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Sequential instillation therapy with mitomycin C and adriamycin for superficial bladder tumors

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Summary. From October 1983 to September 1985, 84 patients with superficial bladder tumor (T_a, T_1, T_{is}) were treated with sequential instillation of mitomycin C (MMC) and adriamycin (ADM). Doses of 20 mg MMC on day 1 and 40 mg ADM on day 2 were instilled into the bladder and retained for at least 2 h; this was repeated once a week for 5 consecutive weeks. Patients who achieved complete response (CR), were randomized and underwent prophylactic treatment taking the form of either intermittent instillation of MMC or daily oral administration of 5-fluorouracil. Of 79 evaluable patients, 72 (91%) had received prior treatment for superficial bladder tumors, 69 (87%) had high-grade tumors, and 18 (23%) had non-papillary T_{is}. The overall response rate was 68%, made up of CR in 43 patients (54%) and partial response (PR) in 11 (14%). Patients with either five or more tumors or tumors larger than 1 cm showed a significantly lower response rate than those with fewer than five tumors and tumors smaller than 1 cm, respectively. There was no correlation between tumor growth pattern, tumor grade and response rate, though non-papillary T_{is} appeared to respond better than papillary tumors. A history of prior instillation therapy or of toxicity to this treatment had no significant influence on the response rate. Although no systemic toxicity was observed, 62 patients (74%) experienced cystitis and the treatment had to be discontinued within 4 weeks in 13 of 33 cases with severe symptoms. The preliminary conclusion of prophylactic treatment was that intermittent instillation of MMC was superior to 5-FU medication in reducing the recurrence rate for at least 2 years after the treatment.

Introduction

TUR is unquestionably the treatment of choice in the management of superficial bladder cancer. Other treatment methods, however, should be considered both for patients with carcinoma in situ (CIS) [5] that is not detected on cystoscopic examination and for those with frequently recurring papillary tumor after TUR, because they are at high risk of subsequently developing invasive cancer [2]. Total cystectomy can resolve this problem, but bladder salvage may be desirable when a patient has superficial tumors. A pilot study [4] of therapeutic instillation using mitomycin C (MMC) and adriamycin (ADM) in combination obtained a favorable outcome in 19 patients with recurrent papillary tumors or CIS, leading to a multicenter study of this intravesical combination chemotherapy. The present paper reports the immediate ablative effect of the combination therapy on bladder tumors and the preliminary results of a follow-up study conducted in patients who achieved complete response (CR) and took part in a randomized trial of prophylactic treatment.

Materials and methods

Mitomycin C (MMC) and adriamycin (ADM) were sequentially instilled into the empty bladder through a catheter (10–12 F): 20 mg MMC on day 1 and 40 mg ADM on day 2. Each agent was dissolved in 20 ml normal saline. Patients were asked to refrain from ingesting fluids for several hours prior to the instillation and to retain the drug in the bladder for more than 2 h. The treatment was repeated once a week for 5 consecutive weeks. When patients suffered from severe bladder irritation the treatment was withheld for 1–2 weeks or discontinued. The response was assessed 1–2 weeks after the last treatment by both cystoscopic and cytologic examinations. Response criteria were as follows. Complete response (CR) means complete disappearance of all cystoscopically visible tumors with normalization of urinary cytology. In CIS patients negative histologic findings in multiple mucosal biopsies were also required for CR to be recorded. Complete disappearance without cytologic improvement or more than 50% regression in the size of papillary tumors was defined as a partial response (PR). In CIS patients, marked improvement of both cytologic and cystoscopic findings without histologic complete remission of CIS or severe atypia was

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defined as PR. No change (NC) represents regression of papillary tumors by less than 50% or no marked cytologic improvement in CIS.

Patients who achieved CR were entered into the randomized study of prophylactic treatment: for at least 1 year, group A underwent MMC instillation (20 mg/20 ml saline) every 2–4 weeks and group B received oral administration of 5-fluorouracil (5-FU) 200 mg/day. The patients who achieved PR underwent either an additional course of MA (MMC + ADM) therapy or TUR, at the discretion of the physician of each patient.

Eighty-four patients in whom superficial bladder tumors were diagnosed from October 1983 to September 1985 at participating centers were entered into the study. Five patients were excluded because of either early (within 2 weeks) discontinuation of treatment (2 patients), no assessment of response [2], or lack of histologic diagnosis before initiation of treatment [1]. Thus, 79 patients were evaluable for response to treatment, and their characteristics are shown in Table 1. There were 58 men and 21 women. The age range was 39–86 years, with a mean of 66. Recurrent tumors were present in 72 of the 79 patients (90%). The number of recurrences before the treatment ranged from 1 to 14, with a mean of 3.74, and the mean recurrence rate was 0.97 per patient per year. There were 61 patients with papillary tumors and 18 with non-papillary CIS. The majority of patients (87%) had grade 2 or grade 3 tumors. Among the patients with papillary tumors, 70% had multiple tumors and 87% had tumors smaller than 1 cm.

