Cancer Chemother Pharmacol (1992) 30 (Suppl): S 37–S 40

Cancer Chemotherapy and Pharmacology

Intravesical combination chemotherapy with mitomycin C and doxorubicin for superficial bladder cancer: a randomized trial of maintenance versus no maintenance following a complete response*

Iwao Fukui[1], Kazunori Kihara[1], Hideaki Sekine[2], Yuichi Tachibana[3], Tsuneo Kawai[3], Daisuke Ishiwata[4], and Hiroyuki Oshima[1]

[1] Department of Urology, Tokyo Medical and Dental University, Japan
[2] Department of Urology, Teikyo Mizonokuchi Hospital, Japan
[3] Department of Urology, Cancer Institute Hospital, Japan
[4] Department of Urology, Showa General Hospital, Japan

Summary. Between November 1986 and April 1989, 101 patients with superficial bladder cancer were treated with intravesical instillations of mitomycin C on day 1 and doxorubicin on day 2 of each week for 5 consecutive weeks. Of 61 complete responders, 23 patients with carcinoma in situ and 28 with papillary cancer were randomly assigned to a non-maintenance group or to a group receiving maintenance therapy consisting of monthly instillations of the same drugs for 12 months. The 2-year non-recurrence rate calculated for patients with carcinoma in situ was significantly better in the maintenance group than in the non-maintenance group. A similar tendency was observed for patients with papillary cancer, although the difference was not significant. Side effects were considerable, with moderate to severe bladder irritation occurring in approximately half of the patients. In addition to our previous findings, the present results indicate that this intravesical combination chemotherapy is effective in eliminating superficial bladder cancers and that since the effect is not durable, even in complete responders, maintenance therapy is necessary to reduce subsequent tumor recurrence.

Introduction

Although intravesical chemotherapy has been proven to be effective in the treatment of superficial bladder cancer in multiple clinical studies, it remains to be determined whether or not maintenance therapy following induction therapy reduces the recurrence or progression of tumors [4, 9, 12, 14, 15, 19]. Since October 1983, we have used intravesical combination chemotherapy with mitomycin C (MMC) and doxorubicin (Adriamycin ADM) for the treatment of superficial bladder cancer and have found it to be more effective in eliminating tumors than conventional single-drug instillation therapy [5, 6, 8]. To elucidate the value of maintenance treatment following this combination intravesical chemotherapy (MA therapy), we conducted a multicenter study of the efficacy of maintenance treatment in patients who had achieved a complete response following MA therapy for superficial bladder cancer.

Patients and methods

During the 2 years and 5 months from November 1986 to April 1989, 101 patients with histologically confirmed superficial [pathologic stages Ta and T1 and carcinoma in situ (CIS)] transitional-cell carcinoma of the bladder underwent MA therapy. The MA induction therapy consisted of sequential instillation of MMC and ADM. In all, 20 mg MMC on day 1 and 40 mg ADM on day 2, each dissolved in 20 ml saline, were instilled into the empty bladder through a 10- to 12-F catheter. Patients were asked to refrain from ingesting fluids for several hours prior to the instillation and to retain the drug in the bladder for at least 2 h. The treatment was repeated once a week for 5 consecutive weeks. The response was assessed at 1–2 weeks after the last treatment by both cystoscopic and urinary cytologic examinations. A complete response (CR) was defined as the complete disappearance of all cystoscopically visible tumors and the normalization of urinary cytology. For patients with CIS, negative histologic findings for multiple mucosal biopsies were also prerequisites for a CR.

A total of 98 patients were evaluable for the response to MA induction therapy; the remaining 3 subjects were removed from the study due to early (<3 weeks) cessation of the induction therapy because of intolerable bladder irritation. In all, 40 patients had CIS and 58 had papillary cancer. The CR rate determined for patients with CIS (63%, or 25/40) was almost the same as that found for subjects with papillary cancer (62%, or 36/58). Among the 61 complete responders, 23 patients with CIS and 28 with papillary cancer (total, 51) were entered in the study of maintenance therapy (Table 1).

The patients were randomly assigned to the two treatment arms by the method of random permuted blocks [16]. The non-maintenance group was followed every 3 months by cystoscopy and urinary cytology and, if necessary, transurethral resection of visible or suspicious tumors was carried out. The maintenance group received 12 monthly instilla-

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

Correspondence to: I. Fukui, Department of Urology, Tokyo Medical and Dental University, School of Medicine, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113, Japan

Table 1. CR of superficial bladder cancer to MA therapy in 98 evaluable patients treated between November 1986 and April 1989

	Cancer in situ	Papillary cancer	Total number of patients
Number of patients	40 (100%)	58 (100%)	98 (100%)
Number of CRs	25 (63%)	36 (62%)	61 (62%)
Number of patients entered in the present study	23	28	51

