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SESSION III

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Prophylactic chemotherapy with anthracyclines (Adriamycin, epirubicin, and pirarubicin) for primary superficial bladder cancer

Abstract A multicentric randomized trial was conducted to evaluate the efficacy of intravesical chemoprophylaxis for primary superficial bladder cancer. The 299 eligible patients with primary superficial bladder cancer were randomized into four groups (A, B, C, and D) after pathological confirmation. Intravesical instillation of drugs, which were dissolved in 20 ml physiological saline (PS; group A, 20 mg Adriamycin; group B, 20 mg epirubicin; group C, 20 mg pirarubicin; group D (control), PS alone], was performed once a week for 2 weeks after trasurethral resection and then once every 2 weeks for 14 weeks, once monthly for 8 months, and once every 3 months for 1 year. No significant difference in the patients' characteristics was found among the four groups. The follow-up period ranged from 3 to 31 months (mean, 14 months). The nonrecurrence rates were estimated by the method of Kaplan and Meier. The relative effects of five variables (the tumor status, size, grade, and stage and the treatment) on the efficacy of the chemoprophylaxis regimens were evaluated using a multiple regression model. Although the nonrecurrence rates determined for groups A and B were significantly higher than that found for group D ($P < 0.05$), no significant difference in the nonrecurrence rate was detected among groups A, B, and C. The multiple regression model indicated that the most important factors in preventing tumor recurrence at 12 or 24 months were the intravesical instillation of an anthracycline and the tumor status (solitary). These results demonstrate that intravesical instillation of the tested anthracyclines is effective for at least 2 years as prophylactic chemotherapy for primary superficial bladder cancer.

Key words Prophylactic chemotherapy · Bladder instillation · Anthracycline · Superficial bladder cancer

Introduction

The major problem in the treatment of superficial bladder cancer is the high incidence of recurrence after treatment. In addition, about 10% of these recurrent tumors progress to invasive carcinoma [11]. Many anticancer drugs have been given intravesically for prophylaxis of tumor recurrence in large collaborative studies. Of these drugs, some anthracyclines, such as Adriamycin, epirubicin, and pirarubicin, are commonly used in Japan and Europe [1, 2, 4, 7–9]. To evaluate the prophylactic efficacy of intravesical chemotherapy with anthracyclines (Adriamycin, epirubicin, and pirarubicin) for primary superficial bladder cancers, a multicentric prospective randomized trial was conducted.

Materials and methods

Patients with histologically proven superficial bladder cancer (stages Ta and T1, grades 1–3) were enrolled in this study, which was conducted jointly by Hokkaido University Hospital and 24 affiliated clinics (Table 1). The eligible patients were randomized into four groups using the envelope method (Table 2). The drug dose was 20 mg each for Adriamycin (ADM, group A), epirubicin (epi-ADM, group B) and pirarubicin (THP-ADM, group C). Each drug was instilled into the bladder in 20 ml physiological saline and then retained for at least 1 h. The patients in group D, who were given normal saline containing no drug, served as the untreated control. The intravesical instillation was started at 1 week after transurethral resection and was performed once

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Sapporo City General Hospital	(N. Ohashi)
Otaru City General Hospital	(K. Kawakura)
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Nayoro City General Hospital	(S. Satoh)
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Chitose Municipal Hospital	(K. Arikado)
Ebetsu Municipal Hospital	(T. Gotoh)
Bibai Rosai Hospital	(H. Morita)
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Hakodate Central Hospital	(N. Miyabe)
Takikawa Municipal Hospital	(N. Sakakibara)
Sapporo JR Hospital	(K. Toyoda)
Wakkanai Municipal Hospital	(H. Harada)
Obihiro Kosei Hospital	(S. Sakashita)
Asahikawa Kosei Hospital	(S. Minami)
Date Red Cross Hospital	(S. Tsubo)
Asahikawa City General Hospital	(A. Otsuka)

Table 2 Protocol for prophylactic treatments[a]

Group A Adriamycin	20 mg/20 ml saline
Group B Epirubicin	20 mg/20 ml saline
Group C Pirarubicin	20 mg/20 ml saline
Group D Control	20 ml saline or no instillation

[a] Intravesical instillation schedule: once a week for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months, then every 3 months for 1 year (total, 21 times during a 2-year period)

Table 3 Classification of patients (*ADM* Adriamycin, *epi-ADM* epirubicin, *THP-ADM* pirarubicin)

Group	Number of patients	
	Entered	Evaluable
A (ADM)	83	80
B (epi-ADM)	87	79
C (THP-ADM)	75	69
D (control)	77	71
Total	322	299

a week for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months, and then every 3 months for 1 year.

The first recurrence noted during follow-up or on the completion of bladder instillation was the end point for evaluation in this study. Recurrence was detected by cystoscopy or urinary cytology repeated at 3-month intervals and had to be confirmed by biopsy. The disease-free interval was defined as the interval between transurethral resection at entry and the date of the first positive pathological finding. Patients without recurrence were censored at the date of the last cystoscope study. Central pathological review was not performed in this study.