Results

Among 79 evaluable patients, the overall response rate was 68%: CR was achieved by 43 patients (54%) and PR, by 11 (14%) (Table 2).

Table 3 shows the relationship between tumor characteristics and response. Tumor growth pattern and tumor anaplasia (grade) did not correlate significantly with the response rate, though non-papillary CIS appeared to respond better than papillary tumors. In contrast, patients with five or more tumors had a significantly lower response rate than those with a single tumor or two to four tumors, and patients with tumors larger than 1 cm also had a significantly lower response rate than those with tumors smaller than 1 cm.

As shown in Table 4, prior instillation therapy did not significantly affect the rate of response to the present treatment, though patients who had not received prior instillation therapy had a tendency to have slightly better responses than those who had.

Although no systemic toxicity was observed, 74% of 84 patients experienced some bladder irritation (Table 5). The symptoms were severe in 33 cases, resulting in discontinuation of the treatment in 13: within 2 weeks in 2 patients, within 3 weeks in 4, and within 4 weeks in 7. However, in all patients but 1, the symptoms improved within 4 weeks after the discontinuation of treatment. One patient who experienced vomiting in addition to severe bladder irritation developed an irreversibly contracted bladder with a capacity of less than 100 ml. In contrast, cystitis symptoms recognized before the initiation of MA therapy markedly improved during the treatment in 7 of 9 CIS patients, along with improvement of both cystoscopic and cytologic findings. Eight patients who had the dose of ADM reduced

Table 1. Characteristics of the 79 evaluable patients

Male : female	58 : 21
Age	39–86 (mean 66)
Untreated : recurrent	7 : 72[a]
Papillary : non-papillary	61 : 18
$G_1 : G_2 : G_3$	10 : 48 : 21
Number of papillary tumors	
1 : 2–4 : ≧5 : X	18 : 29 : 13 : 1
Size of papillary tumors	
< 1 cm : 1–3 cm : X	52 : 7 : 1

[a] Number of recurrences, 1–14 (mean 3.74); recurrence rate, 0.97/patient/year
X, Hardly recognizable because of associated low papillary tumor

Table 2. Overall response

n	CR (%)	PR (%)	NC (%)
79	43 (54)	11 (14)	25 (32)

Table 3. Tumor characteristics and response

	n	CR (%)	PR (%)	NC (%)
A) Tumor growth pattern				
Papillary	61	32 (52)	8 (13)	21 (34)
Non-papillary	18	11 (61)	3 (17)	4 (22)
			$P > 0.05$	
B) Tumor grade				
1	10	6 (60)	1 (10)	3 (30)
2	48	26 (54)	7 (15)	15 (31)
3	21	11 (52)	3 (14)	7 (33)
			$P > 0.05$	
C) Number of tumors				
1	18	11 (61)	2 (11)	5 (28)
2–4	29	18 (62)	3 (10)	8 (28)
≧5	13	2 (15)	3 (23)	8 (62)
		1 vs ≧5, 2–4 vs ≧5 : $P < 0.05$		
D) Size of tumors				
< 1 cm	52	31 (60)	6 (12)	15 (29)
1–3 cm	7	0 (0)	2 (29)	5 (71)
			$P < 0.05$	

Table 4. Relations of prior instillation to response

Instillation	*n*	CR (%)	PR (%)	NC (%)
None	34	22 (65)	4 (12)	8 (24)
MMC	24	11 (46)	4 (17)	9 (38)
ADM	9	4 (44)	2 (22)	3 (33)
MMC + ADM	12	6 (50)	1 (8)	5 (42)
			$P > 0.05$	

Table 5. Toxicity

Side effects	*n* (%)	
Bladder irritability		
−	22 (26)	
+	29 (35)	62
++	33 (39)	(74%)
Vomiting	1 (1)	

from 40 mg to 20 mg during the treatment because of the early complication of bladder irritation had a poor response.

Table 6 shows the relationship between the degree of cystitis symptoms and the response rate. Though also not significant, the more severe the irritation, the better response appeared to be achieved.

Table 7 shows the preliminary follow-up results following MA therapy. Although the patients who achieved CR were entered into the randomized study of prophylactic treatment with either MMC instillation or 5-FU oral medication, 10 of 43 patients who had achieved CR did not undergo prophylactic treatment either because they refused themselves or because their physicians advised against it.

There were more cases with subsequent tumor in the 5-FU group than in the MMC group. One patient in the MMC, 5-FU, PR and NC groups subsequently developed invasive cancer. The number of patients who later underwent total cystectomy was greater in the NC group than in the other groups. Although none of the CR group died of transitional cell carcinoma (TCC), one patient in each of the PR and NC groups died of TCC.