Table 2. Characteristics of 23 complete responders who had CIS

	No maintenance ($n = 11$)	Maintenance: MA therapy ($n = 12$)
Age (years)	54–88 (mean, 68)	48–78 (mean, 63)
Sex (M:F)	9:2	7:5
Type of cancer:		
Primary	6	8
Secondary	4	2
Associated	1	2
Prior instillation therapy:		
Yes	2	1
No	9	11

Table 3. Characteristics of 28 complete responders who had papillary cancer

	No maintenance ($n = 15$)	Maintenance: MA therapy ($n = 13$)
Age (years)	47–81 (mean, 65)	44–74 (mean, 63)
Sex (M:F)	14:1	11:2
Untreated: recurrent	2:13	4:9
G1:G2:G3	3:10:2	3:8:2
Single: multiple	6:7	5:10
Prior instillation therapy:		
Yes	3	3
No	12	10

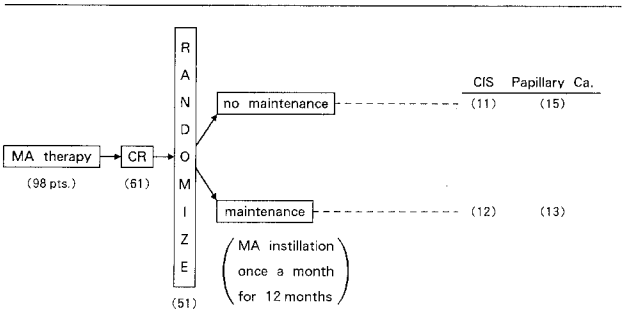

Fig. 1. Study design, showing the number of patients (*pts.*) entered in the present study

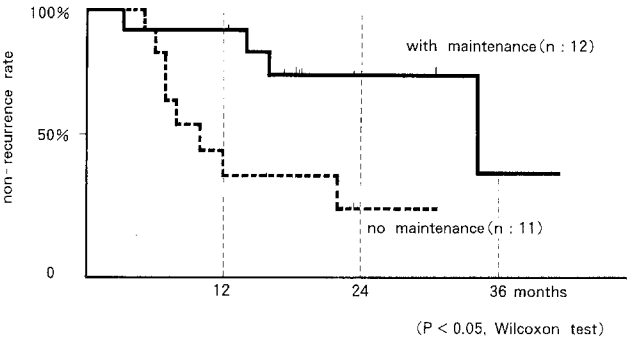

Fig. 2. Non-recurrence (Kaplan-Meier) curves generated for 23 complete responders who had CIS

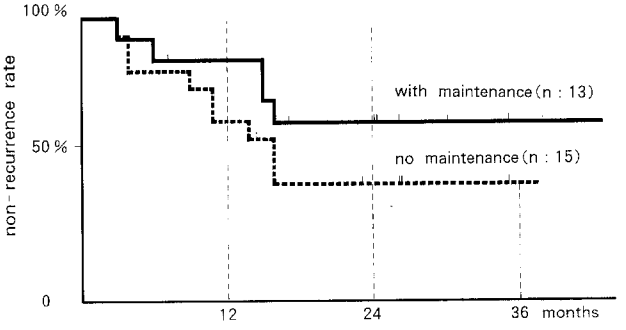

Fig. 3. Non-recurrence (Kaplan-Meier) curves generated for 28 complete responders who had papillary carcinoma

tions of the same regimen used for MA induction therapy and were followed every 3 months as described above. The non-maintenance group consisted of 11 patients with CIS and 15 with papillary cancer, and the maintenance group comprised 12 subjects with CIS and 13 with papillary cancer (Fig. 1).

Tables 2 and 3 show the characteristics of the 51 patients entered in the present study. Of the subjects with papillary cancer, approximately 80% had recurrent and intermediate- or high-grade tumors. In both the CIS and the papillary-cancer groups, no significant difference in the patients' characteristics was found between the maintenance and the non-maintenance groups.

Results

Figure 2 shows the non-recurrence curve generated for patients with CIS. The 2-year non-recurrence rate was 73% in the maintenance group but only 24% in the non-maintenance group; this difference was significant. In patients with papillary cancer, the 2-year non-recurrence rate was 59% in the maintenance group, which was better than the 38% obtained in the non-maintenance group; however, this difference did not reach significance (Fig. 3).

