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Effectiveness of an Immediate Mitomycin C Instillation in Patients with Superficial Bladder Cancer Receiving Periodic Mitomycin C Instillation

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Purpose: We analyzed the impact of immediate intravesical mitomycin C instillation after transurethral resection of the bladder (TURB) on tumor recurrence and progression in patients with periodic mitomycin C instillation.

Materials and Methods: Between June 2000 and June 2006, a retrospective study was performed in a total of 115 patients with primary bladder tumors receiving a 6-week course of mitomycin C instillation after TURB. The patients were assigned to two groups: 53 patients in the immediate mitomycin C (I-MMC) group were treated by immediate instillation of mitomycin C after TURB and periodic instillation (6 times, 1 time per week), and 62 patients in the MMC group received only periodic instillation. Tumor recurrence and progression were compared in the two groups.

Results: During the mean follow-up period of 46.5 months in the I-MMC group and 47.2 months in the MMC group, early recurrence (within 1 year) occurred in 6 of 53 patients (11.3%) in the I-MMC group and in 18 of 62 patients (29.0%) in the MMC group ($p < 0.02$). Although a significantly lower early recurrence rate was observed in the I-MMC group, this difference was not significant for recurrence within 2 or 3 years or for total recurrence. Progression was not significantly different between the two groups regarding the early and total period.

Conclusions: Our study confirmed the positive effect of a single, immediate mitomycin C instillation in patients with non-muscle-invasive bladder tumors who received periodic mitomycin C instillation. This benefit was limited to early recurrence and was not maintained with long-term follow-up. This approach can be an alternative to periodic mitomycin C instillation without immediate instillation.

Key Words: *Intravesical instillation; Mitomycin; Urinary bladder neoplasms*

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INTRODUCTION

Transurethral resection of the bladder (TURB) followed by watchful waiting was usually performed for non-muscle-invasive bladder cancer in the past, but immediate intravesical chemotherapy has recently frequently been used in clinics [1-4]. The European Association of Urology (EAU) guideline recommends performing an one-time, immediate intravesical drug treatment after the surgery in all non-muscle-invasive bladder cancers [5], and intravesical chemotherapy is known to be effective in preventing cancer recurrence by suppressing implantation of the postoperative tumor cells wandering in the bladder after the surgery. On the other hand, in the case of non-muscle-invasive bladder cancer patients in the intermediate risk group (TaG1 with multifocal or >3 cm diameter, TaG2, T1G1, T1G2) [6], periodic intravesical chemotherapy is performed with bacillus Calmette-Guerin (BCG) or mitomycin C after TURB, but it requires waiting 1 to 2 weeks to begin the treatment; thus, it is possible that recurrence

or progression could be affected during this period [7,8]. Therefore, we performed immediate post-TURB mitomycin C treatment in patients with non-muscle-invasive bladder cancer in the intermediate risk group who planned to undergo periodic intravesical mitomycin C instillation and investigated the effect of the treatment on the progression and recurrence of bladder cancer.

MATERIALS AND METHODS

Between June 2000 and June 2006, a retrospective study was performed in patients with primary bladder tumors who underwent a 6-week course of mitomycin C instillation after TURB. Patients were limited to those with intermediate-risk non-muscle-invasive bladder tumors. TURB was conducted by 2 surgeons regardless of the group of patients. Individuals with muscle-invasive or G3 tumors or in situ bladder carcinoma on the pathological examination, non-transitional-cell carcinoma, invasion to the prostate or upper urinary tract, or a history of TURB or intravesical chemotherapy were excluded.

Patients were divided into 2 groups. The immediate mitomycin C (I-MMC) group consisted of 53 patients who received a single dose of mitomycin C, 30 mg diluted in 30 ml of water, within 24 hours after TURB and received periodic mitomycin C instillation after 1 week (1-week interval for 6 weeks). The non-immediate mitomycin C (MMC) group consisted of 62 patients who did not receive mitomycin C within 24 hours after TURB and only received periodic instillation. The instillation was retained for 1.5 to 2 hours by catheter and was then emptied out by self-voiding. Mitomycin C instillation was delayed for 1 or 2 weeks if complications such as severe irritative voiding symptoms, cystitis, allergic reactions, hematuria, fever, erythema, or skin rash appeared.

