

Development and clinical application of an AFC regimen (Adriamycin, Futraful, Cytosine arabinoside) for superficial bladder tumors

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Summary. Our AFC regimen was originally developed to treat superficial bladder tumors. It consists of a daily intravesical administration of 20 mg Adriamycin (ADM) and 200 mg Cytosine arabinoside (CA) dissolved in 20 ml of sterilized distilled water, simultaneously with a daily rectal suppository of 750 mg tegafur (Futraful) for a total of 20 applications.

Our study demonstrated the following characteristics of the AFC modality: (1) It is simple; (2) it is completed in 3 weeks, which is shorter than conventional bladder instillation therapy; (3) the effective rate is reasonable (70%); (4) no local side-effects were observed because the concentrations of ADM and CA were low; (5) interruption of therapy was unnecessary, because whatever general side-effects were caused, they disappeared within several days of completion of treatment.

Introduction

At the First Conference on Treatment of Urinary Tract Tumors with Adriamycin (ADM), we reported the results of ADM bladder instillation therapy [3]. ADM bladder instillation therapy was effective against superficial bladder tumors although it frequently caused severe local side-effects.

To minimize local side-effects without losing high effectiveness in ADM bladder instillation therapy, our AFC regimen was originally developed to treat superficial bladder tumors.

Materials and methods

AFC therapy was performed in 20 patients with superficial bladder tumors, who visited our clinic from September, 1981 to July 1982. The series was made up of 18 males and two females, ranging in age from 42 to 79 years of age, with an average of 64.6 years.

The histological type was transitional cell papilloma in 10 cases and transitional cell carcinoma in the other 10. All cases belonged to stage pTa (12 cases) or pT1 (8 cases) according to the UICC TNM classification [2] and to grades G₀ (10 cases), G₁ (7 cases) or G₂ (3 cases) according to the WHO classification [2] (Table 1).

The patients were requested to reduce fluid intake for about 12 h to maintain adequate drug concentration inside the bladder. The patients were laid on the examination table after they had voided urine, and 20 mg ADM and 200 mg CA

Table 1. Pathological characteristics of cases

Histologic type	Transitional cell papilloma	10 cases
	Transitional cell carcinoma	10 cases
Stage	Ta	12 cases
	T ₁	8 cases
Grade	G ₀	10 cases
	G ₁	7 cases
	G ₂	3 cases

Table 2. AFC regimen for superficial bladder tumors

Intravesical administration	ADM CA	20 mg 200 mg	} dissolved in 20 ml sterilized distilled water
Intrarectal administration	Tegafur	750 mg	
as a suppository			
Daily administration for a total of 20 applications			

dissolved in 20 ml of sterilized distilled water was instilled into the bladder through a catheter. The drug was held in the bladder for as long as possible, usually for about 3 h. This procedure was performed daily for 20 days in 20 patients with bladder tumors as one course of the therapy. Simultaneously daily rectal administration of 750 mg tegafur (Futraful) in suppository form was performed (Table 2).

Cystoscopic examination was performed before and after therapy to evaluate effectiveness. An evaluation of complete disappearance was recorded if the endoscopic findings showed no tumor, while a decrease of 50% or more in tumor size was considered a partial disappearance. A decrease of less than 50%, no change, or an increase in tumor size was categorized as no effect.

Bone marrow and liver function tests were performed before, during, and after treatment to check general side-effects.

Results

The tumors disappeared completely in six (30%) of the 20 cases of superficial bladder tumor treated with the AFC regimen and partially in eight (40%); no effect was seen in six (30%). Accordingly, the total effective rate was 70% (Table 3).

Table 3. Results of AFC therapy

No. of patients	Complete disappearance	Partial disappearance	No effect	Effective rate (%)
20	6 (30%)	8 (40%)	6 (30%)	70

There were no local side-effects in any case, because the concentration of ADM was half that used in the previous study. Two of the 20 patients suffered from general side-effects, such as loss of appetite in one and a slight elevation of serum GOT and GPT values in the other. Such general side-effects disappeared spontaneously several days after the end of AFC therapy.

