Cancer Chemother Pharmacol (1992) 30 (Suppl): S 41–S 44

Cancer Chemotherapy and Pharmacology

Sequential instillation therapy with mitomycin C and Adriamycin for superficial bladder cancer*

Shigeo Isaka, Tatsuya Okano, Kohichi Abe, and Jun Shimazaki

Department of Urology, School of Medicine, Chiba University

Summary. Intravesical chemotherapy involving the sequential instillation of mitomycin C (MMC) and Adriamycin (ADM) was performed in 40 patients with superficial bladder cancer (pathological stages Ta and T1). In all, 20 mg MMC on day 1 and 30 mg ADM on day 2 were instilled into the bladder. This treatment was repeated weekly for 6 consecutive weeks and then monthly for 22 months in cases patients who did not experience serious side effects. A total of 20 patients were treated for multiple recurrences, and the efficacy was evaluated. In all, 9 subjects (45%) achieved a complete response and 6 (30%) showed a partial response, for an overall response rate of 75%. The other 20 patients, including 9 with primary multiple or high-grade tumors and 11 with recurrent tumors, received prophylactic instillation therapy after undergoing transurethral resection (TUR) of their lesions. Of the 9 primary cases, 3 recurred at 19, 8, and 3 months after TUR, respectively, whereas 6 showed no recurrence over a mean follow-up period of 14 months. Of the 11 recurrent cases, the 100-patient-month recurrence rate of 11.9 obtained prior to this treatment fell to 1.4 after the start of therapy. Chemical cystitis was observed in 20 of the 40 patients treated, but the symptoms were transient and tolerable.

Introduction

Many kinds of anticancer drugs have been reported to be effective in the chemoresection and chemoprophylaxis of superficial bladder cancer when they are given as instillations. However, the results obtained using single-agent therapy have been unsatisfactory, especially for high-risk patients such as those with multiple, recurrent, and high-grade tumors. In 1985, Fukui et al. [1] first reported on the use of instillation therapy consisting of a combination of mitomycin C (MMC) and Adriamycin (ADM; MA therapy), which was based on the synchronization theory, and they obtained excellent results in patients with carcinoma in situ (CIS) [2]. We started the present trial in 1986 to evaluate the therapeutic and prophylactic efficacies of MA therapy, and good results were obtained.

Patients and methods

The treatment schedule used in the present study is shown in Table 1. MMC and ADM were sequentially instilled into the bladder of patients with superficial bladder cancer through a catheter as follows: 20 mg MMC dissolved in 40 ml physiological saline was given on day 1, and 30 mg ADM dissolved in 30 ml physiological saline was instilled on day 2. This sequential instillation was called one unit of MA therapy. Patients were asked to retain the drug in the bladder for 2 h. The treatment was repeated once a week for 6 consecutive weeks, and its efficacy was evaluated after completion of the 6-week course. When a complete response was obtained, maintenance treatment consisting of one unit of MA therapy given once a month was started and continued for 22 months. If the tumors were not eradicated, a further 6-week course was added. In patients who showed progression, the MA therapy was stopped and switched to another modality of treatment. The schedule for prophylaxis was the same as that used in the CR group. Cystoscopy and washing cytology were performed every 3 months during the observation period.

This treatment was carried out in 40 patients, being given therapeutically to 20 subjects and as prophylaxis of recurrence to 20 others. Table 2 shows the characteristics of patients who received therapeutic instillations. Recurrent multiple and relatively small tumors of superficial bladder cancer were carefully selected for this arm of the trial. Responses were evaluated at 6–12 weeks after the start of therapy. A complete response (CR) was defined as the complete eradication of tumors as determined by cystoscopy and urinary cytology. A partial response (PR) involved a regression of >50% in the size or number of papillary tumors. No change (NC) represented a reduction of <50% in the size or number of tumors. Progressive disease (PD) was defined as an increase of >25% in the size of the tumor or the appearance of a new lesion.

The characteristics of patients who received prophylactic instillations are shown in Table 3. In all, 20 patients with superficial bladder cancer who were at high risk for disease recurrence were entered into this arm of the trial. Patients at high risk for recurrence were defined as those exhibiting recurrence, multiple lesions, or histological grade G3 tumors.

