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SESSION III

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Comparison of the prophylactic usefulness of epirubicin and doxorubicin in the treatment of superficial bladder cancer by intravesical instillation: a multicenter randomized trial

Abstract A multicentric randomized trial was conducted for the purpose of investigating the prophylactic efficacy of intravesical epirubicin instillation following transurethral resection of superficial bladder cancer in comparison with the efficacy of doxorubicin. The patients were centrally randomized into 2 groups and received 19 intravesical instillations of epirubicin or doxorubicin at 30 mg/30 ml physiological saline twice a week for 4 weeks and then once monthly for 11 months. A total of 150 patients with Ta and T1 superficial bladder cancer were entered in the trial, and 114 were evaluable. The nonrecurrence rates determined for each group at 1 and 2 years by the Kaplan-Meier method were 92.8% and 88.6%, respectively, for the epirubicin group and 86.4% and 81.7%, respectively, for the doxorubicin group. The differences between the two groups were not statistically significant. The main side effects encountered in this study were symptoms of bladder irritation such as micturitional pain, pollakisuria, and hematuria. The respective frequencies of those symptoms were 10%, 15.0%, and 5.0% in the epirubicin group and 14.8%, 14.8%, and 0 in the doxorubicin group. These results suggest that epirubicin is a useful drug, comparable with doxorubicin, for intravesical instillation chemotherapy in the prophylactic treatment of superficial bladder cancer.

Key words Epirubicin · Superficial bladder cancer · Intravesical instillation

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Introduction

The recurrence rate of superficial bladder cancer treated by transurethral resection (TUR) alone is 50%–80% [12, 18]. Intravesical administration of cytotoxic agents seems to be useful for the prevention of tumor recurrence after TUR of superficial bladder cancer [2, 15, 18]. The protocol (dose, volume, frequency, interval, and period) for intravesical treatment as well as the agent to be given, however, remain controversial [1, 16]. Epirubicin is a new anthracycline derivative and appears to have similar antitumor activity as and less toxicity to the heart and other organs than does doxorubicin [5, 6]. The ablative and prophylactic effects of the instillation of epirubicin on superficial bladder cancer have been reported [3, 8, 11, 13, 14, 17, 20], but there are few reports of randomized studies comparing the prophylactic effects of epirubicin and doxorubicin [4]. In this study, we evaluated the usefulness of epirubicin in comparison with doxorubicin on the basis of the nonrecurrence rate and side effects.

Patients and methods

From January of 1990 through December of 1992, 21 hospitals participated in this study, and a total of 150 patients with Ta and T1 superficial bladder cancer were entered in the trial. The criteria for exclusion were the presence of another cancer, residual tumor, or carcinoma in situ; previous treatment with doxorubicin or its derivatives; severe dysfunction of the heart, liver, kidney, or bone marrow; severe complications; and a poor general condition, suggesting that survival for the duration of the study was unlikely. The patients were

Table 1 Handling of the 150 patients studied

Number of patients entered	150		
Data not collected	20		
Ineligible	6		
		T0	2
		T2	2
		Incomplete surgery	2
Eligible	124		
Unevaluable	10		
		Protocol violation	2
		Lost to follow-up	8
Evaluable	114		

Table 2 Clinical and pathological characteristics of 114 evaluable patients (*NS* Not significant)

Background factor	Epirubicin (n = 60)	Doxorubicin (n = 54)	χ^2 test
Mean age (years)	68.8	61.9	$P < 0.01$[a]
Range (years)	35–88	33–87	
Sex:			NS
M	51	47	
F	9	7	
History:			NS
Primary	46	41	
Recurrent	8	8	
Unknown	6	5	
Morphological feature of tumors:			NS
Papillary, narrow stalk	45	46	
Papillary, broad base, sessile	10	6	
Nonpapillary, broad base, sessile	1	1	
Nonpapillary, narrow stalk	2	1	
Velvet-like, granular, ulcerative	2	0	
Tumor size (cm):			NS
<1	27	27	
1–3	24	25	
3–5	8	2	
>5	1	0	
Number of tumors:			NS
Solitary	28	34	
2–4	23	12	
≥5	7	6	
All over surface	1	2	
Unknown	1	0	
Clinical stage:			NS
Ta	21	17	
T1	29	31	
Tx	10	6	
Histological grade:			NS
G1	20	11	
G2	29	36	
G3	7	4	
Unknown	4	3	

