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SESSION III

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A phase II study of prophylactic intravesical chemotherapy with epirubicin in the treatment of superficial bladder cancer

Abstract Intravesical instillation of epirubicin was carried out to investigate the efficacy of this treatment in preventing postoperative recurrence of superficial bladder cancer. The subjects were 100 patients who had been treated with transurethral resection (TUR) for superficial transitional-cell carcinoma of the bladder (classified as primary or recurrent superficial bladder cancer of pathological stage Tis, Ta, or T1 and histological grade G1, G2, or G3) at Tokyo Women's Medical College Hospital and its affiliated hospitals during the 2-year period ranging from April of 1990 through March of 1992. A solution of epirubicin was prepared by dissolving 20 mg in 30 ml physiological saline, and this was instilled into the bladder a total of 17 times during 1 year: once immediately after TUR, once every 2 weeks for the next 4 months, and then once per month for the following 8 months. Thereafter, the course of each patient was followed by performing urinary cytodiagnosis once each month and cystoscopy once every 3 months. Of the 100 patients, 83 were evaluable. The mean duration of follow-up was 461 ± 222 days, and the recurrence rate was 30.1% (25/83 cases). The recurrence rate determined for primary cases was 19.7%, whereas that recorded for recurrent cases was 61.9%. Adverse effects occurred in 9.3% (9/97) of the patients, but these side effects were mild in severity and the instillation regimen did not have to be discontinued in any of the patients. Analysis of the risk factors for recurrence revealed significantly higher recurrence in the recurrent-patient group and the multiple-tumor group. On the basis of these findings, the authors surmised that when given in an intravesical instillation regimen, epirubicin causes few adverse effects, and its efficacy in the prophylaxis of recurrence of superficial bladder cancer is equivalent to that thus for reported for other drugs. At present, the authors are carrying out a controlled clinical study on epirubicin that takes into account the risk factors for recurrence of superficial bladder cancer.

Key words Prophylactic treatment · Epirubicin · Superficial bladder cancer

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Introduction

The prognosis for superficial bladder cancer, which accounts for 70%–80% of all cases of bladder cancer, is relatively good. However, a serious problem remains: a high incidence of tumor recurrence after bladder-preserving surgery. With the objective of preventing recurrence, there have been many attempts at chemotherapy by means of intravesical instillation of various anticancer drugs [2, 9, 13]. Adriamycin (ADM) is considered to be an effective agent in that application, but it is also recognized as causing adverse effects such as symptoms of bladder irritation, among others, in 30%–50% of cases [7].

Table 1 Tokyo Women's Medical College Bladder Cancer Collaborating Group

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Farmitalia Research Institute (Milan, Italy) has developed 4′-epi-Adriamycin (epirubicin), a derivative of ADM. The anticancer effects of epirubicin are said to be equivalent to those of ADM, whereas its adverse reactions seem to be milder in severity. With the objective of preventing tumor recurrence, in the present clinical study the authors gave epirubicin by intravesical instillation to patients who had undergone transurethral resection (TUR) of superficial bladder tumor(s). We then investigated the prophylactic efficacy of this regimen, its adverse effects, and the risk factors for recurrence of superficial bladder cancer.

Patients and methods

The subjects investigated in this study were 100 patients who were diagnosed as having superficial transitional-cell carcinoma of the bladder (classified as primary or recurrent superficial bladder cancer of pathological stage Tis, Ta, or T1 and histological grade G1, G2, or G3) at Tokyo Women's Medical College Hospital and its affiliated hospitals during the 2-year period ranging from April of 1990 through March of 1992 (Table 1). Of the 100 patients entered in this study, 61 with primary tumors, 21 with recurrent disease, and 1 for whom it was unknown as to whether the tumor was primary or recurrent were evaluable. The histological grade was G1 in 40 cases, G2 in 40 cases, and G3 in 6 cases. The pathological stage was Ta in 42 cases, T1 in 29 cases, and Tis in 11 cases (Table 2).

