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SESSION III

Nobuyuki Watanabe · Ikuo Miyagawa · Yuji Higasibori
Takeo Nakahara · Fuminobu Sumi · Goro Ishida
Bungo Abe · Akemichi Inoue · Nobuaki Hanamoto
Tottori University Oncology Group

Phase II study of intravesical chemoprophylaxis of epirubicin after transurethral resection of bladder tumors

Abstract We performed intravesical instillation of epirubicin in 53 patients with the aim of preventing recurrence of bladder tumors. The patients had undergone transurethral resection of superficial bladder tumors (only transitional-cell carcinoma) within the preceding week, between January of 1990 and July of 1991. Recurrence was found in 11.3% (6/53) of cases during follow-up periods lasting from 1 to 20 months. Side effects occurred in 5.7% (3/53) of the patients. The cumulative nonrecurrence rate was 96.0% for a follow-up period of 6 months and 78.4% for 12 months. The results of this study suggest that intravesical instillation of epirubicin is very useful as adjuvant therapy after transurethral resection of superficial bladder tumors.

Key words Epirubicin · TUR-Bt · Intravesical instillation

N. Watanabe (✉)
Division of Urology, San-in Rosai Hospital, Shinden 1-8-1, Kaike, Yonago-City, Tottori 683, Japan

I. Miyagawa
Department of Urology, Tottori University School of Medicine, Yonago, Japan

Y. Higasibori
Division of Urology, Saiseikai Gotsu General Hospital, Gotsu, Japan

T. Nakahara
Division of Urology, Matsue Red Cross Hospital, Matsue, Japan

F. Sumi
Division of Urology, Matsue City Hospital, Matsue, Japan

G. Ishida
Division of Urology, National Yonago Hospital, Yonago, Japan

B. Abe
Division of Urology, San-in Rosai Hospital, Yonago, Japan

A. Inoue
Division of Urology, Saiseikai Sakaiminato General Hospital, Sakaiminato, Japan

N. Hanamoto
Division of Urology, Tottori Prefectural Central Hospital, Tottori, Japan

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Introduction

Transurethral electroresection (TUR) and transurethral electrocoagulation (TUC) are the usual treatment methods for superficial bladder tumors (Ta, T1). To prevent polycentric development and frequent recurrence, postoperative intravesical injection of mitomycin C (MMC), Adriamycin (ADM), and other drugs has been used. Although intravesical injection of ADM has been reported to be especially effective, this entails a significant number of side effects such as irritation of the urinary bladder [3]. It is thought that epirubicin, a derivative of ADM, produces an antitumor effect almost equal to that of ADM and that the frequency and intensity of its side effects are lower than those of ADM [7].

For these reasons, we injected epirubicin intravesically to prevent tumor recurrence after TUR and examined the efficacy and side effects of this treatment. We present the results of this investigation.

Patients and methods

Between January of 1990 and July of 1991, we investigated 53 patients who were diagnosed as having bladder tumors, underwent TUR-Bt, and met the following criteria: (1) primary superficial bladder tumor (Ta, T1); (2) histologically diagnosed as transitional-cell epithelial carcinoma; (3) had received no therapy other than the surgical treatment within the previous 3 weeks; (4) had no severe impairments of heart function, kidney function, liver function, or hematopoietic function; and (5) had no other severe complication.

Epirubicin (20 mg) was dissolved in 40 ml physiological saline and intravesically injected. As a rule, the period between TUR and the first injection was kept to 1 week or less. In the first 2 weeks, instillation was performed once a week. Next, the intravesical instillation was

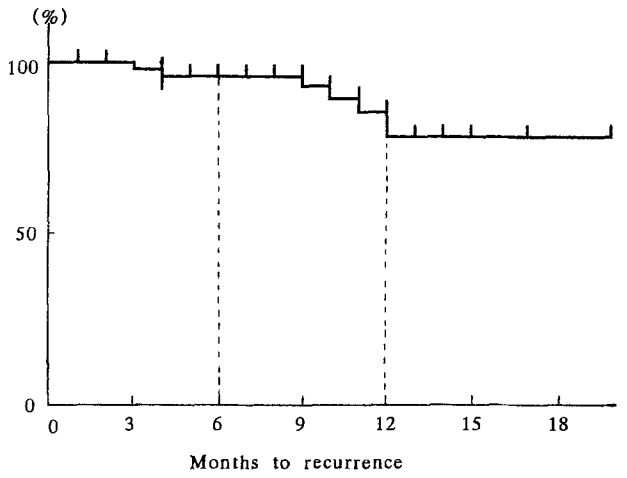

Fig. 1 Nonrecurrence rate for follow-up periods of 6 and 12 months as determined in 53 patients given epirubicin by intravesical instillation for the prevention of recurrence of superficial bladder tumors following TUR

performed seven times at intervals of 2 weeks. Finally, eight intravesical instillations were performed at 1-month intervals. A total of 17 intravesical injections were given over a period of about 1 year.