* Presented at the 4th International Conference on Treatment of Urinary Tract Tumors with Adriamycin/Farmorubicin, 16–17 November 1990, Osaka, Japan

Correspondence to: S. Isaka, Department of Urology, School of Medicine, Chiba University, 1-8-1, Inohana-cho, Chiba-city, Japan

Table 1. Treatment schedule used in the present study

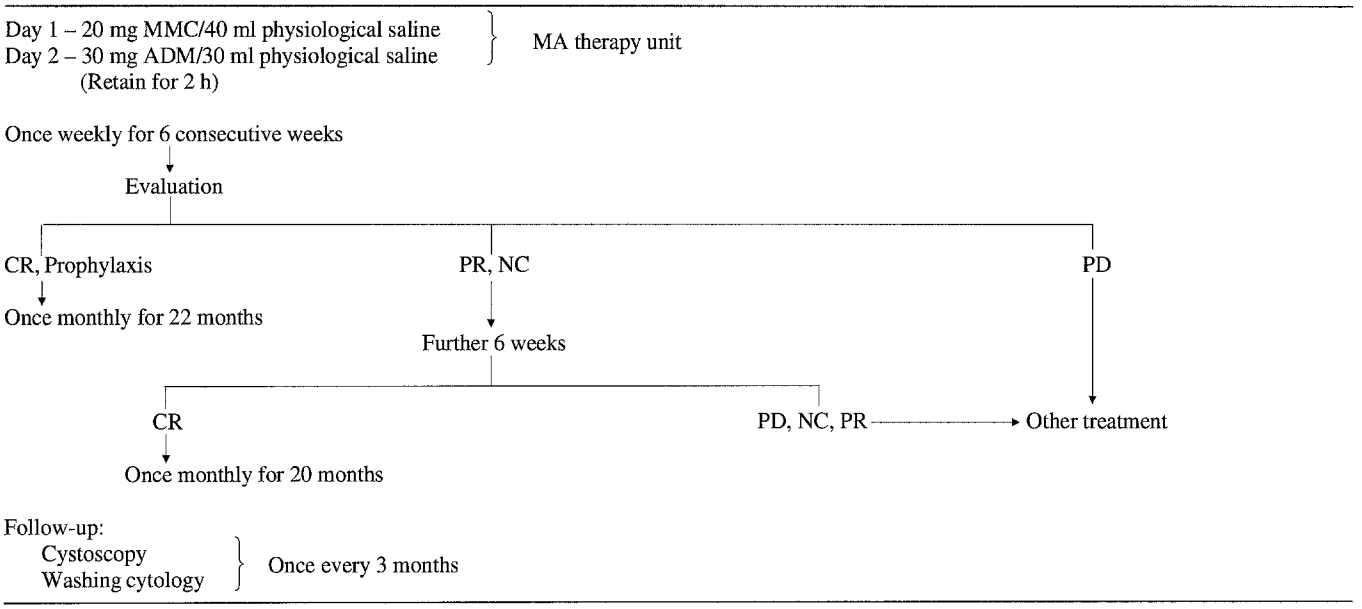

Table 2. Characteristics of 20 patients with recurrent multiple tumors who received therapeutic instillations

	Number of patients
Sex (M/F)	15/5
Age (years)	42–77 (mean, 64.3)
Histological grade (G1/G2/G3)	6/12/2
Pathological stage (Ta/T1)	16/4
Tumor size (<1 cm/≥1 cm)	18/2
Number of tumors (2–4/≥5)	7/13

Table 3. Characteristics of 20 patients who received prophylactic instillations beginning at 1–2 weeks after TUR

	Number of patients
Sex (M/F)	18/2
Age (years)	42–76 (mean, 62.1)
Primary/recurrent disease	9/11
Solitary/multiple tumors	4/16
Histological grade (G1/G2/G3)	4/12/4
Pathological stage (Ta/T1)	5/15
Tumor size (<1 cm/≥1 cm)	12/8

Table 4. Results of therapeutic instillation

Total number of units instilled	6–32 (mean, 14.7)	
Responses obtained:		
CR	9	CR+PR = 75%
PR	6	
NC	2	
PD	3	
Duration of CR (months)	3–32 (mean, 20.4)	
Total number of units required to achieve:		
CR	5–15 (mean, 9)	
PR	6–10 (mean, 6.7)	

Table 5. Correlation between tumor characteristics and responses

Characteristics	Responses			
	CR	PR	NC	PD
Histological grade:				
G1	4	2	–	–
G2	4	4	2	2
G3	1	–	–	1
Pathological stage:				
Ta	8	5	1	2
T1	1	1	1	1
Tumor size:				
<1 cm	8	5	1	2
≥1 cm	1	1	–	–
Number of tumors:				
2–4	6	–	1	–
≥5	3	6	1	3

The MA therapy was started at 1 or 2 weeks after TUR. The prophylactic effect was evaluated by comparison of the 100-patient-month recurrence rates obtained before and after the start of therapy.