Table 2 Patients' characteristics (n = 83)

	Patients	%
Type of disease:		
Primary	61	73.5
Recurrent	21	25.3
Tumor size:		
<1 cm	38	45.8
1–3 cm	34	41.0
3–5 cm	6	7.2
>5 cm	1	1.2
Number of tumors:		
1	52	62.7
2–4	20	24.1
>5	6	7.2
Almost confluent	1	1.2
Pathological stage:		
Ta	42	47.2
T1	29	32.6
Tis	11	12.4
Histological grade:		
G1	40	43.5
G2	40	43.5
G3	6	6.5

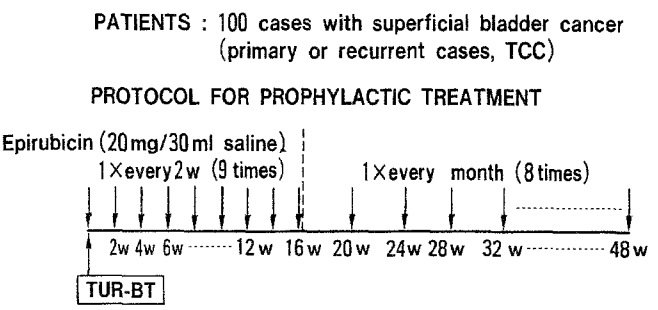


Fig. 1 Protocol for prophylactic treatments given to 100 patients following TUR of superficial bladder tumors

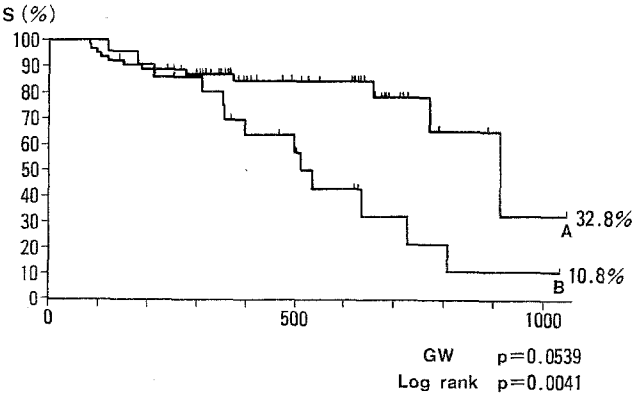
The treatment schedule is shown in Fig. 1. The patients underwent TUR and were then given epirubicin by intravesical instillation with the objective of preventing recurrence. The solution for instillation was prepared by dissolving 20 mg epirubicin in 30 ml physiological saline. This was instilled into the bladder, and the patients were requested to retain the drug solution in the bladder for at least 30 min. This intravesical instillation was performed a total of 17 times during 1 year: once immediately after TUR, once every 2 weeks for the next 4 months, and then once per month for the following 8 months. Thereafter, the course of each patient was followed by performing urinary cytodiagnosis once each month and cystoscopy once every 3 months with the objective of detecting recurrence.

The mean duration of follow-up was 461 ± 222 days as of April of 1993. The nonrecurrence rate was determined by the Kaplan-Meier method, and the data were tested for statistical significance by Wilcoxon's test and the log-rank test. A P value of <0.05 was defined as indicating statistical significance.

Results

Recurrence was detected in 25 (30.1%) of the 83 evaluable patients. Tumor recurrence after TUR occurred in 12 of 61 (19.7%) primary cases and in 13 of 21 (61.9%) recurrent cases. The incidence of recurrence observed in the recurrent cases was significantly higher than that seen in the primary cases (P <0.05, Fig. 2).

Fig. 2 Nonrecurrence rates determined according to type of disease. *A*: primary (n = 61); *B*: recurrence (n = 21)



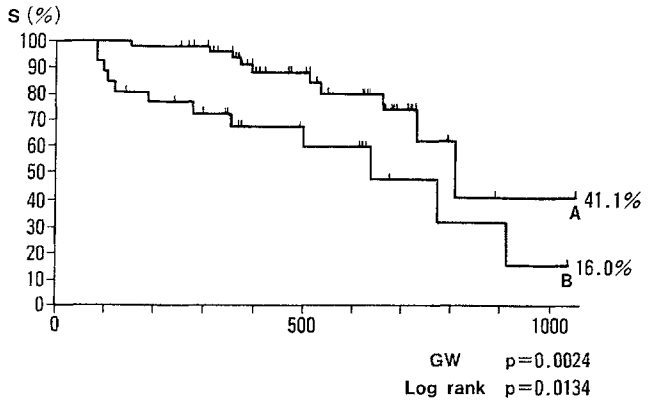


Fig. 3 Nonrecurrence rates determined according to tumor multiplicity. *A*: single (n = 52); *B*: multiple (n = 26)

