Cancer Chemother Pharmacol (1994) 35 (Suppl): S 31–S 35

SESSION III

Kikuo Okamura · Tatsuro Murase · Koji Obata
Shinichi Ohshima · Yoshinari Ono · Takao Sakata
Yasuhiro Hasegawa · Toshio Shimoji · Koji Miyake
The Nagoya University Urological Oncology Group

A randomized trial of early intravesical instillation of epirubicin in superficial bladder cancer

Abstract A total of 135 patients with superficial bladder cancer diagnosed as totally resectable were entered into a randomized multicenter trial to investigate the efficacy of early intravesical epirubicin instillation after resection in comparison with transurethral resection (TUR) alone. Epirubicin (40 mg/40 ml saline) was given within 24 h of TUR and once during the 1st week, weekly for 4 weeks, and then monthly for 11 months. In all, 122 patients (90.4%) were eligible and 119 (88.1%) were evaluable. The interval to initial recurrence was significantly longer (P = 0.02) in the epirubicin group (36 months; 95% confidence interval, 32–40 months) than in the group receiving TUR alone (28 months; 95% confidence interval, 24–32 months). The recurrence rate per year in the epirubicin group was less than that in the TUR-alone group (0.13 versus 0.29 annual recurrences). Disease progression was observed in only one patient in the epirubicin-instillation group. The main toxicity encountered was bladder irritation (13.8%). These results demonstrate that early intravesical epirubicin instillation is efficacious in preventing local recurrence.

Key words Superficial bladder cancer · Intravesical instillation · Epirubicin

K. Okamura (✉) · T. Shimoji · K. Miyake
Department of Urology, Nagoya University School of Medicine, 65, Tsurumai-cho, Showa-ku, Nagoya 466, Japan

T. Murase
Department of Urology, Japanese Red Cross Nagoya First Hospital, 3-35, Michishita-cho, Nakamura-ku, Nagoya 453, Japan

K. Obata
Department of Urology, Japanese Red Cross Nagoya Second Hospital, 2-9, Myoken-cho, Showa-ku, Nagoya 466, Japan

S. Ohshima
Department of Urology, Shakai Hoken Chukyo Hospital, 1-1-10, Sanjo, Minami-ku, Nagoya 457, Japan

Y. Ono
Department of Urology, Komaki Shimin Hospital, 1-20, Tsunebushin, Komaki 485, Japan

T. Sakata
Department of Urology, Shiritsu Yokkaichi Hospital, 2-2-37, Shibata-cho, Yokkaichi 510, Japan

Y. Hasegawa
Department of Physiology, Nagoya City University Medical School, 1, Aza Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan

Paper presented at the 5th International Conference on Treatment of Urinary Tract Tumors with Adriamycin/Farmorubicin, 24–25 September 1993, Hakone, Japan

Introduction

Approximately 75%–80% of bladder cancers are superficial at the time of initial presentation [5], and primary lesions are usually eradicated by transurethral resection (TUR). However, prophylaxis against tumor recurrence and progression is clinically important. Becillus Calmette-Guérin (BCG) instillation is considered to be the most effective treatment [6, 8, 13], but the toxicities caused by BCG are known to be more severe and to occur more frequently than those caused by other chemotherapeutic agents [9, 15]. Intravesical instillation of chemotherapeutic agents remains the standard prophylactic treatment against recurrences.

Epirubicin is an analogue of doxorubicin that was developed because it exerted stronger anticancer effects and lower toxicity than doxorubicin [16]. However, we do not have sufficient information about the prophylactic benefit of epirubicin [2, 3, 11]. This study investigated the efficacy of early epirubicin instillation after TUR in the prophylaxis of bladder cancer recurrence.

Patients and methods

A total of 135 patients with superficial bladder cancer diagnosed as totally resectable by transurethral surgery were entered in this study at 20 participating institutions between November of 1989 and August of 1991 (Table 1). Registration was performed by telephone at the Tokai Tumor Registry. Patients with primary carcinoma in situ, a performance status of above 2, an age of over 85 years, or an uncontrollable urinary tract infection were excluded. The patients were stratified into a newly diagnosed solitary-tumor group, a newly diagnosed multiple-tumor group, and a recurrent-tumor group and were randomly allocated to a therapy arm. In all, 66 patients were assigned to arm A, consisting of prophylactic epirubicin instillation after TUR, and 69 were randomized to arm B, consisting of TUR alone.