We enrolled 322 patients in this study from November 1989 to February 1992. The number of dropout and ineligible patients was 23. Therefore, a total of 299 patients were evaluable (Table 3). The clinical and pathological characteristics of the 299 patients are shown in Table 4. No significant difference was found among the four groups

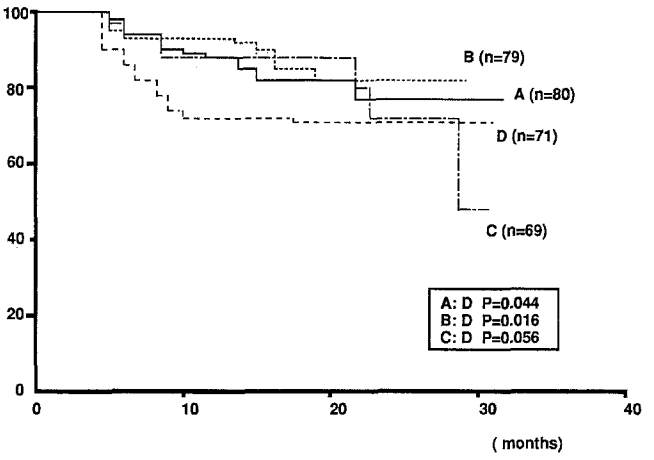

Fig. 1 Comparison of the overall recurrence-free rates determined for the four groups. Statistical analysis was carried out using the generalized Wilcoxon test

in terms of the patients' sex or age or the tumor size, multiplicity, histological grade, or pathological stage. The follow-up period for the evaluable patients ranged from 3 to 32 months (mean, 12.7 months).

Nonrecurrence rates were calculated by the Kaplan-Meier method. Statistical analysis was carried out using the chi-square (χ^2) test or the generalized Wilcoxon test. To determine the relative importance of some variables regarding tumor recurrence at 12 and 24 months, a multiple regression model was also applied [6]. We employed five variables: (1) tumor multiplicity, (2) tumor size, (3) histological grade, (4) pathological stage, and (5) administration of an anthracycline.

Results

Figure 1 shows the recurrence-free curves as analyzed by the Kaplan-Meier method. The nonrecurrence rates determined for groups A and B were significantly higher than that found for group D ($P < 0.05$). No significant difference was found among groups A, B, and C.

Table 5 shows the number of patients with tumor progression and the time to progression. Tumor progression, defined as an increase in the grade and/or stage of the tumor, occurred in less than 5% of the patients in each of the four groups. There was no significant difference in the incidence of tumor progression or the time to progression among the four groups.

The relationships between the prophylactic effect of the treatment and some background factors, that is, the tumor size, multiplicity, grade, and stage, are summarized in Table 6. Each group was compared with group D (untreated control) by the generalized Wilcoxon test. A significant effect was observed in patients of group A with a solitary tumor. Group B included a significantly greater number of patients with a tumor measuring more than 3 cm in diameter, those with multiple lesions, and those with a T1 tumor. Furthermore, group C included a significantly higher number of patients with a tumor measuring more than 3 cm in diameter, those with a solitary lesion, and those with a T1 tumor. When the three groups (groups A, B, and C) were categorized as

Table 4 Clinical and pathological characteristics (*NS* Not significant)

Background factor	Group				χ^2 test
	A (ADM)	B (epi-ADM)	C (THP-ADM)	D (control)	
Sex (M/F)	59/21	56/23	54/15	57/14	NS
Mean age (years)	65.0	66.1	64.9	66.5	NS*
Tumor size (<1 cm/1–3 cm/>3 cm)	31/41/8	25/39/15	29/28/11	24/35/11	NS
Multiplicity (solitary/multiple)	49/31	53/26	40/29	47/24	NS
Grade (G1/G2/G3)	20/42/8	20/48/11	21/41/7	26/40/5	NS
Stage (Ta/T1/Tis)	39/40/1	29/47/2	26/41/1	37/31/1	NS

* Student's *t*-test

Table 5 Tumor progression according to grade and/or stage

	Group			
	A (ADM)	B (epi-ADM)	C (THP-ADM)	D (control)
Progression:				
Grade	1	1	2	3
Stage	2	1	0	0
Grade & stage	1	1	1	0
Total (%)	4/80 (5%)	3/79 (4%)	3/69 (4%)	3/71 (4%)
Time to progression (months)	4,5,9,10	3,9,20	5,7,7	3,4,10

Table 6 Prophylactic effect of the therapy in relation to each background factor (– Not significant)

Background factor	Group			
	A[a] (ADM)	B (epi-ADM)	C (THP-ADM)	A+B+C (anthracycline)
Size:				
<1 cm	–	–	–	–
1–3 cm	–	–	–	–
>3 cm	–	*	*	*
Multiplicity:				
Solitary	*	–	*	*
Multiple	–	*	–	*
Grade:				
G1	–	–	–	–
G2	–	–	–	–
G3	–	–	–	–
Stage:				
Ta	–	–	–	–
T1	–	*	*	*

* Statistically significant ($P < 0.05$)

[a] Compared with the value obtained for group D (control) based on the nonrecurrence rate (generalized Wilcoxon test)

the anthracycline-treatment group, a prophylactic effect was observed in patients with a tumor measuring more than 3 cm in diameter, those with solitary and multiple tumors, and those with a T1 tumor as compared with the control group (group D).