Patients were evaluated by urine cytology and cystoscopy at 3, 6, 9, 12, 18, and 24 months and then once yearly postoperatively. If hematuria developed, evaluation was done immediately. Tumor grade, stage, time of recurrence, grade of recurrent tumors, and progression of the two groups were compared by unpaired t-tests and chi-square tests. Values were considered statistically significant at $p < 0.05$.

RESULTS

Both groups (total of 115 patients), 53 patients in the I-MMC group and 62 patients in the MMC group, were comparable in terms of clinical and pathological characteristics (Table 1). There were no statistically significant differences between the 2 groups.

Recurrence timing was considered by using different cut-off points when determining the possible impact of a single early instillation of mitomycin C on cell implantation as a mechanism of early recurrence. Early recurrence (within 1 year) occurred in 6 of 53 patients (11.3%) in the I-MMC group and in 18 of 62 patients (29.0%) in the MMC group (p=0.020) (Table 2). Although the early recurrence rate was significantly lower in the I-MMC group, the difference between groups was not significant for recurrence within 3 years or for total recurrence, which occurred in 16 of 53 patients (30.2%) in the I-MMC group versus 29 of 62 patients (46.8%) in the MMC group. Progression to a more advanced stage occurred in 2 of 53 patients (3.8%) in the I-MMC group and in 3 of 62 patients (4.8%) in the MMC group within 1 year (p=0.780), and in 6 of 53 patients (11.3%) in the I-MMC group and in 9 of 62 patients (14.5%) in the MMC group within 3 years (p=0.612). Two of 53 patients (3.8%) in the I-MMC group and 2 of 62 patients (3.2%) in the MMC group had progression to muscle-invasive bladder cancer.

TABLE 1. Patient characteristics

	Immediate MMC group (%)	Non-immediate MMC group (%)	p-value
No. of patients	53	62	
No. of tumors	53	62	
Mean age (yr)	61.5±12.6	64.9±11.5	0.629
Clinical stage			
Ta	25/53 (47.2)	26/62 (41.9)	0.573
T1	28/53 (52.8)	36/62 (58.1)	0.573
WHO grade			
Grade I	26/53 (49.1)	30/62 (48.4)	0.943
Grade II	27/53 (50.9)	32/62 (51.6)	0.943
Mean follow up period (mo)	46.5±11.5	47.2±9.1	0.513

MMC: mitomycin C

TABLE 2. Recurrence and progression in each group according to follow-up period

	Immediate MMC group (%)	Non-immediate MMC group (%)	p-value
Recurrence			
Within 1 year	6/53 (11.3)	18/62 (29.0)	0.020
Within 3 year	16/53 (30.2)	29/62 (46.8)	0.069
Progression			
Within 1 year	2/53 (3.8)	3/62 (4.8)	0.780
Within 3 year	6/53 (11.3)	9/62 (14.5)	0.612

MMC: mitomycin C

DISCUSSION

Post-TURB intravesical chemotherapy has been used for non-muscle-invasive bladder cancer for more than 40 years, and thiotepa, Adriamycin, Epodyl, epirubicin, and mitomycin C have been used for the periodic intravesical chemotherapy [6]. There have been several reports about the timing to begin the intravesical chemotherapy. Soloway and Masters reported in a study with murine bladder that post-TURB intravesical chemotherapy was effective even though it was performed after 24 hours [9], whereas Pan et al insisted that intravesical chemotherapy was effective only

when it was performed within 1 hour after the surgery [10]. According to an EORTC study that was conducted later using thiotepa, doxorubicin, and cisplatin, the disease-free interval was longer in the group in which the post-TURB intravesical chemotherapy was performed on the 4th to the 14th day than in the group in which it was performed 0 to 3 days after TURB or after the 14th day [11]. Furthermore, in a study conducted using mitomycin C and doxorubicin, it was reported that there was more benefit in the group in which the intravesical chemotherapy was performed between the 7th and 15th day than in the group in which the intravesical chemotherapy was performed on the day of the operation [12].

