

SESSION III

Yasunari Uekado · Atsuyuki Hirano · Toshiaki Shinka
Tadashi Ohkawa

The effects of intravesical chemoimmunotherapy with epirubicin and bacillus Calmette-Guérin for prophylaxis of recurrence of superficial bladder cancer: a preliminary report

Abstract The effects of intravesical chemoimmunotherapy with epirubicin and bacillus Calmette-Guérin (BCG) for prophylaxis of recurrence of superficial bladder cancer (pTa, pT1) were investigated in 29 patients aged a median of 70 years between January of 1991 and May of 1993. The patients received intravesical instillation of 40 mg epirubicin immediately after transurethral resection (TUR) of the bladder cancer. At 1 week after TUR, 80 mg Tokyo-strain BCG was instilled into the bladder once a week for 6 weeks. Thereafter, the patients were followed by cystoscopy and urinary cytology at 3-month intervals until recurrence was detected. Of the 29 patients, 28 had no evidence of disease over a mean follow-up period of 20 months. The 1 case of recurrence occurred at 3 months after TUR and that patient died of cancer progression. The simple recurrence rate was 3.5% after therapy. According to the person-years method, the number of recurrent tumors per 100 patient-months was 0.17. The cumulative nonrecurrence rate determined for all cases was 96.5% at 30 months. Adverse reactions, including urinary frequency, urgency, and miction pain, among others, were observed in 27 patients (93%). Only 1 patient was withdrawn from the treatment because of severe bladder-irritation symptoms due to the BCG instillation. The intravesical chemoimmunotherapy with epirubicin and BCG seemed to be effective for prophylaxis of recurrence of superficial bladder cancer.

Key words Bladder cancer · Chemoimmunotherapy · BCG · Epirubicin

Introduction

Approximately 80% of bladder cancers present initially as superficial tumors that are confined to the mucosa and lamina propria [12]. Transurethral resection (TUR) with cystoscopic and cytological follow-up is currently the standard therapy for superficial bladder cancer. The major problem in the management of superficial bladder cancer is the high recurrence rate of 40%–85% and malignant progression after TUR [9, 12]. Because multifocal field changes may contribute to the recurrence of bladder tumors, additional treatment may be an appropriate supplement to endoscopic resection in selected patients. Intravesical chemotherapy or immunotherapy has been advocated for these patients at high risk for tumor recurrence or progression, and both of these therapies have proved to be effective in preventing the recurrence of bladder cancer [1, 2, 4, 6]. However, there are few reports concerning the use of a combination of chemotherapy and immunotherapy as prophylaxis of recurrence after TUR.

The present study was undertaken to evaluate the effects of chemoimmunotherapy with epirubicin and bacillus Calmette-Guérin (BCG) for prophylaxis of recurrence after TUR.

Patients and methods

Patient selection

A total of 29 patients with superficial bladder cancer were entered in the trial from January of 1991 through May of 1993. All patients had histologically documented transitional-cell carcinoma at entry. Patients with concomitant carcinoma in situ or muscle-invasive bladder cancer were excluded. The characteristics of the patients are listed in Table 1. There were 24 men and 5 women ranging in age from 39 to 91 years. Of the 29 patients, 7 had grade 1 cancer, 15 had grade 2 cancer, and the remaining 7 had grade 3 cancer. The pathological stage was pTa in 14 patients and pT1 in 15 patients. In all, 7 patients had undergone prior TUR of bladder cancer with or without intravesical chemotherapy or immunotherapy.

