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Minimization of inflammation in the treatment of bladder tumors by intravesical instillation of Adriamycin

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Summary. *The purpose of this trial was to minimize local inflammation caused by intravesical instillation of antitumor agents, especially Adriamycin, in the treatment of bladder tumor. Tranexamic acid was chosen as the solvent vehicle for Adriamycin and IV bolus injection of an antiallergic drug, Stronger neo-minophagen C, was given at the time of each instillation.*

Of 81 cases scheduled for Adriamycin instillation therapy, nine cases (11.1%) dropped out due to severe bladder inflammation, while 17 other cases (21%) experienced local side-effects which were tolerated. Of 62 evaluable cases in whom more than eight instillations were performed, complete regression was observed in six cases (9.7%) and partial regression in 20 cases (32.3%).

Introduction

In 1948 Semple [11] obtained regression of bladder tumors by intravesical instillation of podophyllin in all of four cases of papilloma and papillary carcinoma. Since thio-TEPA instillation by Jones and Swinney [3], intravesical instillation therapy in the treatment of bladder cancer has become a common procedure (Table 1). Intravesical instillation of antitumor agents has also been shown to have prophylactic effects against the recurrence of bladder cancer [4, 7, 10, 12, 13, 15].

Adriamycin was first used for intravesical chemotherapy by Niijima et al. [6] in Japan. Reports by Ozaki [8] and Uyama and Kagawa [14] followed.

Although antitumor effects of Adriamycin were demonstrated, the side-effects, especially chemical cystitis, were considerable. The purpose of this study was to minimize local side-effects of Adriamycin instillation therapy.

Materials and methods

1. Selection of vehicle. Precipitation was observed when Adriamycin was dissolved in Stronger neo-minophagen C solution (SNMC, containing glycyrrhizin, cysteine and glycine; Minophagen Pharmaceutical Co. Tokyo, Japan) but not in tranexamic acid (t-AMCHA) solution. Therefore, t-AMCHA solution (1 ampoule 10 ml) diluted with twice its volume of distilled water was chosen as the solvent vehicle for Adriamycin.

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Table 1. Historical reviews of intravesical chemotherapy on bladder cancer

Preparation	Author(s)	Year of publication
Podophyllin	Semple	1948
Thio-TEPA	Jones & Swinney	1961
	Veenema et al.	1962
	Oravisto	1965
	Esquivel et al.	1965
	Wescott et al.	1966
	Abbassian & Wallace	1966
	Saito et al.	1968
	Tomiyama	1972
Mitomycin C	Shida et al.	1967
	Nishiura et al.	1968
	Tsai et al.	1968
	Ogawa	1969
5-Fluorouracil	Esquivel et al.	1965
Actinomycin D	Esquivel et al.	1965
Carboquone	Tsuchida & Kumagai	1976
	Obata et al.	1976
FT-207	Mishina et al.	1976
Neocazinostatin	Kobayashi	1979

2. Intravesical instillation in rats. Male Wistar rats weighing approximately 300 g were used, with five rats to each group. Group A animals received transurethral instillations of 1 ml 2,000 μg/ml of Adriamycin dissolved in diluted t-AMCHA as above twice a week. An IV bolus injection of 0.2 ml SNMC was given after each instillation. Group B animals received instillations of the same concentration of Adriamycin dissolved in sterilized distilled water in the same manner, but no SNMC injection was given. Instillation was performed either one, three, or five times. Animals were sacrificed the day after the last instillation.

3. Adriamycin instillation in patients with bladder tumors. Eighty-one cases of bladder tumor treated at the urology clinic of Kagoshima University Hospital and affiliated hospitals were evaluated. The clinical background is shown in Table 2. Adriamycin 30 mg dissolved in 20 ml of the diluted t-AMCHA solution was instilled twice a week for 5 weeks. An IV bolus injection of 20 ml SNMC was given at the same time as each instillation. Blood cell counts and laboratory data were checked and adverse effects were also checked with meticulous care.