To assess the relative importance of each factor, we utilized a multiple regression model to determine the relative importance of some variables regarding tumor recurrence at 12 and 24 months (Table 7). For multiplicity, at 12 months the coefficient/SE (t value) was +7.7 ($P < 0.001$), which means that multiple tumors carried a higher risk of recurrence as compared with solitary tumors. For the anthracycline treatment, the t value was +6.9 ($P < 0.001$), indicating that tumor recurrence was more frequent in the untreated control group as compared with the patients receiving anthracycline treatment. The other variables, that is, the tumor size, grade, and stage, did not show a significant correlation with tumor recurrence. When

Table 7 Multivariate analysis of tumor recurrence at 12 and 24 months[a]

Variable	Code	12 months		24 months	
		Coefficient/SE (*t* value)	*P* value	Coefficient/SE (*t* value)	*P* value
Multiplicity	Solitary = 1 Multiple = 2	+7.7	<0.001	+3.4	<0.01
Size	<1 cm = 1 1–3 cm = 2 >3 cm = 3	+1.2	NS	+1.6	NS
Grade	G1 = 1 G2 = 2 G3 = 3	+0.12	NS	+1.4	NS
Stage	Ta = 1 T1 = 2	+1.8	NS	+1.2	NS
Treatment (anthracycline)	Instillation (+) = 1 Instillation (–) = 2	+6.9	<0.001	+4.9	<0.001

[a] Recurrence (–) = 0, recurrence (+) = 1

the same analysis was performed at 24 months, the *t* value was +4.9 for anthracycline treatment ($P < 0.001$) and +3.4 for multiplicity ($P < 0.01$). Again, the other variables showed no statistically significant correlation.

Discussion

The high incidence of recurrence of superficial bladder cancers after initial transurethral surgery has presented a major therapeutic challenge to urologists. In fact, 40%–85% of these patients experience recurrence within 2–5 years after standard transurethral resection (TUR), and about 10% of these recurrent tumors show a higher stage and grade [11]. For these reasons, many kinds of anticancer drugs have been given intravesically for prophylaxis of tumor recurrence, and this approach has been proven to be effective [1, 3, 4, 9, 10]. However, as these drugs sometimes cause systemic adverse effects or severe local toxicity, there is a need for new, improved drugs for the prevention of tumor recurrence.

Epirubicin and pirarubicin are new anthracycline analogues that have potent anticancer activity and a lower toxicity profile than the older drugs. It has been reported that epirubicin shows prophylactic efficacy against tumor recurrence [2, 7, 8]. Therefore, we designed the present prospective randomized trial to determine whether other anthracycline analogues (epirubicin and pirarubicin) as well as Adriamycin show prophylactic efficacy against tumor recurrence. The present study demonstrated that Adriamycin and epirubicin were equally effective in preventing tumor recurrence, although the observation period was relatively short. In addition, in comparison with the untreated patients after TUR, pirarubicin showed a tendency to prevent tumor recurrence that was not statistically significant. Therefore, it seems that these anthracyclines are useful in the chemoprophylaxis of primary superficial bladder cancer.

To clarify further the prophylactic efficacy of treatment with these anthracyclines, we first compared the treatment outcomes with regard to various tumor factors. We demonstrated that when Adriamycin, epirubicin, and pirarubicin were categorized as anthracyclines, a significant benefit was achieved in patients undergoing intravesical administration of an anthracycline with respect to the tumor size, multiplicity, and pathological stage. However, since some of the factors described herein show mutual correlations, it is difficult to assess the relative importance of each factor by this statistical method. Therefore, we performed a multivariate analysis to determine the relative importance of some background factors with respect to the tumor recurrence. Analysis using the multiple regression model at 12 and 24 months revealed that the most important variables affecting tumor recurrence were the anthracycline treatment and the tumor multiplicity. According to the coding of these variables, tumor recurrence is more frequent in untreated patients with multiple tumors. In other words, intravesical instillation of anthracyclines is effective in patients with a solitary lesion.

Additionally, in the present study, the rate of tumor progression did not differ between patients receiving one of the three anthracyclines (Adriamycin, epirubicin, and pirarubicin) and the untreated control group. Whereas a few studies on the management of superficial bladder cancer with bacille Calmette-Guérin (BCG) have indicated a statistically significant benefit in terms of tumor progression [5], the benefit of treatment against tumor progression with anthracyclines has been unclear. Further studies are necessary to prove the efficacy of anthracyclines in retarding progression.

Although further study over a long observation period may be required, the present data suggest that the intravesical instillation of an anthracycline should be effective for at least 2 years as prophylactic chemotherapy of primary superficial bladder cancer, especially in patients with a solitary tumor.

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