Y. Uekado (✉) · A. Hirano · T. Shinka · T. Ohkawa
Department of Urology, Wakayama Medical College 27,
7-ban-cho, Wakayama City 640, Japan

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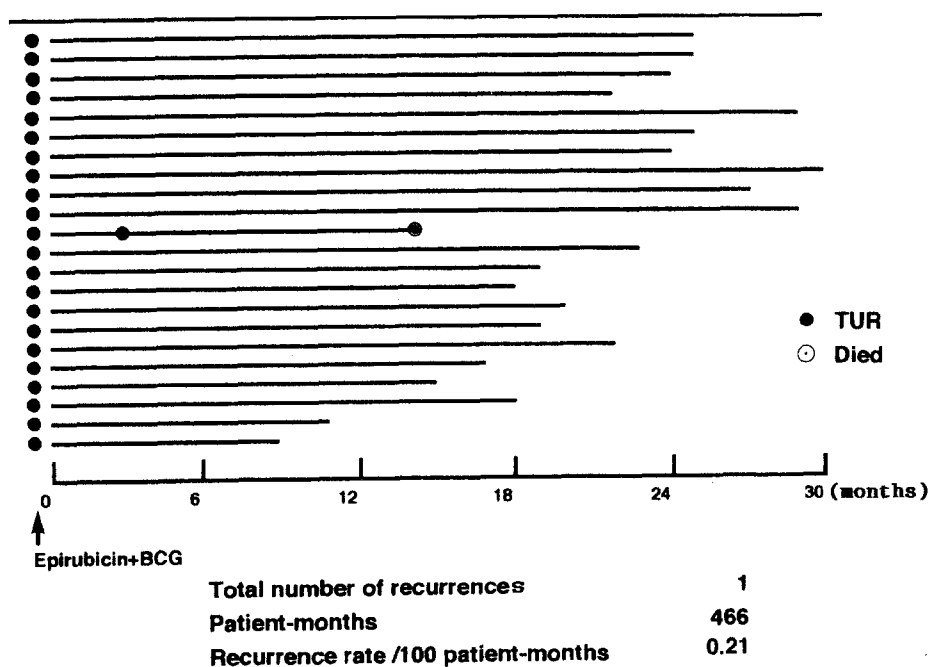
Table 1 Characteristics of patients

Number of patients	29
Median age (years)	70 (range, 39–91)
M:F	24:5
New occurrence	22
Recurrence	7
Number of tumors:	
Single	15
Multiple	14
Size of tumor:	
< 1 cm	10
1–3 cm	18
> 3 cm	1
Configuration of tumor:	
Papillary	25
Nonpapillary	4
Grade of tumor:	
1	7
2	15
3	7
Stage of tumor:	
pTa	14
pT1	15

Protocol design

The patients received intravesical instillation of epirubicin (40 mg in 40 ml physiological saline) immediately after TUR of bladder tumors. The epirubicin was retained in the bladder for 1 h. At 1 week after TUR, Tokyo-strain BCG (80 mg in distilled water, $2-5 \times 10^7$ colony-forming units) was instilled into the bladder and retained for 2 h once a week for 6 weeks. Thereafter, the patients were followed by cystoscopy and urinary cytology at 3-month intervals until recurrence or progression was detected.

Fig. 1 Clinical course of and recurrence rate determined for bladder-cancer patients (first occurrence) after chemoimmunotherapy ($n = 22$)

**Table 2** Response to chemoimmunotherapy

	Number of patients	Median follow-up period (months)
No evidence of disease	28	20
Recurrence and progression	1	14

Table 3 Recurrence rate

Number of patients with recurrence/total number of patients	1/ 29 (3.5%)
Number of recurrences/100 patient-months	1/566 (0.17)

Evaluation of response

The response to the chemoimmunotherapy was evaluated by cystoscopic examination with biopsy and cytology study. For the assessment of the efficacy of combined intravesical therapy, the results were estimated by the simple recurrence rate, by a modification of the person-years method [8], and by the cumulative nonrecurrence rate using the Kaplan-Meier method.