Hematoxylin-eosin-stained slides of TUR specimens were sent to the referee pathologist (T. S.) to obtain uniform diagnosis of the grade and the stage category. The eligibility requirements included histological confirmation of superficial (pTa, pT1) papillary transitional-cell carcinoma without other components.

A total of 17 intravesical instillations were performed on the patients in arm A; 40 mg epirubicin in 40 ml normal saline was given within 24 h of TUR and once during the 1st week, weekly for 4 weeks, and then monthly for 11 months.

Cystoscopy and urinary cytology were performed at 4 weeks and then every 3 months after TUR. Local and systemic toxicities were monitored during the instillation. When recurrence was noted, TUR was performed and a specimen slide was sent to the referee pathologist.

The primary end point was the recurrence-free interval, which was defined as the interval between the initial TUR and the date of the first subsequent TUR to demonstrate the first positive pathology. On the basis of the intent-to-treat analysis, all eligible patients in both arms were included in the recurrence-free interval analysis. The recurrence-free intervals were also evaluated in the low-risk subgroup (patients with newly diagnosed solitary tumors) and the high-risk subgroup (patients with newly diagnosed multiple and recurrent tumors). The recurrence rate per year in each group was defined as the total number of positive cystoscope studies divided by the total years of follow-up. The recurrence-free intervals were calculated by the Kaplan-Meier method and compared by the generalized Wilcoxon test.

Table 1 Members of the Nagoya University Urological Oncology Group

Institution	Director
Nagoya University	K. Miyake
Shiritsu Okazaki Hospital	T. Kinukawa
Shiritsu Handa Hospital	M. Kobayashi
Ichinomiya Shimin Hospital	H. Ito
Meitetsu Hospital	T. Takita
Komaki Shimin Hospital	Y. Ono
Red Cross Nagoya First Hospital	T. Murase
Kariya Sogo Hospital	Y. Tsumura
Chubu Rosai Hospital	S. Otani
Red Cross Nagoya Second Hospital	K. Obata
Kakegawa Shiritsu Sogo Hospital	S. Kanai
Kenritsu Tajimi Hospital	Y. Suzuki
National Nagoya Hospital	K. Yoshida
Shakaihoken Chukyo Hospital	O. Matsuura
Aichi Saiseikai Hospital	H. Asano
Narita Kinen Hospital	S. Hirabayashi
Hekinan Shimin Hospital	M. Gotoh
Shizuoka Saiseikai Hospital	N. Kato
Kasugai Shimin Hospital	O. Kuriki
Atsumi Hospital	S. Takamura

Results

As based on the referee pathological diagnosis, 13 patients were judged to be ineligible; they included 2 patients with an adenomatous component, 1 with pure adenocarcinoma, 2 with muscle invasion, and 1 with an inflammatory polyp in arm A; and 3 patients with components other than transitional-cell carcinoma, 1 with a papilloma, 1 with muscle invasion, 1 with an inflammatory polyp, and 1 whose tumor was pGX, pTX in arm B. Thus, a total of 122 patients (90.4%) entered in this trial were eligible. One patient in arm A and two patients in arm B, who underwent cystectomy based on the local pathological diagnosis (pG3, pT1), were excluded from the study. Accordingly, a total of 119 patients (88.1%) were evaluable, including 59 patients in arm A and 60 patients in arm B. The patients were followed for an average of 31 months (maximum, 45 months).

Figure 1 shows the distribution of the number of instillations given to the patients in arm A. A total of 36 (61%) patients received all of the 17 scheduled instillations. Of the 23 patients who did not receive the prescribed 17 instillations, 7 did not appear for regular visits; 5 experienced recurrence before the 17th instillation; 5 discontinued the prophylactic treatment because of side effects; 2 received more than 17 instillations and 3 received 16 instillation, due to the inattention of some doctors; and 1 who was diagnosed as having pG2, pTa disease by the center pathologist received only 3 installations because he had been diagnosed as having papilloma by the local pathologist.

Patients' characteristics

Between the two arms, there was no significant difference in the age or gender of the patients, the tumor status at diagnosis, or the size, number, grade, or stage of the tumors (Table 2).

