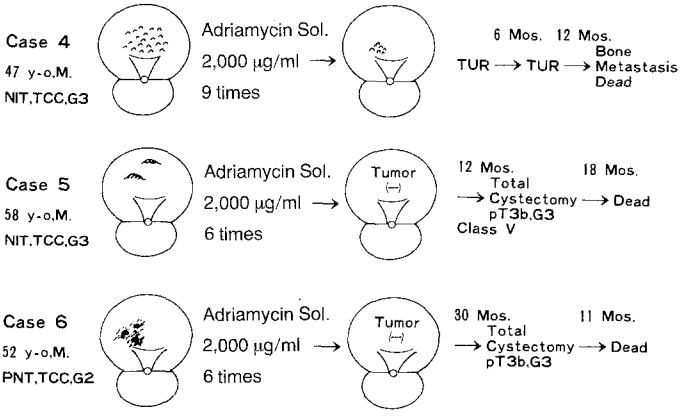

Fig. 3. Poor clinical courses following instillations of ADM

Case 3: 56-year-old male, TCC, G2. ADM 1,600 μg/ml × 15, followed by TUR. He is alive 13 months postoperatively, and is disease-free.

In the above cases, intravesical instillation of ADM resulted in regression and reduction of the tumor so that the damage caused to the bladder by TUR was limited to a minimum and there was loss of bladder capacity while tumor extirpation remained possible.

Patients with multiple tumors and poor courses

Three patients had high-grade, but limited lesions (Fig. 3). ADM instillation resulted in temporarily tumor-free or nearly tumor-free conditions cystoscopically, but these patients experienced tumor recurrence and invasion within such short periods of time that the possibility of radical treatment was lost, and all ended in early death.

Case 4: 47-year-old male, TCC, G3. ADM 2,000 μg/ml × 9, followed by TUR. Progressed to class V 6 months later, whereupon another TUR was performed. One year later, bone metastasis and death occurred.

Case 5: 58-year-old male, TCC, G3. ADM 2,000 μg/ml × 9. Total cystectomy at G3, pT3b was performed, but the patient died 2.5 years later.

Case 6: 52-year-old male, TCC, G2. ADM 2,000 μg/ml × 6, but progressed to class V 2.5 years later, total cystectomy at G3, pT3b, V(+) was performed at this time but the patient died 11 months later.

Discussion

Adriamycin is characterized by its concentration-dependency, its strong tissue affinity and its high molecular weight (579.97) compared with other chemotherapeutic agents that have been used previously, such as thio-TEPA and MMC. The authors therefore considered that ADM was suitable for administration in local instillations in cases of bladder tumors. O-B_1 invasion according to the Jewett-Marshall classification was considered an indication for this treatment modality. The aim of the procedure was not total eradication of the bladder tumors, but rather to facilitate transurethral resection, which we considered to be a significant aim.

As ADM is concentration-dependent, with rising concentrations increasingly marked effects can be anticipated, but since stimulation of the normal bladder mucosa and side-effects caused by penetration of the mucosa could be anticipated, dosage was started at a concentration of 1,000 μg/ml, first 20 mg in 20 ml physiological saline and 30 mg in 30 ml, then, in another groups, 1,600 μg/ml (50 mg ADM in 30 ml saline) and 2,000 μg/ml (60 mg in 30 ml). In view of the effects and side-effects observed, it was considered that 2,000 μg/ml was the highes concentration justifiable.

It was concluded that 1,600 μg/ml was the most suitable concentration. Also, in tumors recurring after surgical treatment administration of a concentration of 1,000 μg/ml failed to obtain effects in four of 10 cases, but an evaluation of effective or remarkably effective was recorded when these were subsequently treated with concentrations of 2,000 μg/ml. Of eight cases treated with 1,600 or 2,000 μg/ml in whom the results were initially evaluated as effective but who later developed recurrence, in only two was ADM judged as ineffective after repeated instillation, and it was therefore considered that resistance was not acquired.

The effectiveness of this agent was compared with that of other agents. Recent reports concerning the use of thio-TEPA for treatment of bladder tumors include those of Tomiyama (1972) [13] and Kano [5]. According to these and other reports [1, 2, 4, 16], complete disappearance was seen in 37 of 119 cases of noninvasive tumors (31.1%), partial remission in 47 (39,5%), and the preparation was ineffective in 35 (29.4%); effective rates of 60%–70% were demonstrated.