Table 2. Clinical background of patients

Characteristic		No. of cases
Male		61
Female		20
Initial tumor		72
Recurrent tumor		9
Single tumor		55
Multiple tumors		26
Papillary tumor	Pedunculated	49 (60.5%)
	Non-pedunculated	20 (24.7%)
Non-papillary tumor	Pedunculated	2 (2.5%)
	Non-pedunculated	8 (9.9%)
Flat tumor		2 (2.5%)
		81

Table 3. Single intravesical instillation of ADM in rats

Group[a]	No.	WBC	OB	Histology
A	11	600		Almost normal epithelium
	12	2,100	+	Epithelial cells partly picnotic
	13	9,400	−	Epithelial exfoliation in some part
	14	1,000	+ +	Normal epithelium
	15	5,700	+	Some epithelial exfoliation
B	16	2,300	+ +	Severe exfoliation, eosin casts
	17	5,500	+ +	Epithelial exfoliation, casts
	18	6,600	+ + +	RBC in space, submucosal bleeding
	19	2,600		Epithelial vacuolation and exfoliation
	20	5,600	+	Epithelial vacuolation

[a] A: ADM 2,000 μg/ml in double-diluted t-AMCHA with bolus injection of 0.2 ml SNMC; B: ADM 2,000 μg/ml in distilled water

Results

1. Adriamycin instillation in rats

Group A animals receiving one instillation demonstrated minimal histopathological changes in the bladder mucosa, while group B animals showed minimum to moderate exfoliation and vacuolation of the epithelial cells and exudation in the bladder space (Table 3, Figs. 1 and 2). One animal in each group survived after three instillations. Bacterial cystitis was prominent in animals in both groups. Bladder mucosa in surviving animals showed multiform epithelial cells (Table 4, Figs. 3 and 4). Only one animal survived after five instillations, and it had severe cystitis (Fig. 5).

2. Antitumor effects and side-effects of Adriamycin instillation in patients

Of 81 patients scheduled for instillation therapy, 63 (77.8%) tolerated more than eight instillations. Eighteen were forced to discontinue because of side-effects and other reasons (Table 5). Of these 18 cases, nine (11.1%) dropped out due to severe bladder inflammation. Of 63 cases in which more than eight instillations were performed, 46 (73%) tolerated the therapy without bladder inflammation. The remaining 17 cases complained of local inflammation, but seven tolerated the inflammation after medication and 10 without medication (Table 6). As shown in Table 7, among 81 cases, bladder inflammation was observed in 26 (32.1%) and hematuria in 11 (13.6%) as local side-effects, as opposed to the general side-effects of fever in three (3.7%) and gastrointestinal disturbance, leucocytopenia, and rising transaminase in one case each.

Tumor disappearance was confirmed cystoscopically in a patient who received five instillations (Table 5). Of 63 cases in which more than eight instillations were performed total

Table 4. Intravesical instillation of ADM[a] in rats

Group[b]	No.	Results	WBC	Histology
A	21	Died after 2		Bacterial cystitis
	22	Died after 2		Bacterial cystitis
	23	Alive	8,200	Bacterial cystitis, cystic cystitis
	24	Died after 3		Bacterial cystitis
	25	Died after 3		Bacterial cystitis
B	26	Alive	500	Epithelial exfoliation, hemorrhagic
	27	Died after 3		Bacterial cystitis
	28	Died after 2		
	29	Died after 2		
	20	Died after 2		

[a] Three instillations, two per week

[b] A: ADM 2,000 μg/ml, t-AMCHA, SNMC; B: ADM 2,000 μg/ml in distilled water

Table 5. Reasons for discontinuation of ADM instillation

Instillations	Bladder inflammation	Others
2	1	
3	3	TUR 1
4	1	Total cystectomy 1 Pace maker 1
5	1	No visit 1, Tumor destroyed 1 Total cystectomy 1
6	1	
7	2	GI distress 1, leukopenia 1 GOT, GPT ↑ 1,
Total	9 (11.1%)	9 (11.1%)

Table 6. Course of intravesical ADM instillation

Instillation discontinued due to bladder inflammation	9 (11.1%)	
Instillation discontinued due to other side-effects	3 (3.7%)	
Instillation discontinued due to other reasons	6 (7.4%)	
Bladder inflammation, but tolerated with medication	7 (8.6%)	63 (77.8%)
Bladder inflammation, but tolerated without treatment	10 (12.3%)	
No bladder inflammation	46 (56.8%)	
Total	81	