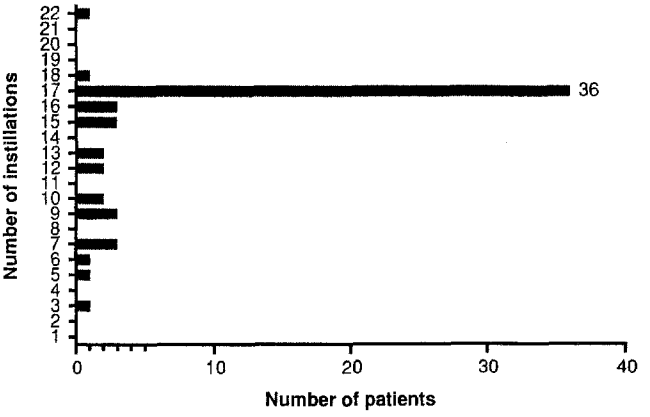

Fig. 1 Distribution of the number of epirubicin instillations in arm A

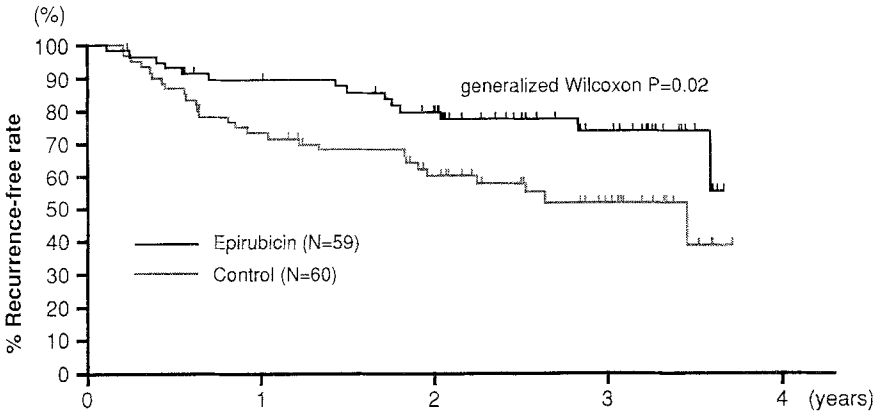

Fig. 2 Interval to initial recurrence in each treatment group

Treatment efficacy

The mean recurrence-free interval was 36 months (95% confidence interval, 32–40 months) in arm A and 28 months (95% confidence interval, 24–32 months) in arm B (Fig. 2). The difference was statistically significant in favor of the epirubicin group ($P = 0.02$). The recurrence-free rates at 2 years after TUR were 77.8% (95% confidence interval, 66.4%–89.2%) in arm A and 59.9% (95% confidence interval, 46.9%–72.9%) in arm B. When disease progression was defined as the development of pathologically confirmed muscle-invasive disease or metastatic disease or both, only 1 patient in arm A had disease progression. The recurrence rate per year was 0.13 in arm A and 0.29 in arm B.

The recurrence-free interval observed for the low-risk subgroup within arm A was significantly lower than that seen for the same subgroup within arm B ($P = 0.03$; Fig. 3). However, in the high-risk subgroup, the recurrence-free interval was not prolonged by the epirubicin therapy (Fig. 4).

Toxicity

The main toxicity of epirubicin instillation was local, involving bladder irritation in 8 (13.8%) cases and gross hematuria in 1 (1.8%) case. In all, 3 patients requested a temporary interruption, and 2 required discontinuation of the treatment. Chest discomfort immediately after the

Table 2 Characteristics of 119 evaluable patients (*NS* Not significant)

	Group		χ^2test
	Arm A (TUR+epirubicin)	Arm B (TUR only)	
Stratification:			
New, solitary	36	40	
New, multiple	14	12	NS
Recurrent	9	8	
Gender:			
M	44	52	
F	15	8	NS
Average age (years)	62.9 ± 11.8	60.1 ± 12.8	NS
Size of largest tumor:			
<1 cm	27	27	
1–3 cm	23	21	NS
>3 cm	9	12	
Number of tumors:			
1	37	44	
2	10	6	NS
>3	12	10	
Histological grade:			
G1	17	19	
G2	37	38	NS
G3	5	3	
Pathological stage:			
pTa	54	56	
pT1	5	4	NS
Number of evaluable patients	59	60	