Reviewing the effectiveness of intravesical instillation of MMC on the basis of reports in the literature, it was reported to be effective in 75.8% of 115 cases of intravesical instillation in noninvasive tumor cases [3, 6, 8, 9, 12, 13].

On the basis of these figures it appears that MMC yielded superior results compared with thio-TEPA, but as the evaluation standards and the dosage and administration schedules of different investigators are extremely varied this is not necessarily the case.

As stated above, the object of the present clinical series was not total eradication of the tumor, and electrosurgery was planned after ADM treatment. Therefore no case of complete remission was observed. Instillations were limited to a maximum of six which is significantly fewer than in the above reports. Furthermore, the evaluation criteria employed were also stricter than in the above reports; the fact that in spite of these factors similar results were obtained with ADM to those recorded in the studies with thio-TEPA and MMC shows the good tumoricidal effects of ADM.

We examined the factors affecting the tumoricidal effects of intravesical instillation based on the effects obtained by ADM therapy.

First concerning the effects in terms of the site of the lesion, while no statistically significant difference based on the χ^2 method was recognized, effective rates of 80.0% and 87.5% were obtained in tumors located in the anterior wall and in the bladder neck. To the best of our knowledge, there has been no report of varying effectiveness according to the site of the lesion in the bladder and it is therefore impossible to compare ADM with other drugs with reference to this factor, but the high rate of effectiveness of ADM in tumors in the anterior wall and the bladder neck, which traditionally have been locations in which it is difficult to obtain effects, emphasizes the antitumor effects of ADM. In addition, the results suggested that such effects could be obtained simply by the instillation method employed by the authors. Furthermore, concerning the effectiveness of ADM in terms of the size of the tumor, considering tumors sized 2.5 × 2 cm as medium in size, effects were seen in 76.2% of large tumor cases, 68.8% of medium-size tumors, and 73.8% of smaller tumors. In the case of thio-TEPA, Jones and Swinney [14] reported effects in tumors up to 0.5 cm in size, while in the case of MMC, Ogawa [9] and Mishina et al. [6] suggested 1 cm as the largest size in which effects could be anticipated. Our results demonstrated that in the case of ADM no significant difference in effectiveness was seen in relation to the size of the tumor.

While the effectiveness in low-grade-malignancy tumors (67%) was slightly higher than that in high-grade-malignancy tumors (53%), there was no significant statistical difference. While it has been generally assumed since the reports of Veenema's group [14–16] that this method of treatment is ineffective in high-grade and high-stage cases, it can be said that when ADM was employed no significant difference was observed in relation to grade. Furthermore Veenema's group [14–16] suggested that in relation to histologic type, papillary type was an indication for this method; Mishina et al. [6] agreed with this contention in their report on treatment with MMC, but the results of the present study suggest that this method with ADM can be indicated even in high-grade low-stage disease.

Concerning the systemic side-effects of this treatment, there was only one case each of alopecia, decrease in platelet count, and exacerbation of ECG findings. In terms of local side-effects, irritation of the bladder was seen in 34% of these cases. In an investigation of thio-TEPA, Tomiyama [13] reported systemic side-effects of decreased WBC in 30 of 42 cases (71.2%), decreased platelet count in 16 of 21 cases (76.2%), pancytopenia in two of 56 cases (3.6%), and irritation of the bladder in 19 of 56 cases (34.0%). In Ogawa's study of intravesical instillation of MMC in 25 cases, systemic side-effects were slight: drug rash, decreased WBC, and a tendency to bleed were observed in one case each, decreased platelet count in two, and anemic tendency in four, while locally marked local inflammation of the bladder was seen in eight cases and mild inflammation in six.

Therefore the side-effects of ADM intravesical instillation treatment according to the schedule constructed by the authors cannot be said to be particularly more marked than those of thio-TEPA and MMC.

Conclusions

1. The therapeutic effects of intravesical instillation of ADM were favorable in papillary multiple tumors.

2. The therapeutic effectiveness is not influenced by the degree (grade) of histopathologic differentiation.

3. Sufficient care must be exercised in the treatment of infiltrating tumors, including TIS.

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