As a rule in the 1st year after TUR, patients were monitored for recurrence by cystoscopy and cytodiagnosis of the urine every 2–3 months. Thereafter, the examination was performed every 3–6 months.

Results

The 53 subjects included 40 men and 13 women. The age distribution ranged from 34 to 83 years, and the mean age was 65.0 years. Follow-up was performed for 1–20 months (mean, 9.25 months) after TUR. During the follow-up period, 6 of the 53 patients (11.3%) experienced recurrence. The nonrecurrence rate determined for a follow-up period of 6 months was 96.0%, and that obtained for 1 year was 78.4% (Fig. 1).

The recurrence rates calculated for men and women showed no significant difference; 4 of the 40 men (10%) and 2 of the 13 women (15.4%) experienced recurrence. However, patients in whom the preoperative size of the primary superficial bladder tumor was large showed a high recurrence rate. Tumors (Ta, T1) exceeding 3 cm in maximal diameter showed an especially high value, with 3 of 4 patients (75%) experiencing recurrence (Table 1).

Of 22 individuals with multiple tumors, 4 (18.2%) experienced recurrence. This is a high recurrence rate in comparison with that obtained for the 30 patients with a single tumor, which showed 2 (6.7%) cases of recurrence (Table 2). No recurrence was observed in cases with a histological classification of grade 0 or grade 1. The recurrence rate increased with the grade (Table 3). The recurrence rate also increased with the stage classification (Table 4).

Side effects were observed in only 3 cases (5.7%), and most were symptoms of bladder irritation such as pollakisuria. There was no severe side effect (Table 5).

Table 1 Number of patients with recurrence in relation to tumor size

Size	Recurrence (+)	Recurrence (–)	Totals
≦1 cm	2	26	28
1–3 cm	1	19	20
≧3 cm	3	1	4
Totals	6	46	52

Table 2 Number of patients with recurrence in relation to tumor number

Number	Recurrence (+)	Recurrence (–)	Totals
Multiple	4	18	22
Solitary	2	28	30
Totals	6	46	52

Table 3 Number of patients with recurrence in relation to tumor grade

Grade	Recurrence (+)	Recurrence (–)	Totals
0	0	4	4
1	0	15	15
2	5	25	30
3	1	3	4
Totals	6	47	53

Table 4 Number of patients with recurrence in relation to tumor stage

Stage	Recurrence (+)	Recurrence (–)	Totals
pTis	0	1	1
pTa	1	8	9
pT1a	2	24	26
pT1b	3	14	17
Totals	6	47	53

Table 5 Side effects

	<pT1b
Turbid urine	0
Miction pain	2
Pollakisuria	3
None	50
Total	53[a]

[a] Overlapping cases included

Discussion

There have been many reports stating that the recurrence rate of superficial bladder tumor after TUR is 10%–40% at 1 year and 30%–70% at 3 years. This high rate of recurrence is a serious problem [3–6].

We found correlations between the recurrence rate and the preoperative status, including the tumor size, number, grade, and stage. These findings are similar to the results indicated in other reports [1, 2, 8]. The nonrecurrence rate we obtained was also not inferior to that reported for ADM.

Side effects were observed in only 3 cases (5.7%), most of which involved bladder-irritation symptoms such as

pollakisuria. No severe side effect occurred. Thus, epirubicin is a suitable agent for intravesical instillation to prevent postoperative recurrence of superficial bladder tumors, and high efficacy can be expected. However, since a small number of patients were involved in this study and the follow-up period was short, further investigation is necessary.

We gave epirubicin to 53 patients with superficial bladder tumors by intravesical instillation to prevent postoperative recurrence after TUR and obtained the following results:

1. Conducting follow-up over a period of 1–20 months (mean, 9.25 months), we found an overall recurrence rate of 11.3% (6 of the 53 patients), a 6-month nonrecurrence rate of 96.0%, and a 1-year nonrecurrence rate of 78.4%.
2. The recurrence rate was higher in patients whose preoperative status included large or multiple tumors.
3. A comparison based on the histological classification revealed high recurrence rates for high-grade and high-stage tumors.
4. Side effects were observed in only 3 cases (5.7%). Most of the side effects involved symptoms of bladder irritation such as pollakisuria, and none was severe.

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