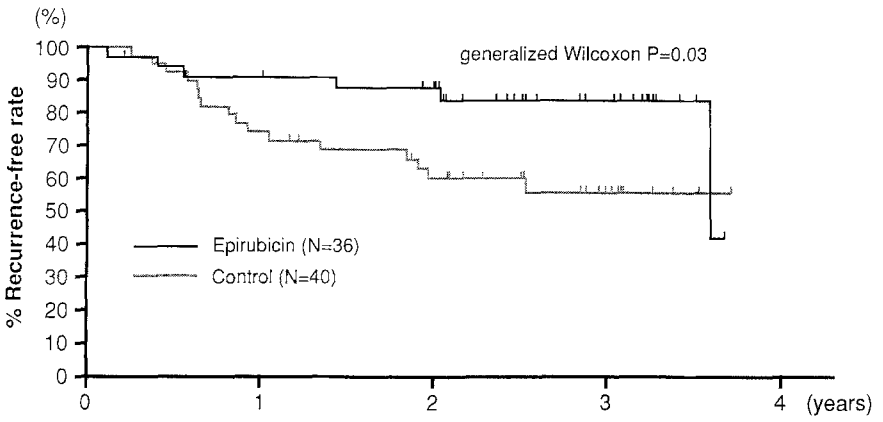

Fig. 3 Interval to initial recurrence in the low-risk subgroup

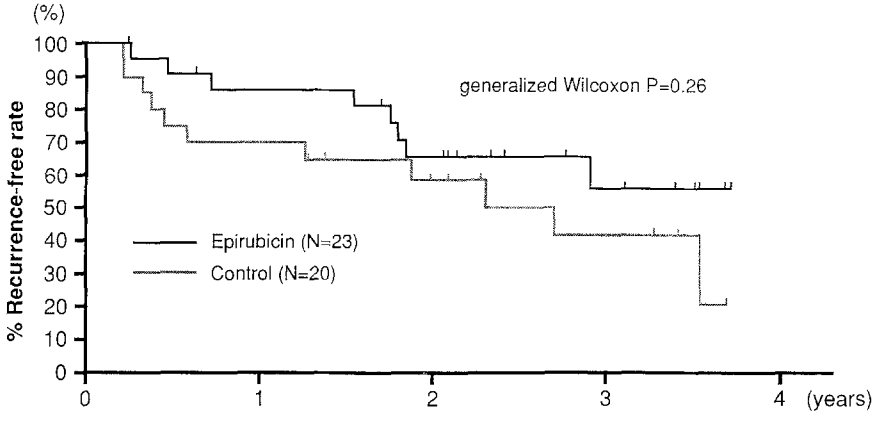

Fig. 4 Interval to initial recurrence in the high-risk subgroup

instillations was observed in 1 patient, and the instillations were thus discontinued. Atrioventricular (A-V) block and myocardial infarction were encountered in 1 patient each.

Discussion

The goal of treatment of superficial bladder cancer is prevention of recurrence and progression. Such chemotherapeutic agents as thiotepa, doxorubicin, and mitomycin C are known to be effective in terms of prophylaxis [7, 10, 12]; however, the prophylactic effect of a new anthracycline derivative, epirubicin, has not yet been clearly determined [2, 3, 11, 16]. In our study, epirubicin instillation reduced the initial recurrence rate after 2 years by 18% as compared with the control group. The interval to initial recurrence was significantly longer in the epirubicin group. The recurrence rate observed in the epirubicin group was less than half that seen in the control group because epirubicin reduced the rate of initial recurrence and extended the recurrence-free interval. The results of our study imply that epirubicin has prophylactic effects equivalent to those of thiotepa, doxorubicin, and mitomycin C.

Factors such as the number, size, grade, and stage of the tumor and prior recurrence rates affect disease recurrence and progression. In our study, patients with a newly diagnosed solitary tumor were considered to be a low-risk subgroup for recurrence and progression, whereas those with either newly diagnosed multiple tumors or recurrent tumors were considered to be a high-risk subgroup. In our study, only one patient in arm A experienced progression. This may have been due to the high proportion of low-risk patients involved in the study (approximately two-thirds of the evaluable patients). In the low-risk subgroup, the interval to initial recurrence was significantly longer after epirubicin instillation. Since in the absence of prophylactic treatment approximately half of the patients, even in the low-risk subgroup, experienced recurrence, intravesical epirubicin appears to be a suitable treatment for low-risk patients.

We hesitate to perform BCG instillation in low-risk patients because of the frequently associated bladder irritation and potential major side effects such as contracted bladder and generalized infection, among others [9]. However, epirubicin did not prevent initial recurrence in the high-risk subgroup, for which BCG has recently been reported to be the treatment of choice [5, 6, 8, 13]. Moreover, the number of patients involved in our study were insufficient to enable us to conclude that epirubicin is not an appropriate drug for high-risk patients. Recent studies have indicated that chemotherapeutic agents can prevent early recurrence but that there is no difference in the recurrence rates observed after 5 years between the treatment group and the control group [1, 4, 14]. Further investigation is needed regarding this point.

Local toxicity was the major side effect encountered in the present study, but only two patients required treatment discontinuation because of severe symptoms. Chest discomfort may be caused by an allergic reaction to epirubicin.