Results

Table 4 shows the results of therapeutic instillation. Of the 20 patients thusly treated, 45% achieved a CR and 30% showed a PR, for an overall efficacy rate of 75%. The CR lasted for 3–32 months (mean, 20.4 months). In all, 5–15 MA therapy units were needed to achieve a CR and 6–10 units were required to obtain a PR. Cases of PD were managed using other treatment modalities such as instillation of bacille Calmette-Guérin (BCG), TUR, and total cystectomy.

Table 5 shows the correlation between tumor characteristics and responses. Patients presenting with a lower

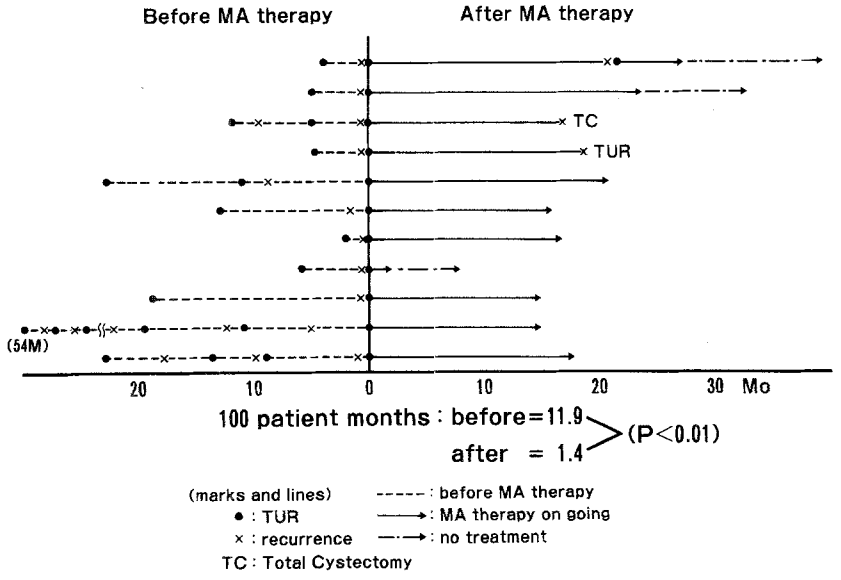

Fig. 1. Results of prophylactic instillation (11 recurrent cases). *Mo*, Months

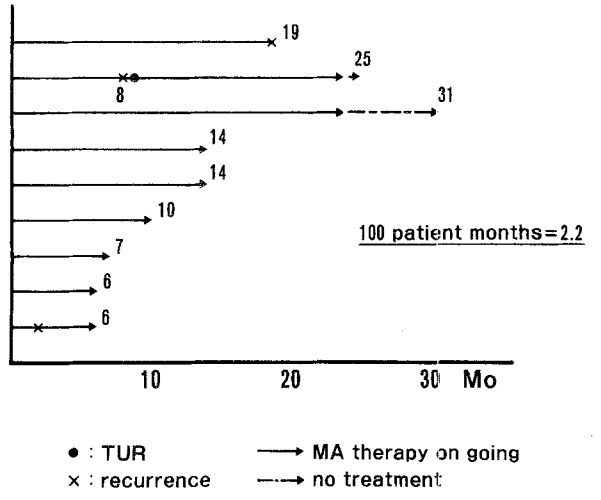

Fig. 2. Results of prophylactic instillation (9 primary cases). *Mo*, Months

histological grade and a smaller number of tumors responded better than did those with a higher grade and a larger number of lesions. As for the pathological stage and size of the tumors, most were classified as Ta and measured <1 cm in diameter; therefore, no correlation could be found.

The results obtained in the 11 recurrent cases treated prophylactically are shown in Fig. 1. In all, 19 cases recurred within a total of 158 months prior to the beginning of MA therapy, whereas only 3 recurred within a total of 220 months after the start of MA therapy. The 100-patient-month recurrence rate was 11.9 prior to this treatment and decreased to 1.4 after the beginning of therapy; this difference was statistically significant.

Figure 2 shows the post-TUR courses of nine patients with primary tumors who received prophylactic MA therapy; they constituted the high-risk group, bearing high-grade or multiple tumors. Three patients developed disease recurrence at 19, 8, and 3 months after TUR, respectively, but six showed no recurrence over the mean follow-up period of 14 months. The 100-patient-month recurrence rate was 2.2, and this value was similar to that obtained for the 11 recurrent cases following MA therapy. Thus, tumor recurrence might be suppressed by this therapy in cases of primary disease, although no control group was used in the present study.

Table 6. Toxicity of MA therapy

Side effect	Number of patients
Micturitional pain	13 (32.5%)
Pollakisuria	13 (32.5%)
Hematuria	6 (15.0%)
Epididymitis	1 (2.5%)
Prostatitis	1 (2.5%)
None	20 (50.0%)

Table 6 shows the side effects encountered during MA therapy. Although no systemic toxicity was observed, half of the patients experienced some side effects. Symptoms of bladder irritation, such as micturitional pain, pollakisuria, and hematuria, were the most common side effects. One subject developed epididymitis and another had prostatitis. Three patients had to discontinue the instillation therapy because of the side effects; however, in all cases the symptoms improved soon after discontinuation of the treatment.