[a] t-test

centrally randomized into 2 groups and received 19 intravesical instillations of epirubicin or doxorubicin at 30 mg/30 ml physiological saline for 1 year after transurethral resection. The intravesical instillation was performed twice a week for 4 weeks and then once monthly for 11 months. All of the patients entered in the trial were followed

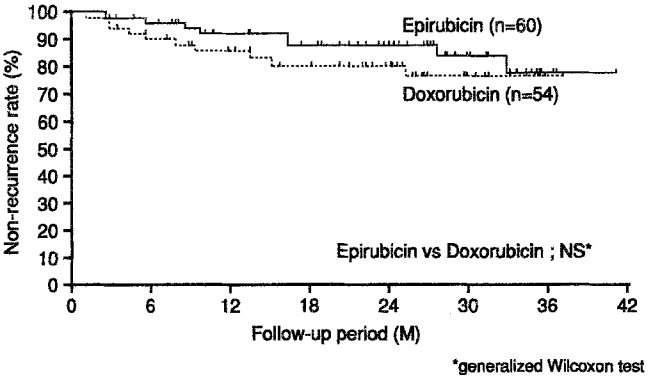

Fig. 1 Nonrecurrence rates of the patients as determined for each treatment

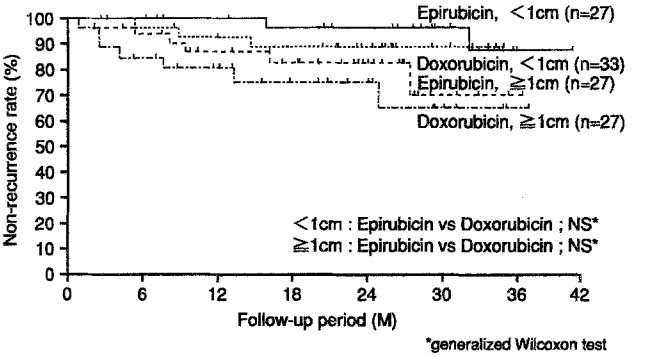

Fig. 2 Nonrecurrence rates of the patients as determined for each treatment and tumor size

until the first recurrence by cystoscopic examination every 3 months for 3 years and by urinary cytology monthly for the 1st year and then every 3 months for 3 years. The results were evaluated on the basis of the nonrecurrence rate and side effects. The nonrecurrence rates according to the tumor size (<1 cm, ≧1 cm), number (solitary, multiple), grade (G1, G2, G3), and stage (Ta, T1) and to the history of primary or recurrent disease in each group and in all patients were estimated by the Kaplan-Meier method and compared by the generalized Wilcoxon test. The frequency of side effects in each group was evaluated by the chi-square test.

Results

Of the 150 patients entered in this study, 20 had insufficient data, 6 were ineligible because of stage T0 or T2 disease and incomplete surgery, and 10 were unevaluable due to protocol violation or loss to follow-up (Table 1). Finally, 60 patients received epirubicin and 54 received doxorubicin, and no significant difference in the characteristics of the patients was found between the two groups by the chi-square test, except for age ($P < 0.01$, t-test; Table 2). The follow-up period was 674 ± 315 days (mean ± SD) in the epirubicin group and 606 ± 318 days in the doxorubicin group, with no significant difference being found (t-test).

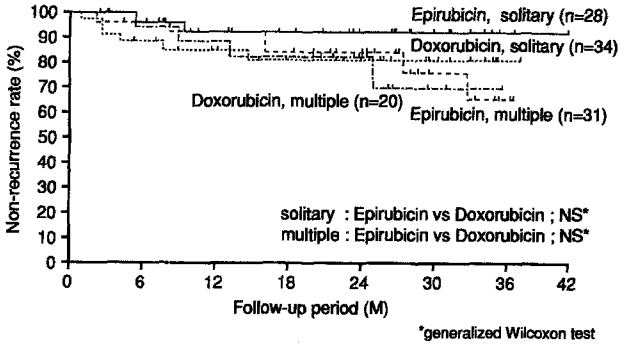

Fig. 3 Nonrecurrence rates of the patients as determined for each treatment and tumor multiplicity