Table 4 summarizes the follow-up results for the patients with CIS. Recurrence was detected in 8 of 11 patients in the non-maintenance group and in 4 of 12 subjects in the maintenance group. Treatment of the 12 patients with CIS who experienced disease recurrence after they had achieved a CR included a second MA therapy in 7 cases, instillation therapy of bacille Calmette-Guérin (BCG, Tokyo strain) in 4 cases, and instillation of interferon in 1 case (Table 5). In all, 3 of the 7 patients who underwent additional MA therapy again achieved a CR; of

Table 4. Follow-up results: CIS

	Number of patients	Follow-up period (months)	Number of recurrences	Number of progressions
No maintenance	11	16–42 (mean, 25)	8 (75%)	1[a]
Maintenance	12	12–44 (mean, 27)	4 (33%)	3[b]

[a] Invasive bladder cancer
[b] Bone metastasis, ureteral cancer, and urethral cancer, respectively

Table 5. Treatment of 12 recurrent patients who had CIS

	Total number of patients	Second MA therapy	BCG therapy	Other treatment
Number of patients	12 (4)	7 (2)	4 (2)	1
CRs	5	3 (1)	1	1
Non-CRs	7	4 { (BCG, etc.)	3 (2) { (cystectomy, etc.)	0

Figures in parentheses indicate the number of patients who underwent maintenance therapy

Table 6. Follow-up results: papillary cancer

	Number of patients	Follow-up period (months)	Number of recurrences	Number of progressions
No maintenance	15	14–41 (mean, 30)	9 (60%)	0
Maintenance	13	7–43 (mean, 28)	5 (38%)	0

Table 7. Toxicity encountered in the present study

Side effect (moderate to severe)	Number of patients
Pollakisuria	48 (49%)
Pain on urination	39 (40%)
Hematuria	20 (20%)

the 4 non-responders, 3 underwent BCG therapy, with 2 achieving a CR. Of the 4 patients who received BCG therapy as the second treatment, only 1 achieved a CR; of the 3 non-responders, 1 each underwent total cystectomy and partial cystectomy. Malignant progression included invasive bladder cancer in 1 patient in the non-maintenance group and bone metastases, ureteral cancer, and urethral cancer in 3 subjects in the maintenance group, respectively (Table 4). The 2 patients who developed bone metastases and ureteral cancer displayed no bladder lesion at the time of diagnosis of progression. The urethral cancer developed in a patient who had undergone BCG instillation therapy for recurrent CIS.

Table 6 summarizes the follow-up results for the patients with papillary cancer. In all, 9 of 15 patients (60%) in the non-maintenance group and 5 of 13 subjects (38%) in the maintenance group experienced disease recurrence during the follow-up period. Most of the 14 patients with recurrent papillary cancer underwent transurethral resection of the tumors followed by maintenance treatment with MA or BCG therapy. No malignant progression has been seen as of this writing in the patients with papillary cancer.

Toxicity related to the MA therapy occurred frequently, although there no systemic side effect was encountered. Moderate to severe bladder irritation was seen in approximately half of the patients (Table 7). Non-steroidal anti-inflammatory agents (suppository) given in the presence or absence of antibiotics were effective in most cases, but one patient was successfully treated with systemic steroid administration (20–40 mg prednisolone daily) for approximately 2 weeks to relieve severe pollakisuria and dysuria that occurred during the maintenance therapy.

Discussion

Our series of studies confirm the efficacy of MA induction therapy, which yields a high CR rate in both papillary cancer and CIS of the bladder as compared with the results achieved using single agents such as thio-tepa [12], ADM [4, 15], and mitomycin C (MMC) [9, 14, 19]. However, the present randomized trial indicates the necessity of maintenance treatment following induction therapy to reduce tumor recurrence, even when a CR has been achieved, especially in patients with CIS. As maintenance therapy, we used monthly MA instillations for 1 year (12 treatments) in the present trial and obtained a high 2-year non-recurrence rate of 73% in patients with CIS. However, this result is not markedly superior to the 3-year non-recurrence rate of 66% previously obtained using maintenance therapy with MMC alone in our study of MA therapy in 30 patients with CIS [8]. Considering the much lower incidence of side effects following treatment with MMC alone, MMC maintenance therapy appears to be clinically more feasible than the present maintenance regimen consisting of MMC and ADM. The optimal dose and duration of maintenance chemotherapy as well as the selection of drugs remain to be investigated.

In the present study, tumor progression developed in three patients with CIS who underwent MA maintenance therapy and in one who did not. However, the maintenance therapy was not likely to have been ineffective in reducing tumor progression, as the three maintenance-group patients developed bone metastases or extravesical (ureteral and urethral) tumors without developing invasive bladder tumors. The only lesion found in the bladder was a small focus of CIS in a patient who developed urethral cancer. Therefore, these progressions appear to be independent of the effects of the maintenance therapy. As mentioned in other reports [7, 17], extravesical tumor development elsewhere in the urinary tract is not uncommon and should be carefully monitored during the follow-up of patients with CIS. Topical chemotherapy cannot prevent such tumor development.