Discussion

Thio-TEPA, ADM and MMC have been widely used for the intravesical chemotherapy of superficial bladder tumors [3, 6–15]. However, the effectiveness still remains unsatisfactory, regardless of whether the aim is therapeutic or prophylactic. This may be due in part to the fact that most clinical trials are concerned with single-drug therapies. Therefore, in the present study we applied the principle mostly followed in systemic chemotherapy, i. e., use of a combination of drugs, in topical chemotherapy. Since thio-TEPA was rejected because of the generalized toxicity

Table 6. Relation of side effects (bladder irritation) to response

Irritation	*n*	CR (%)	PR (%)	NC (%)	Drop-out
–	22	8 (36)	3 (14)	9 (41)	2 (9)
+	29	16 (55)	4 (14)	8 (28)	1 (3)
++	33	19 (58)	4 (12)	8 (24)	2 (6)

$P > 0.05$

Table 7. Follow-up results

	CR			PR	NC
	MMC	5FU	None		
Number of patients	15	18	10	11	25
Average follow-up periods (months) (range)	22 (10–32)	18 (5–31)	19 (9–28)	15 (4–26)	19 (7–32)
Cases with subsequent tumors	4 (27%)	10 (56%)	3 (30%)	/	/
stage ≧ T_2	1 (7%)	1 (6%)	0	1 (9%)	1 (4%)
Cases undergoing cystectomy	1 (7%)	0	0	1 (9%)	5 (20%)
Fatalities due to TCC	0	0	0	1	1
Other cause	0	0	0	0	1

	influence on cell cycle traverse	most sensitive phase
MMC	G2 block prolongation of S	G1
ADM	G2 ---> M	S S/G2

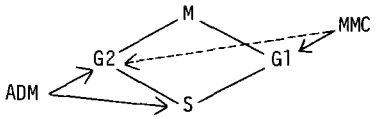

Fig. 1. Effects of MMC and ADM on cell cycle progression

[8] resulting from its high absorption through the bladder wall, MMC and ADM were used for the present combination trial.

MMC and ADM have different mechanisms of cytocidal or cytostatic effects [1]. MMC, an alkylating agent, appears to be not only cytotoxic, mainly in the G_1 phase, but also to inhibit the cell cycle transition at the phase of S-G_2 threshold, leading to an increase of cells in the S-G_2 phase following treatment with MMC (Fig. 1). On the other hand, ADM is known to be highly cytotoxic to the cells in these phases [1]. Therefore, sequential administration, with ADM following MMC, was expected to yield higher clinical effectiveness than simultaneous administration of the two drugs, which were thus administered sequentially in the present trial.

Previous studies show that MMC has a CR rate of 37%–77% in the treatment of superficial bladder tumors. CR rates in Japanese trials are below 50% even when 20 or more doses of MMC have been instilled (Table 8). On the other hand, ADM has a CR rate of over 50% in Europe, as opposed to only 28% in Japan (Table 9). This is probably due to the difference in the doses of ADM administered. The high doses of 80–100 mg generally used in Europe seem to cause intolerable toxic side effects in Japanese subjects.

Table 8. Previous results of therapeutic instillation of MMC

Dose of MMC	*n*	CR (%)	Reference
20 mg 3/week × 7	50	22 (44)	[10]
20 mg daily × 20	27	10 (37)	[15]
40 mg daily × 20	20	10 (50)	
20 mg 3/week × 7	23	17 (77)	[6]
30–40 mg weekly × 8	70	27 (39)	[14]

Table 9. Previous results of therapeutic instillation of ADM

Dose of ADM	*n*	CR (%)	Reference
20–60 mg 3/week × 2	80 (T_a-T_2)	22 (28)[a]	[12]
80 mg monthly × 1–26	30 (CIS) 23 (T_1)	20 (67) 10 (43)	[3]
40 or 80 mg biweekly or monthly for 1 year	23 (T_1) 15 (CIS)	10 (43) 10 (67)	[7]
100 mg weekly × 16	44 (T_a)	22 (50)	[9]

[a] More than 90% regression

The present results achieved with MA therapy seem to be clinically acceptable. Because more than half the patients achieved CR with only 5 weeks' treatment, the total doses of MMC and ADM used in the present study were low and the majority of patients studied had recurrent and high-grade tumors that had been refractory to previous treatments. Therefore, the present treatment seems to be suitable for patients with superficial tumors that cannot be controlled by means of TUR or a single drug instillation. Maintenance therapy, however, seems to be mandatory to prevent recurrence, and this point needs further investigation.

On the other hand, intravesical combination chemotherapy with MMC and ADM caused bladder irritation in more than two-thirds of our patients, which was so serious in 30% of patients that the treatment was either interrupted for a period or completely discontinued. It is essential to take care to avoid contracted bladder.

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