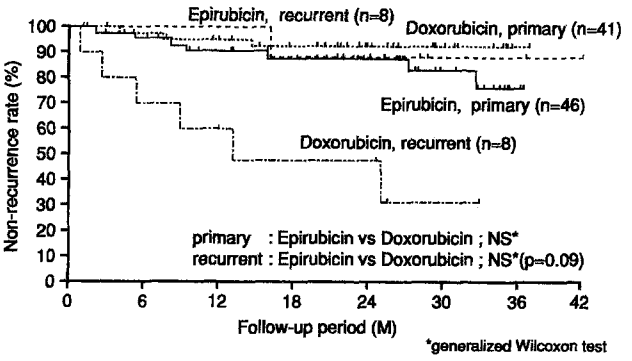

Fig. 6 Nonrecurrence rates of the patients as determined for each treatment and tumor history

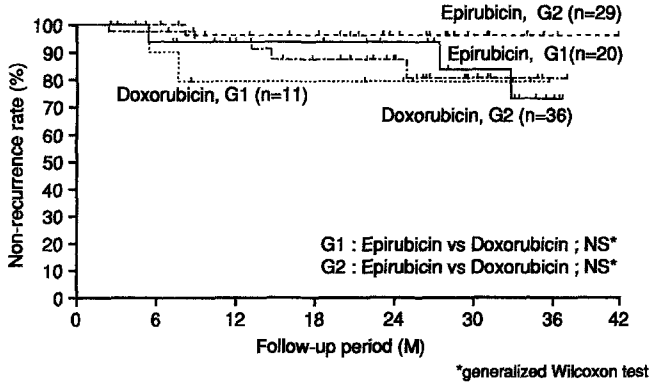

Fig. 4 Nonrecurrence rates of the patients as determined for each treatment and histological grade

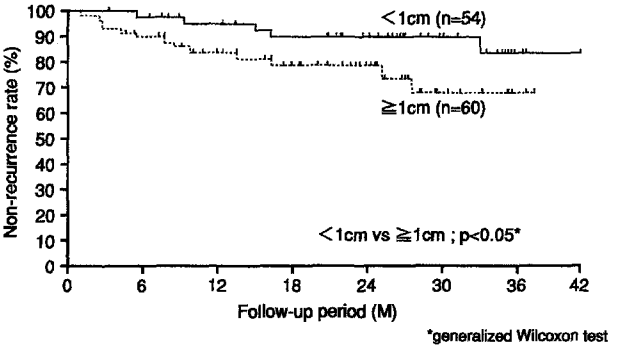

Fig. 7 Nonrecurrence rates for the patients as determined according to tumor size

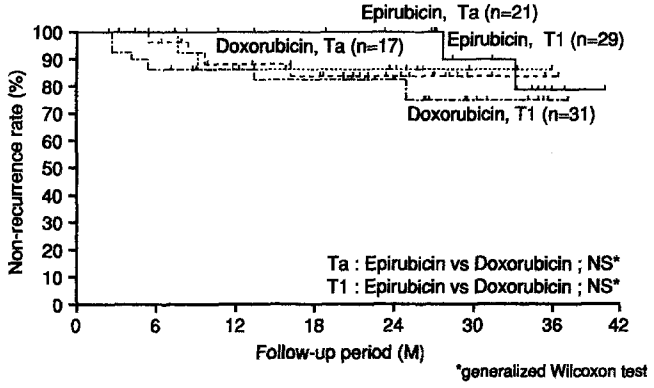

Fig. 5 Nonrecurrence rates of the patients as determined for each treatment and clinical stage

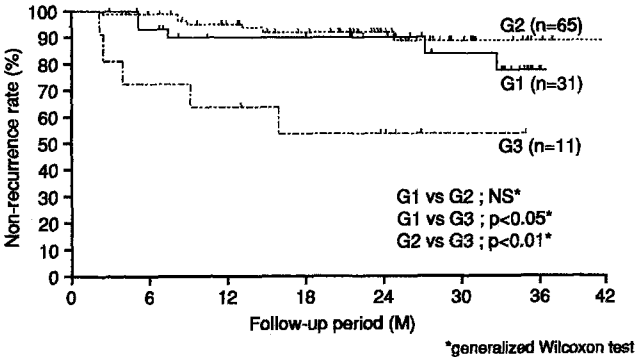

Fig. 8 Nonrecurrence rates for the patients as determined according to histological grade