Results

Response

Of the 29 patients, 28 completed this protocol; 1 patient was discontinued from the treatment before the protocol was completed. The mean follow-up period was 19 months (range, 5–30 months). Overall, 28 of 29 patients had no evidence of disease over a mean follow-up period of 20 months (Table 2). The remaining patient had a recurrent tumor at 3 months after the initial TUR and died of cancer

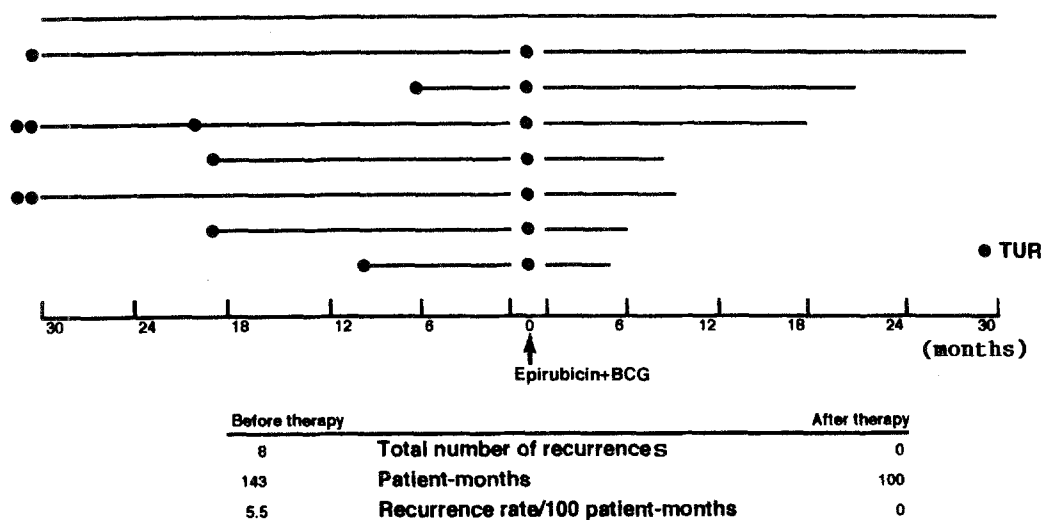


Fig. 2 Clinical course of and recurrence rate determined for recurrent bladder-cancer patients ($n = 7$)

Table 4 Adverse reactions

Adverse reaction	Number of patients (%)
Vesical irritation symptoms	25 (86%)
Mild to moderate	24 (83%)
Severe	1 (3%)
Flu-like symptoms	5 (17%)
Fever	4 (14%)
Gross hematuria	1 (3%)

progression at 14 months after the initial treatment. The simple recurrence rate was 3.5%.

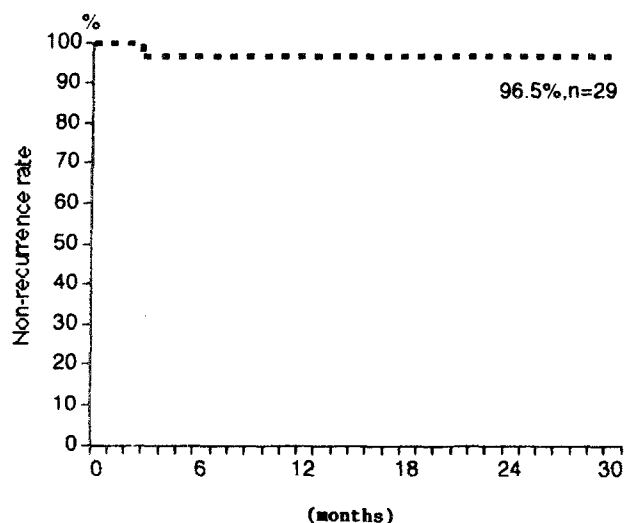
According to the person-years method, the number of recurrences per 100 patient-months was 0.17 because there was 1 episode of tumor development in 566 patient-months after epirubicin and BCG therapy (Table 3). Of 22 patients who initially presented with a bladder tumor, 1 patient had

1 episode of tumor recurrence in 466 patient-months after therapy (Fig. 1). The recurrence rate in those patients was 0.21/100 patient-months. In all, 7 patients had at least 1 recurrent tumor during the 30 months preceding the chemoimmunotherapy and were considered to be at high risk for further recurrence. They showed 8 episodes of tumor development in 143 patient-months before chemoimmunotherapy. After treatment, there was no episode of tumor recurrence in 100 patient-months (Fig. 2). Figure 3 shows the curves generated for the time to first recurrence according to the Kaplan-Meier method. The cumulative nonrecurrence rate was 96.5% at 30 months.