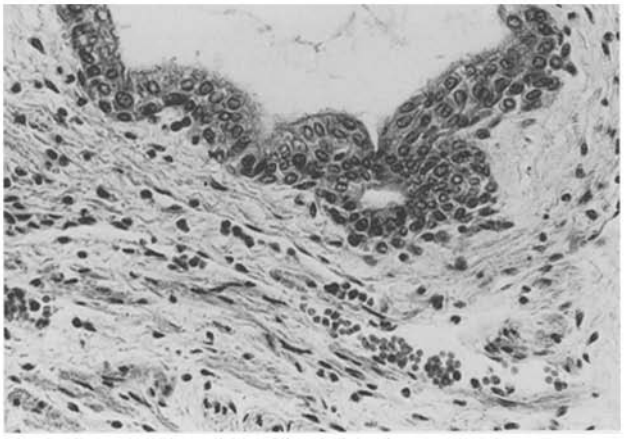

Fig. 1. Group A, no. 13 rat. One instillation of ADM 2,000 μg/ml dissolved in double-diluted t-AMCHA, with 0.2 ml SNMC by IV injection was given. No particular changes in the epithelial cells are seen. HE, ×100

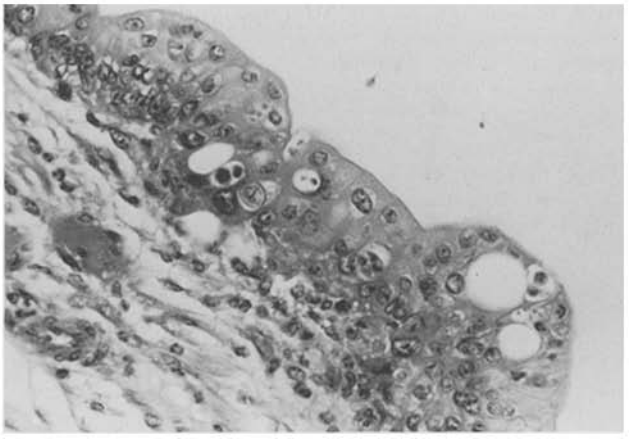

Fig. 3. Group A, no. 23 rat. Three instillations were performed. Thickness of the epithelial layer and vacuolation are prominent. HE, ×100

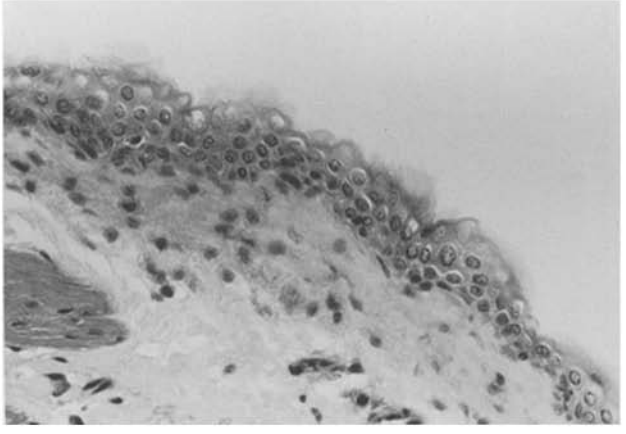

Fig. 2. Group B, no. 20 rat. One instillation of ADM 2,000 μg/ml dissolved in distilled water was given. Vacuolation and exudation are seen. HE, ×100

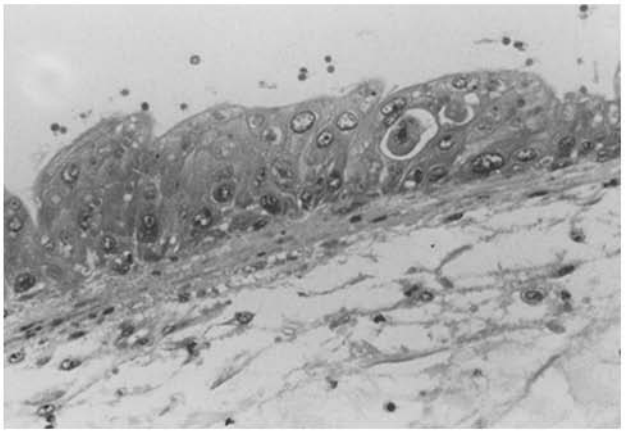

Fig. 4. Group B, no. 26 rat. Three instillations were given. Thickness of the epithelial layer, vacuolation and submucosal edema are observed. HE, ×100