The nonrecurrence rates obtained in each group at 1 and 2 years were 92.8% and 88.6%, respectively, for the epirubicin group and 86.4% and 81.8%, respectively, for the doxorubicin group. There was no statistically significant difference between the two groups (Fig. 1). The relative nonrecurrence rate as a function of the tumor size, number, grade, stage, and history showed no significant difference between the two groups (Figs. 2–6). Grade 3 tumors were not analyzed because of the small number of cases. Among the patients with grade 3 tumors, 2/7 in the epirubicin group and 2/4 in the doxorubicin group experienced recurrence. Table 3 shows the nonrecurrence rates determined for each subgroup. In all patients, regardless of the treatment group, significant differences were found in relation to the tumor size ($P = 0.034$, Fig. 7) and histological grade (G1 versus G3, $P = 0.015$; G2 versus G3, $P = 0.001$; Fig. 8) but not in

Table 3 Nonrecurrence rates determined according to tumor characteristics and treatment

Tumor	Nonrecurrence rate (%)		*P* value[a]
	Epirubicin (1-year/2-year)	Doxorubicin (1-year/2-year)	
Overall	92.8/88.6	86.4/81.8	0.218
Size:			
<1 cm	100.0/95.2	91.8/87.5	0.342
≧1 cm	87.4/83.6	81.1/76.1	0.325
Number of tumors:			
Solitary	92.4/92.4	85.1/81.2	0.193
Multiple	92.9/84.6	88.5/82.6	0.744
Grade:			
Grade 1	94.7/94.7	80.0/80.0	0.509
Grade 2	96.0/96.0	94.2/87.5	0.225
Stage:			
Ta	100.0/100.0	87.5/87.5	0.201
T1	88.3/83.6	86.8/82.9	0.554
History:			
Primary	90.5/87.6	92.4/86.6	0.966
Recurrent	100.0/87.5	62.5/62.5	0.091

[a] Generalized Wilcoxon test

Table 4 Nonrecurrence rates determined according to tumor characteristics

Tumor	Number of patients	Nonrecurrence rate (%) (1-year/2-year)	*P* value[a]
Tumor size (cm):			
<1	54	95.8/91.3	0.034
≧1	60	84.5/80.2	
Number of tumors:			
Solitary	62	88.4/86.3	0.816
Multiple	51	91.3/84.9	
Grade:			
G1	31	89.4/89.4	G1 vs G2 = 0.537
G2	65	95.0/91.2	G1 vs G3 = 0.015
G3	11	63.6/53.0	G2 vs G3 = 0.001
Stage:			
Ta	38	94.3/94.3	0.135
T1	60	87.6/83.4	
History:			
Primary	87	91.4/87.1	0.115
Recurrent	16	81.3/74.5	

[a] Generalized Wilcoxon test

relation to the tumor multiplicity, clinical stage, or history (Table 4). Progression to invasive disease was seen in 1 epirubicin-group case (by stage alone) and in 3 doxorubicin-group cases (2 by grade, 1 by stage). The effect in preventing disease progression was unclear due to the low incidence of such cases.

The main side effects encountered in this study were symptoms of bladder irritation such as micturitional pain, pollakisuria, and hematuria. The respective frequencies of those symptoms were 10%, 15.0%, and 5.0% in the epirubicin group and 14.8%, 14.8%, and 0 in the doxorubicin group (Table 5). There was no significant difference between the two treatment groups as determined by the chi-square test.

Discussion

In this randomized study, we tried to confirm the prophylactic usefulness of epirubicin in comparison with doxorubicin, which is commonly used for intravesical chemotherapy. The nonrecurrence rate at 2 years was 88.6% for the epirubicin group, and this rate may be superior to previous reports [4, 14]. However, the results cannot be easily compared because of differences in the treatment protocol and patients' profiles. Epirubicin can be considered to be comparable with doxorubicin (nonrecurrence rate, 81.8%). In the relative nonrecurrence rates determined as a function of the tumor characteristics, no significant difference between the two groups was found (Table 3). Although for recurrent tumors epirubicin showed a tendency to be