Discussion

A high recurrence rate and a malignant progression rate of about 10% are the major problems involved in the treatment of superficial bladder cancer. Many kinds of prophylactic treatment have been used in attempts to reduce the recurrence rate and to prevent malignant progression. Postoperative prophylactic instillation of anticancer drugs has recently become the most popular method. Thiotepa, MMC, and ADM have been used widely in Japan, and their prophylactic effects have been demonstrated in a multicenter, prospective, randomized study organized by the

Japanese Urological Cancer Research Group for Adriamycin [3]. We have also reported that long-term instillation of ADM is more effective than a short course [4]. However, the prophylactic effect obtained using single-agent treatment has been unsatisfactory, especially for the high-risk group of patients with multiple, high-grade, and recurrent tumors. Prophylactic instillation also has disadvantages such as the need for frequent visits, pain resulting from catheterization, bladder irritability, and high cost. Therefore, Soloway et al. [5] have recommended that the decision as to whether or not a patient should undergo prophylactic therapy should be made by the patient if the tumor is of a low histological grade and is pathologically classified as Ta. However, these authors have also noted that more effective prophylactic treatment is needed for high-grade cancers.

Therapeutic instillation is preferable for the objective evaluation of the effects of a newly developed treatment modality. The CR rates have been reported to be 26% for thiotepa, 39% for MMC [6], and 31% for ADM [7] used as single agents. In 1985, Fukui et al. [1] first reported using sequential instillation therapy with MMC and ADM. This treatment was based on the theory that MMC blocks the cell cycle at the G2 phase, resulting in enhancement of the action of ADM. The CR rate reported by Fukui et al. [1] was 56%, and this value seemed to be higher than that obtained using single-agent therapy. Thereafter, these investigators tested MA therapy in patients with CIS of the bladder and reported excellent efficacy that was comparable with that obtained following BCG instillation [2].

Although the present treatment schedule was almost same as that used by Fukui et al. [2], we modified the dose of ADM (from 40 mg/40 ml physiological saline to 30 mg/30 ml physiological saline) and extended the duration of one course (from 5 weeks to 6 weeks) in an attempt to reduce the adverse effects. The CR rate and the incidence of side effects were both reduced slightly by these modifications. Both the therapeutic effect and the adverse effects seemed to correlate with the ADM dose. We concluded that the efficacy of MA therapy lay midway between that of conventional single-agent therapy and that of BCG therapy. We think that small, multiple, recurrent tumors are good targets for therapeutic MA therapy and that patients at high-risk for recurrence are suitable candidates for prophylactic MA therapy.

References

1. Fukui I, Sekine H, Yamada T, Kihara K (1985) Sequential intravesical chemotherapy with mitomycin C and Adriamycin for superficial bladder tumor (preliminary report). Acta Urol Jpn 31: 623
2. Fukui I, Sekine H, Kihara K, Yamada T, Kawai T, Washizuka M, Ishiwata D, Oka K, Hosoda K, Ikegami S, Sakai K, Ohwada F, Negishi T, Suzuki S, Tohma T, Oshima H (1987) Sequential instillation therapy with mitomycin C and Adriamycin for superficial bladder tumor. Cancer Chemother Pharmacol 20 [Suppl]: S52
3. Niijima T, Koiso K, Akaza H (1983) Randomized clinical trial on chemoprophylaxis of recurrence in cases of superficial bladder cancer. Cancer Chemother Pharmacol 11 [Suppl]: S79
4. Isaka S, Okano T, Shimazaki J, Igarashi T, Murakami S, Higa T, Ishikawa T, Zama S, Kataumi S, Kataumi Z, Kitamura Y (1987) Prophylaxis of superficial bladder cancer with instillation of Adriamycin or mitomycin C. Cancer Chemother Pharmacol 20 [Suppl]: S77
5. Soloway MS, Jordan AM, Murphy WM (1989) Rationale for intravesical chemotherapy in the treatment and prophylaxis of superficial transitional cell carcinoma: In: EORTC Genitourinary Group (eds) Monograph 6: BCG in superficial bladder cancer. Alan R. Liss, New York, p 215
6. Heney NM (1985) First line chemotherapy of superficial bladder cancer: mitomycin C versus thiotepa. Urology 26: 27
7. Torti FM (1987) Approaches to the treatment of bladder cancer at Stanford. Cancer Chemother Pharmacol 20 [Suppl]: S63