regression was observed in six cases (9.5%) and partial regression in 20 cases (31.7%). The antitumor effects in these 26 of 62 cases (41.9%) are shown in Table 8. Complete tumor regression was observed in six of 38 cases (15.8%) with tumor size less than 1 cm, and antitumor effects (CR + PR) were evident in 18 cases (47.4%). Of 39 cases with papillary and pedunculated tumors, antitumor effects were observed in 14 cases (35.9%). On the other hand, nine (52.9%) of 17 cases with papillary and non-pedunculated tumors responded. Response was confirmed in one case of flat tumor and two cases of non-papillary tumors. Of 36 cases with low-grade tumors (G_0-G_1), more than 50% tumor regression was observed in 12 cases (33.3%), while two high-grade tumors (G_2-G_3) reduced in size. No response was noticed in cases of squamous cell carcinoma. Of 42 cases of solitary tumor, total regression was confirmed in four (9.5%) and partial response in 13 cases (30.8%), whereas antitumor effects were shown in nine of 20 cases (45.0%) with multiple tumors.

Leucocytopenia of less than 3,000/mm^3 was noticed in one case after seven instillations (Fig. 6); however, thrombocytopenia of less than 5×10^4/mm^3 was not observed in any of these cases (Fig. 7).

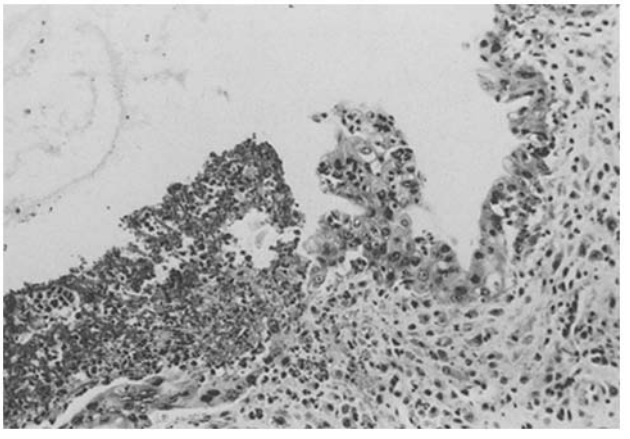

Fig. 5. Group A, no. 5 rat. Five instillations were given. Cystitis is seen. HE, ×50

Discussion

Adriamycin, an anthracycline antibiotic, was isolated from a mutant of *Streptomyces peucetius* in 1967 [1]. Middleman et al.

Table 7. Side-effects caused by ADM instillation

Local:	Bladder inflammation	26 (41.3%)
	Hematuria	11 (13.6%)
General:	Fever	3 (3.7%)
	Nausea and vomiting	1 (1.2%)
	Leukopenia (less than 3 000)	1 (1.2%)
	Rise of transaminase	1 (1.2%)