Table 5 Incidence of side effects

Side effect	Grade[a]	Epirubicin (n = 60)	Doxorubicin (n = 54)	χ^2 test
Micturitional pain:				
	1	2	4	
	2	3	3	
	3	1	1	
	Total	6 (10.0%)	8 (14.8%)	NS
Pollakisuria:				
	1	1	4	
	2	7	3	
	3	1	1	
	Total	9 (15.0%)	8 (14.8%)	NS
Hematuria:				
	1	1	0	
	2	2	0	
	3	0	0	
	Total	3 (5.0%)	0 (0)	–

[a] Grade 1, the symptom required no treatment; grade 2, some treatment was required to continue the intravesical instillation; grade 3, intravesical instillation could not be continued

superior to doxorubicin (86.6% versus 62.5%, P = 0.091) and the nonrecurrence rate obtained for recurrent tumors was higher than that reported from previous studies [11, 14], its superiority could not be clearly confirmed because of the small number of cases involved; a larger study is thus required. The risk factors for recurrence of superficial bladder cancer are considered to be the tumor number, grade, stage, and history. In this study, since a control arm of TUR alone without any prophylactic treatment was not included in the design, the risk factors for untreated tumors are unknown. In all patients, regardless of treatment with either epirubicin or doxorubicin, significant differences were found in the tumor size and grade (G1 and G2 versus G3; Table 4). Whether prophylactic intravesical administration is more useful in the low- or the high-risk group remains controversial [1, 14, 17], but the present results suggest that for high-risk tumors another protocol may have to be adopted.

In terms of toxicity, micturitional pain and pollakisuria due to chemical cystitis were observed in 10%–15% of each group and hematuria was observed in 5% of the patients in the epirubicin group. The frequency of these side effects in the epirubicin group were lower than previously reported [3, 13, 14], but the data cannot be easily compared because of differences in the protocols. Nevertheless, the side effects were mild and there was no significant difference between the two groups despite the expectation of less toxicity for epirubicin, as has been suggested in an earlier report [19].

Recently, bacille Calmette-Guérin (BCG) was shown to be a very effective agent for carcinoma in situ as well as for Ta and T1 tumors [7, 9], and it was also noted to cause severe systemic and local side effects [10]. Therefore, the indication of BCG therapy should be carefully decided. However, if toxicity similar to that of BCG is considered permissible, intravesical administration of cytotoxic agents at a high concentration may not be inferior to BCG at all. In fact, the efficacy of high-dose intravesical instillation of epirubicin (80 mg/50 ml) for carcinoma in situ has been reported to be comparable with that of BCG and to produce less local toxicity [8]. This finding suggests that if used at a high concentration, cytotoxic agents commonly used for low-risk superficial bladder cancer can be the first-line chemotherapy prior to BCG for carcinoma in situ or high-risk patients. For epirubicin, further studies on dose escalation will be necessary to prove its advantageousness.

In conclusion, although statistical superiority of epirubicin over doxorubicin could not be demonstrated, epirubicin is a useful drug, comparable with doxorubicin, for intravesical chemotherapy in the prophylactic treatment of superficial bladder cancer. A second randomized study on the optimal drug concentration and instillation volume has been designed and is in progress. That study may demonstrate the efficacy of epirubicin more clearly.

Appendix 1

The Kobe University Urological Oncology Group

Kobe University	(S. Kamidono)
Kawachi General Hospital	(S. Den)
Yodogawa Christian Hopital	(M. Hazama)
Labour Welfare Corporation Kansai Rosai Hospital	(K. Hirooka)
Hyogo Prefectural Amagasaki Hospital	(G. Hamami)
Konan Hospital	(J. Itani)
Labour Welfare Corporation Kobe Rosai Hospital	(H. Saito)
Shinko Hospital	(N. Yamanaka)
Shakaihoken Kobe Central Hospital	(N. Ito)
Kokuritsu Kobe Hospital	(K. Umezu)
Miki City Hospital	(K. Kondo)
Akashi Municipal Hospital	(S. Obe)
Nishiwaki Municipal Hospital	(N. Kataoka)
Kasai Municipal Hospital	(T. Izumi)
Hyogo Prefectural Kaibara Hospital	(M. Matsushita)
Hyogo Prefectural Kakogawa Hospital	(H. Oshima)
Himeji Red Cross Hospital	(O. Tomioka)
Takasago Municipal Hospital	(H. Nagata)
Hyogo Prefectural Awaji Hospital	(S. Ka)
Rokko Hospital	(K. Goto)
Hyogo Medical Center for Adults	(A. Fujii)

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