Discussion

We reported the results of ADM bladder instillation therapy at the First Conference on Treatment of Urinary Tract Tumors with ADM [3].

With a daily dosage of 40 mg for 2 weeks, the tumors disappeared completely in eight (40%) of 20 cases of bladder tumors treated and partially in five (25%); no effect was seen in seven (35%). Accordingly, the total effective rate was 65%. Among the 16 cases with low-stage tumors, the tumors disappeared completely in eight cases, partially in five, and in three were unaffected. Accordingly, the total effective rate was 81% in this group.

Frequent and painful urination was encountered as a local side-effect in all cases, and interruption of the therapy was requested in two cases, but no evidence of general side-effects was observed.

Our study showed that although ADM bladder instillation therapy was effective for superficial bladder tumors it frequently caused severe local side-effects. Such frequent side-effects were thought to be caused by daily bladder instillation of a high concentration of ADM.

Ozaki [6] performed ADM bladder instillation therapy three times weekly and reported that local side-effects appeared in 17 cases of 46 (37%) treated with 2,000 µg/ml of ADM (60 mg ADM in 30 ml saline), and in two cases of nine (22%) treated with 1,000 µg/ml of ADM (20 or 30 mg of ADM in 20 or 30 ml saline). The frequency of local side-effects in Ozaki's study was lower than in our series.

To minimize local side-effects in ADM bladder instillation therapy, it was considered necessary not to give instillations daily and to lower the concentration of ADM. Our AFC regimen was thus developed to treat superficial bladder tumors because: (1) An effective rate of 33% with no local side-effects was obtained in CA bladder instillation therapy [1]; and (2) an effective rate of 35% with no local side-effects and only 10% transient general side-effects was obtained in patients with rectal tegafur suppositories [4, 5] (Table 4).

In the single instillation of ADM or CA, the concentration of ADM was 40 mg/20 ml and that of CA was 400 mg/20 ml. In our AFC therapy, the concentrations of ADM and CA were reduced to half these.

Complete disappearance of tumor was obtained in six (30%) of the 20 cases of superficial bladder tumors treated with the AFC regimen, partial disappearance in eight (40%), and no effect in six (30%). Accordingly, the total effective rate was 70%. Though simultaneous bladder instillation of both ADM and CA was performed every day, no local side-effects were observed in any case. In addition, the total effective rate was

Table 4. Results of intravesical administration of ADM and CA with intrarectal administration of Tegafur suppository

	No. of patients	Effective rate (%) ^a	Local side-effects (%)	General side-effects (%)
Adriamycin (ADM)	20	65 (81)	100	0
Cytosine arabinoside (CA)	30	33 (42)	0	0
Tegafur	20	35	0	10

^a Figures in parentheses give effective rate in superficial bladder tumors

Table 5. Effectiveness in relation to grade of malignancy

Grade	No. of patients	Complete disappearance	Partial disappearance	No effect	Effective rate (%)
G ₀	10	4	2	4	60
G ₁	7	2	4	1	86
G ₂	3	0	2	1	67

similar to that for instillation of higher doses of a single drug. Two of the 20 patients suffered from general side-effects, which might have been caused by the tegafur suppository. Since they appeared only during previous treatment with tegafur suppositories and not during previous ADM or CA bladder instillation therapies [4].

As regards the relationship between effectiveness and tumor malignancy, the tumors disappeared completely in four of the 10 cases of G₀ tumors and partially in two, indicating an effective rate of 60%. The tumors disappeared completely in two of the seven cases of G₁ tumors and partially in four, indicating an effective rate of 86%. The tumors disappeared completely in two of the three cases of G₂ tumors, indicating an effective rate of 67%. The difference in effect according to grade was not statistically significant (Table 5).

It is presumed from these clinical results that the AFC regimen might be useful for superficial bladder tumors. Although no local side-effects were encountered, attention must be paid to general side-effects.

References

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