Recently, many clinical studies have been performed regarding the effect of one-time immediate post-TURB mitomycin C instillation in the low-risk group of non-muscle-invasive bladder cancer patients. Solsona et al reported in a randomized study with 131 subjects by short-term follow-up that the recurrence-free interval was longer and the recurrence rate was lower in the group in which post-TURB immediate mitomycin C instillation was performed than in the group in which only TURB was performed for non-muscle-invasive bladder cancer [13]. Sylvester et al analyzed the studies on intravesical chemotherapy and reported that post-TURB immediate intravesical instillation of mitomycin C, epirubicin, or pirarubicin showed a lower recurrence rate than TURB only [14]. In our study, the effect of immediate MMC treatment was compared in the patients to which MMC treatment was performed periodically for intermediate-risk non-muscle-invasive bladder cancer, and the results showed that the recurrence rate within 1 year was significantly lower in the I-MMC group (11.3%) than in the MMC group (29.0%). Kaasinen et al investigated the factors for post-TURB recurrence in non-muscle-invasive bladder cancer patients and reported that the relative risk of recurrence was reduced to half when the first instillation of the periodic mitomycin C treatment was performed within 24 hours after TURB [15]. Our result was also similar to this report, and thus it can be assumed that the timing of mitomycin C administration affects the catamnesis. On the other hand, the recurrence rate within 3 years was lower in the I-MMC group (30.2%) than in the MMC group (46.8%) but not significantly so. Thus, it is hard to conclude that post-TURB immediate intravesical chemotherapy is effective for the long-term suppression of recurrence. Additionally, tumor recurrence increased about 3 times between within 1 year (11.3%) and within 3 years (30.2%) in I-MMC group, whereas it increased about 1.5 times between within 1 year (29.0%) and within 3 years (46.8%) in the MMC group. Thus, patients who receive immediate MMC instillation may need more frequent follow-up than patients who do not receive immediate MMC instillation. Additional studies are required in this regard through the study of a greater number of cases.

In a study with 43 low-risk non-muscle-invasive bladder cancer patients, Barghi et al reported that there was no significant difference in tumor progression between the group in which immediate post-TURB intravesical chemotherapy was performed and the group in which only TURB was performed [6]. In another study with 63 low-risk non-muscle-invasive bladder cancer patients, El-Ghobashy et al reported that immediate post-TURB intravesical chemotherapy did not show any effect on tumor progression [16]. In our study also, tumor progression in the I-MMC group was 3.7% within 1 year and 11.3% within 3 years, and that in the MMC group was 4.8% within 1 year and 14.5% within 3 years, showing no significant difference.

The effect of immediate post-TURB intravesical chemotherapy may be chemoresection of the residual tumor that can be implanted on the resection site or the tumor cells wandering inside the bladder [6]. This article is the first study that investigated the effect of immediate post-TURB mitomycin C instillation in an intermediate-risk group of non-muscle-invasive bladder cancer patients in whom periodic mitomycin C treatment was performed. Our results suggest that chemoresection may be effective not only in the low-risk group but also in the intermediate-risk group of non-muscle-invasive bladder cancer patients.

There is a possibility that the number of total intravesical mitomycin C instillations may affect the results, because the I-MMC group had 7 instillations, whereas the MMC group had 6 instillations. Additional studies might be required in this regard.

CONCLUSIONS

In the intermediate-risk group of non-muscle-invasive bladder cancer patients in whom periodic post-TURB mitomycin C instillation is performed, one-time immediate post-TURB mitomycin C instillation does not affect the long-term recurrence or progression of bladder cancer but is effective in the suppression of early recurrence.

Conflicts of Interest

The authors have nothing to disclose.

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