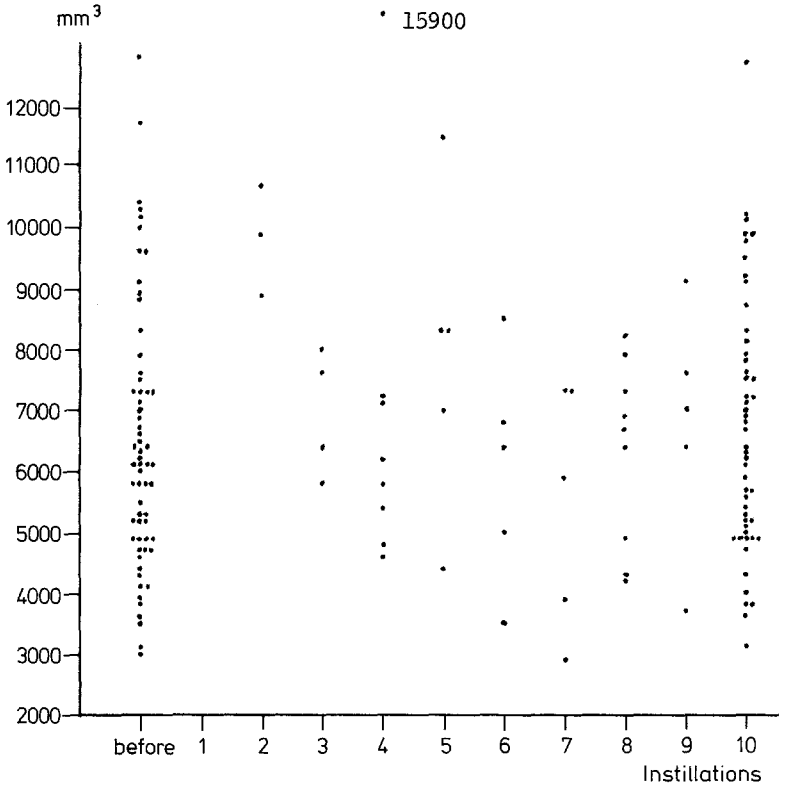

Fig. 6. Peripheral leukocytes following instillation

Table 8. Clinical evaluation

			Cases	Evaluated	CR[a]	PR[b]	No effect	Effective rate
No. of instillations	− 5		12	9	1	2	6	33.3%
	6,7		6	6	0	3	3	50.0%
	8−10		63	62	6	20	36	41.9%
	Total		81	77	7	25	45	41.6%
Tumor size	< 1 cm		39	38	6	12	20	47.4%
	1−3 cm		22	22	0	7	15	31.8%
	3 cm <		2	2	0	1	1	
	Total		63	62	6	20	36	41.9%
Tumor shape	Papillary	pedunculated	40	39	4	10	25	35.9%
		non-preduncul.	17	17	1	8	8	52.9%
	Non-papillary		5	5	0	2	3	40.0%
	Flat		1	1	1	0	0	
Grading	Low-grade		36	36	0	12	24	33.3%
	High-grade		5	5	0	2	3	40.0%
	Gx		20	19	6	6	7	63.2%
	SCC		2	2	0	0	2	
Numbers	Solitary		43	42	4	13	25	40.5%
	Multiple		20	20	2	7	11	45.0%

[a] CR (complete response), more than 90% tumor regression
[b] PR (partial response), more than 50% tumor regression