The cases of arrhythmia (A-V block) and myocardial infarction seen in this study cannot be related to epirubicin because the amount of epirubicin absorbed from the bladder is extremely small.

In conclusion, prophylactic intravesical epirubicin instillation is a safe and effective treatment to prevent tumor recurrence in patients with superficial bladder cancer. It seems that low-risk patients receive greater benefit from the epirubicin instillation than do high-risk patients. Epirubicin is an expensive drug, and a protocol of 17 instillations may thus be expensive for the patient. Further studies, including a clinical trial comparing the efficacy of a lower number of epirubicin instillations, are warranted.

References

1. Akaza H, Koiso K, Kotake T, Matsumura Y, Isaka S, Machida T, Obata K, Ohashi Y, Ohe H, Shimazaki J, Tashiro K, Ueda T, Kagawa S, Niijima T, the Japanese Urological Cancer Research Group for Adriamycin (1992) Long-term results of intravesical chemoprophylaxis of superficial bladder cancer: experience of the Japanese Urological Cancer Research Group for Adriamycin. Cancer Chemother Pharmacol 30 [Suppl]: S15
2. Burk K, Kurth KH, Newling D (1989) Epirubicin in treatment and recurrence prophylaxis of patients with superficial bladder cancer. Prog Clin Biol Res 303: 423
3. da-Silva FC (1989) The role of adriamycin and epirubicin in superficial bladder cancer and carcinoma in situ. Prog Clin Biol Res 303: 401
4. Heney NM, Ahmed S, Flanagan MJ, Frable W, Corder MP, Hafermann MD, Hawkins IR (1983) Superficial bladder cancer: progression and recurrence. J Urol 130: 1083
5. Herr HW, Laudone VP, Whitmore WF (1987) An overview of intravesical therapy for superficial bladder tumors. J Urol 138: 1363
6. Herr HW, Laudone VP, Badalament RA, Oettgen HF, Sogani PC, Freedman BD, Melamed MR, Whitmore WF (1988) Bacillus Calmette-Guérin therapy alters the progression of superficial bladder cancer. J Clin Oncol 6: 1450
7. Koontz WW, Prout GR, Smith W, Frable WJ, Minnis JE (1981) The use of intravesical thiotepa in the management of noninvasive carcinoma of the bladder. J Urol 125: 307
8. Lamm DL (1985) Bacillus Calmette-Guérin immunotherapy for bladder cancer. J Urol 134: 40
9. Lamm DL (1992) Complications of bacillus Calmette-Guérin immunotherapy. Urol Clin North Am 19: 565
10. Matsumura Y, Akaza H, Isaka S, Kagawa S, Koiso K, Kotake T, Machida T, Niijima T, Obata K, Ohashi Y, Ohe H, Ohi Y, Shimazaki J, Tashiro K, Ueda T, the Japanese Urological Cancer Research Group for Adriamycin (1992) The 4th study of prophylactic intravesical chemotherapy with Adriamycin in the treatment of superficial bladder cancer: the experience of the Japanese Urological Cancer Research Group for Adriamycin. Cancer Chemother Pharmacol 30 [Suppl]: S10
11. Melekos MD, Dauaher H, Fokaefs E, Barbalias G (1992) Intravesical instillations of 4-epi-doxorubicin (epirubicin) in the prophylactic treatment of superficial bladder cancer: results of a controlled prospective study. J Urol 147: 371
12. Niijima T, Koiso K, Akaza H, the Japanese Urological Cancer Research Group for Adriamycin (1983) Randomized clinical trial on chemoprophylaxis of recurrence in cases of superficial bladder cancer. Cancer Chemother Pharmacol 11 [Suppl]: S79
13. Pagano F, Bassi P, Milani C, Meneghini A, Maruzzi D, Garbeglio A (1991) A low dose bacillus Calmette-Guérin regimen in superficial bladder cancer therapy: is it effective? J Urol 122: 27
14. Prout GR, Koontz WW, Coomms LJ, Hawkins IR, Friedell GH (1983) Long-term fate of 90 patients with superficial bladder cancer randomly assigned to receive or not to receive thiotepa. J Urol 130: 677
15. Thrasher JB, Crawford ED (1992) Complications of intravesical chemotherapy. Urol Clin North Am 19: 529
16. Tsushima T, Matsumura Y, Ozaki Y, Yoshimoto J, Obama T, Akagi T, Nasu Y, Ohmori H (1984) Intravesical chemotherapy with 4′-epi-adriamycin in patients with superficial bladder tumors. Jpn J Cancer Chemother 11: 2502