Adverse reactions

Adverse reactions occurred in 27 of the 29 patients (93%, Table 4). There was no local or systemic toxicity due to the epirubicin instillation. Almost all of the adverse reactions were considered to have been caused by the BCG instillation. Local irritation symptoms were seen in 25 patients, usually beginning after 3 or 4 instillations of BCG. Systemic reactions, including flu-like symptoms and fever, were observed in 9 patients. Most of the bladder-irritation symptoms were mild to moderate and, when necessary, could be readily controlled with antispasmodics and nonsteroidal anti-inflammatory drugs such as indomethacin. As the number of instillations increased, the severity of the irritation symptoms also progressed. Only 1 patient was discontinued from the treatment due to severe bladder-irritation symptoms. No antituberculous agent such as isoniazid was given to any of the patients with systemic reactions.

Fig. 3 Cumulative nonrecurrence rate determined following intravesical therapy. ■ + BCG



Discussion

At present, the standard treatment for superficial bladder cancer is TUR with cystoscopic and cytologic follow-up [10]. However, reports show that 40%–85% of patients with resected superficial bladder tumors develop a recurrent tumor and that most tumors recur within 2 years of the initial treatment [8, 12].

The major problem in the management of superficial bladder cancer is the high recurrence rate after endoscopic resection. This high recurrence rate is attributable to many factors, including continuous exposure of the bladder epithelium to carcinogens, multifocal growth of the tumors, the implantation of tumor cells during TUR, and incomplete tumor resection [3, 7, 12]. For these reasons, intravesical chemotherapy or immunotherapy has been advocated for these patients at high risk for recurrence and progression [1, 2, 4, 6, 11]. The agents most commonly used for bladder instillation are thio-tepa, mitomycin C, doxorubicin, and BCG [6]. All have been effective in preventing tumor recurrence, achieving various success rates, as compared with TUR alone. The most effective of these agents appears to be BCG. Numerous studies performed around the world have demonstrated the effectiveness of BCG as a prophylactic agent [6, 9].

Since 1983, intravesical BCG immunotherapy has been used in our institute as prophylaxis after TUR of superficial bladder tumors, achieving a high success rate [9]. In our previous study, about 30% of patients had tumor recurrence after endoscopic resection and BCG instillation. Therefore, since 1991 we have used epirubicin instillation immediately after TUR for superficial bladder cancer in an attempt to enhance the antitumor effect of BCG and reduce the recurrence. Epirubicin is one of a series of new derivatives of doxorubicin synthesized with the aim of finding anthracycline analogues having an improved spectrum of antitumor activity and lower toxicity. To date, epirubicin has been proven to be effective for superficial bladder tumor and carcinoma in situ [5].

In this study, topical treatment of superficial bladder cancer with epirubicin and BCG proved to be effective as prophylaxis of recurrence of the disease. Only one patient experienced recurrence and died of cancer progression. The simple recurrence rate was 3.5%, and the recurrence rate

according to the person-years method was 0.17. The nonrecurrence rate as estimated by the Kaplan-Meier method was 96.5%. Although most of the patients tolerated the 6-week instillation schedule, the major problem in this treatment modality appeared to be a high incidence of local adverse reactions. However, only one patient had to be withdrawn from the treatment due to severe vesical irritation symptoms.

The results reported herein must be considered as preliminary, since the observation period was relatively short. A further prospective randomized study will be necessary to investigate whether the effectiveness observed in this study is an indicator of genuine long-term benefits.

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