On the other hand, BCG is now being aggressively used as intravesical immunotherapy, with satisfactory therapeu-

tic results being equal or superior to those obtained using the present MA therapy [3, 10]. The necessity of maintenance therapy following induction therapy also remains controversial, although recent prospective randomized trials indicate that maintenance therapy does not improve the therapeutic results [1, 2, 11]. If this is indeed true, BCG therapy would be clinically more feasible than MA therapy. However, BCG may cause considerable side effects, including generalized infections such as pneumonitis, hepatitis, or even fatal sepsis [13, 18]. Therefore, careful consideration should be required prior to the application of BCG therapy, and efforts should also be continued to develop an intravesical therapy that is more effective and less toxic than either MA or BCG therapy.

References

1. Badalament RA, Herr HW, Wong GY, Gnecco C, Pinsky CM, Whitmore WF Jr, Fair WR, Oettgen HF (1987) A prospective randomized trial of maintenance versus nonmaintenance intravesical bacillus Calmette-Guérin therapy of superficial bladder cancer. J Clin Oncol 5: 441
2. Brosman SA (1985) The use of bacillus Calmette-Guérin in the therapy of bladder carcinoma in situ. J Urol 134: 36
3. deKernion JB, Huang M-Y, Lindner A, Smith RB, Kaufman JJ (1985) Management of superficial bladder tumors and carcinoma in situ with intravesical bacillus Calmette-Guérin. J Urol 133: 598
4. Edsmyr F, Berlin T, Borman J, Duchek M, Esposti PL, Gustafson H, Wijkstrom H, Collste LG (1980) Intravesical therapy with Adriamycin in patients with superficial bladder tumors. Eur Urol 6: 132
5. 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
6. Fukui I, Sekine H, Kihara K, Yamada T, Kawai T, Washizuka M, Ishiwata D, Oka K, Hosoda K, Ikegami S, Sakai K, Owada F, Negishi T, Suzuki S, Tohma T, Oshima H (1987 a) Sequential instillation therapy with mitomycin C and Adriamycin for superficial bladder tumor. Cancer Chemother Pharmacol 20 [Suppl]: S52
7. Fukui I, Yokokawa M, Sekine H, Yamada T, Hosoda K, Ishiwata D, Oka K, Sarada T, Tohma T, Yamada T, Oshima H (1987 b) Carcinoma in situ of the bladder: effect of associated neoplastic lesions on clinical course and treatment. Cancer 59: 164
8. Fukui I, Sekine H, Kihara K, Yamada T, Takeuchi S, Yokokawa M, Kawai T, Hosoda K, Owada F, Suzuki S, Oshima H (1989) Intravesical combination chemotherapy with mitomycin C and doxorubicin for carcinoma in situ of the bladder. J Urol 141: 531
9. Harrison GSM, Green DF, Newling DWW, Richards B, Robinson MRG, Smith PH (1983) A phase II study of intravesical mitomycin-C in the treatment of superficial bladder cancer. Br J Urol 55: 676
10. Herr H, Pinsky CM, Whitmore WF Jr, Sogani PC, Oettgen HF, Melamed MR (1986) Long-term effect of intravesical bacillus Calmette-Guérin on flat carcinoma in situ of the bladder. J Urol 135: 265
11. Hudson MA, Ratliff TL, Gillen DF, Haaff EO, Dresner SM, Catalona WJ (1987) Single course versus maintenance bacillus Calmette-Guérin therapy for superficial bladder tumors: a prospective, randomized trial. J Urol 138: 295
12. Koontz WW Jr, Prout GF Jr, Smith W, Frable WJ, Minnis JE (1981) The use of intravesical thio-tepa in the management of noninvasive carcinoma of the bladder. J Urol 125: 307
13. Lamm DL, Stogdill VD, Stogdill BJ, Crispen RG (1986) Complications of bacillus Calmette-Guérin immunotherapy in 1278 patients with bladder cancer. J Urol 135: 272
14. Mishina T, Oda K, Murata S, Ohe H, Mori R, Takahashi T (1975) Mitomycin C bladder instillation therapy for bladder tumors. J Urol 114: 217
15. Ozaki Y (1977) Bladder instillation of Adriamycin in the treatment of bladder tumors: 1. Clinical results. Jpn J Urol 68: 934
16. Pocock SJ (1979) Allocation of patients to treatment in clinical trials. Biometrics 35: 183
17. Prout GR Jr, Griffin PP, Daly JJ, Heney NM (1983) Carcinoma in situ of the urinary bladder with and without associated vesical neoplasms. Cancer 52: 524
18. Rawls WH, Lamm DL, Lowe BA, Crawford ED, Sarosdy MF, Montie JE, Grossman HB, Scardino PT (1991) Fatal sepsis following intravesical bacillus Calmette-Guérin administration for bladder cancer. J Urol 144: 1328
19. Soloway MS (1985) Treatment of superficial bladder cancer with intravesical mitomycin C: analysis of immediate and long-term response in 70 patients. J Urol 134: 1107