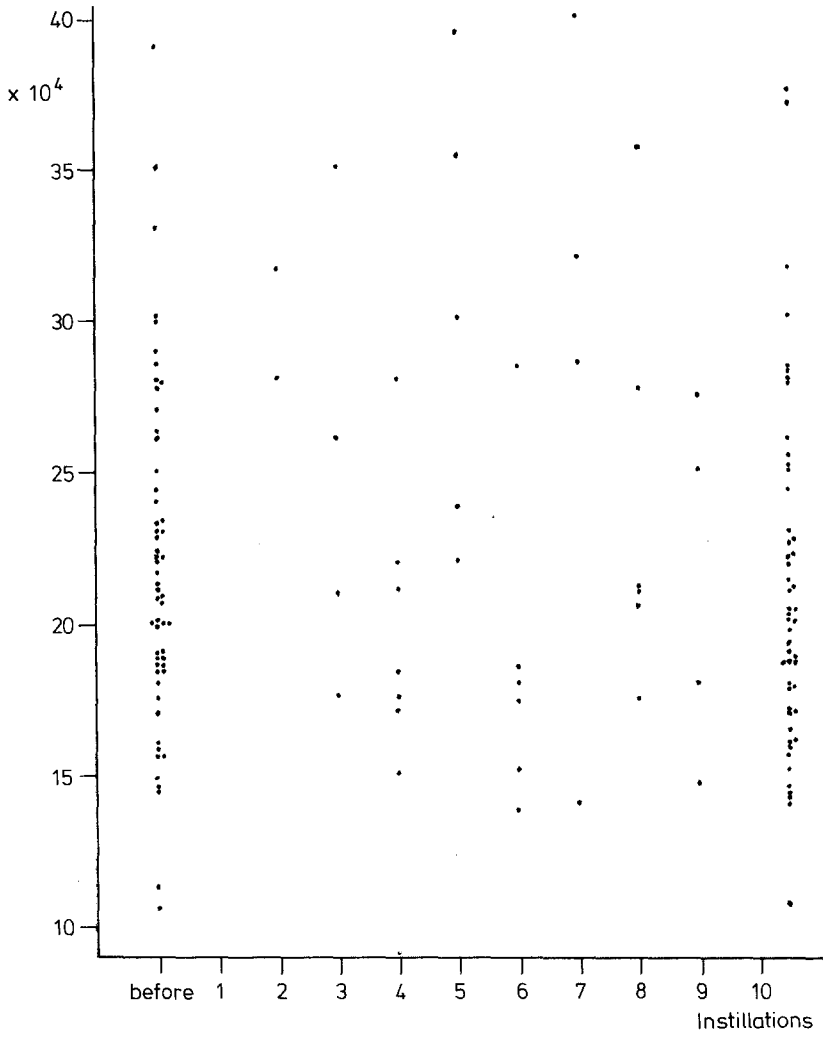

Fig. 7. Platelet counts following instillation

[5] first reported that four of seven cases with transitional cell carcinoma responded to parenteral use of Adramycin. Intravesical therapy with Adriamycin was first attempted by Niijima et al. [6] in Japan, and more than 50% tumor regression was observed in seven of 11 cases. Ozaki [8], reporting on results in 80 cases, stated that the response rate was 56% in nine cases (20 mg/20 ml or 30 mg/30 ml), 72% in 25 cases (50 mg/30 ml) and 74% in 46 cases (60 mg/30 ml). Uyama and Kagawa [14] also reported response rates of 33.3% with a concentration of 1,000 μg/ml (30 mg/30 ml) and 48.6% with 2,000 μg/ml (60 mg/30 ml) in the treatment of 52 cases with bladder tumor. Edsmyr et al. [2] used monthly instillation of 80 mg Adriamycin in 18 cases with superficial tumor, and reported that 50% were tumor-free at the end of treatment. These reports clearly indicated that efficacy of Adriamycin be concentration-dependent. In our series (30 mg/30 ml), of 62 evaluable patients who received more than eight instillations, 26 (42%) were responders.

The reasons for giving Adriamycin in intravesical instillation are related to its special characteristics; concentration-dependent cytocidal effects, affinity for tumor tissues and DNA, and little absorption through the bladder wall [6, 14].

The side-effects reported for parenterally administered Adriamycin are cardiac toxicity, alopecia, mucositis, and myelosuppression [5]. However, because of its high molecular weight (579.97), transference of instilled Adriamycin into the bloodstream through the bladder wall is low [8]. Substances with a molecular weight less than 200 are easily absorped through the bladder wall [3]. In fact, only one patient displayed leukocytopenia less than 3,000/mm^3, and no thrombocytopenia was noticed in our series. Thus the general side-effects caused by Adriamycin instillation were minimal in comparison with those of thio-TEPA [10, 12].

On the other hand, chemical cystitis was a major side-effect of intravesical instillation therapy of antitumor drugs. Adriamycin was not exceptional. Uyama and Kagawa [14] reported local inflammation in 50% of their cases. Neither further instillation nor transurethral resection of tumor can be scheduled when severe chemical cystitis is present. Anti-inflammatory and anti-allergic drugs such as t-AMCHA and SNMC have been evaluated as effective in preventing chemical cystitis in clinical trials. Corticosteroids have been used [8] but might enhance bacterial cystitis. In this series of 81 cases, 26 patients (32.1%) experienced bladder inflammation: nine (11.1%) of these dropped out, seven tolerated side-effects with medication, and 10 cases tolerated side-effects without medication. Thus local inflammation seemed to decrease with the use of t-AMCHA as a vehicle of Adriamycin and IV bolus injection of SNMC on each instillation.

It has been suggested that transurethral resection might play a role in the recurrence of bladder tumor [9]. As far as prevention of tumor recurrence is concerned, no other

treatment than intravesical instillation or glucarolactone (SLA) administration is available. Therefore, efforts should be made to minimize local inflammation due to intravesical topical chemotherapy.

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