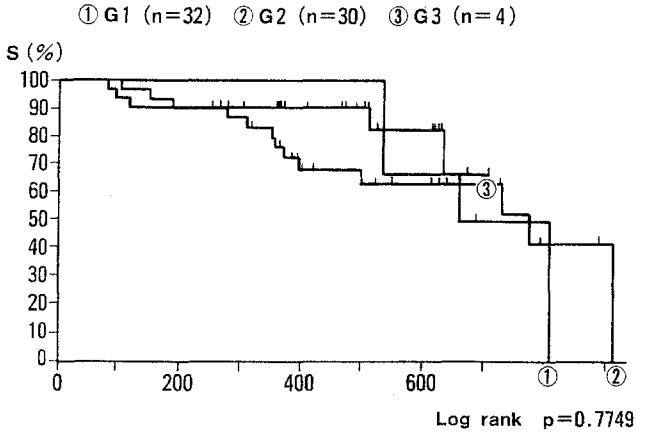


Fig. 4 Nonrecurrence rates determined according to histological grade

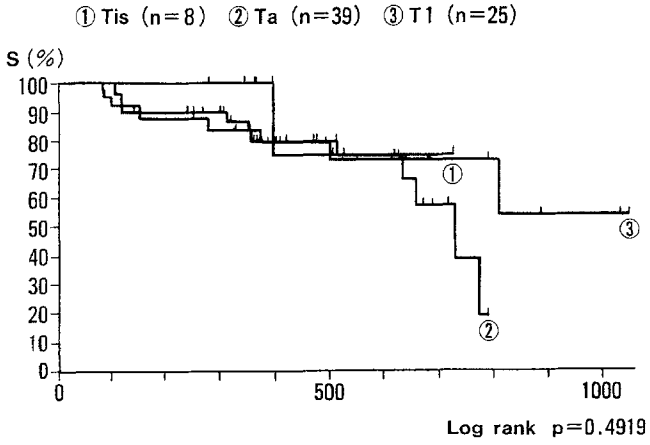


Fig. 5 Nonrecurrence rates determined according to pathological stage

The relationship between tumor recurrence and tumor multiplicity was also investigated. Of 52 patients with a single tumor, 10 showed recurrence, whereas of 27 patients with multiple tumors, 13 showed recurrence. There was a significant tendency for recurrence in the multiple-tumor group ($P < 0.01$, Fig. 3).

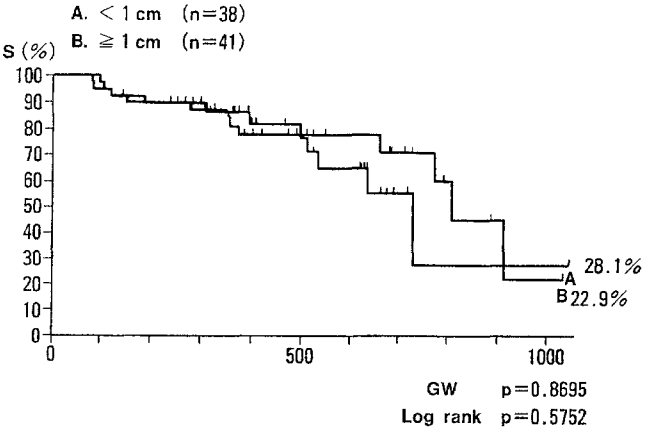


Fig. 6 Nonrecurrence rates determined according to tumor size

Next, the relationship between tumor recurrence and the histological grade of the tumors was investigated. As can be seen from Fig. 4, there was no significant difference among the various tumor-grade groups. In terms of tumor stage (i.e., Tis, Ta, or T1), no significant difference in the nonrecurrence rate was observed among the different tumor-stage groups (Fig. 5). Similarly, when the relationship between recurrence and tumor size (i.e., < 1 cm versus ≥1 cm was investigated, no significant difference was found (Fig. 6).

On the basis of these findings, it was surmised that the risk factors for recurrence of superficial bladder cancer are prior recurrence and multiple tumors. Next, we investigated the relationship between recurrence and these two factors (disease history and tumor multiplicity). For the patients with primary disease, a comparison of the single-tumor and multiple-tumor subgroups revealed a significantly higher rate of recurrence in the multiple-tumor subgroup ($P < 0.001$). In contrast, for the patients with recurrent disease, a comparison of the single-tumor and multiple-tumor subgroups did not show any statistically significant difference in the recurrence rate (Fig. 7).

With regard to the safety of the epirubicin intravesical instillation regimen employed in this study, adverse effects occurred in 9 of 97 patients, for an overall incidence of 9.3%. Those symptoms consisted of pain on urination, pollakisuria, and hematuria. However, each such event was mild in severity, and in no case during this clinical trial did treatment have to be discontinued due to those adverse effects (Table 3).

Table 3 Incidence of adverse effects[a]

	Severity of reaction			
	+	++	+++	Total
Pain on urination	7	1	0	8 (8.2%)
Pollakisuria	4	0	1	5 (5.2%)
Hematuria	1	0	0	1 (1.0%)

[a] Overall incidence, 9.3% (9/97 patients)

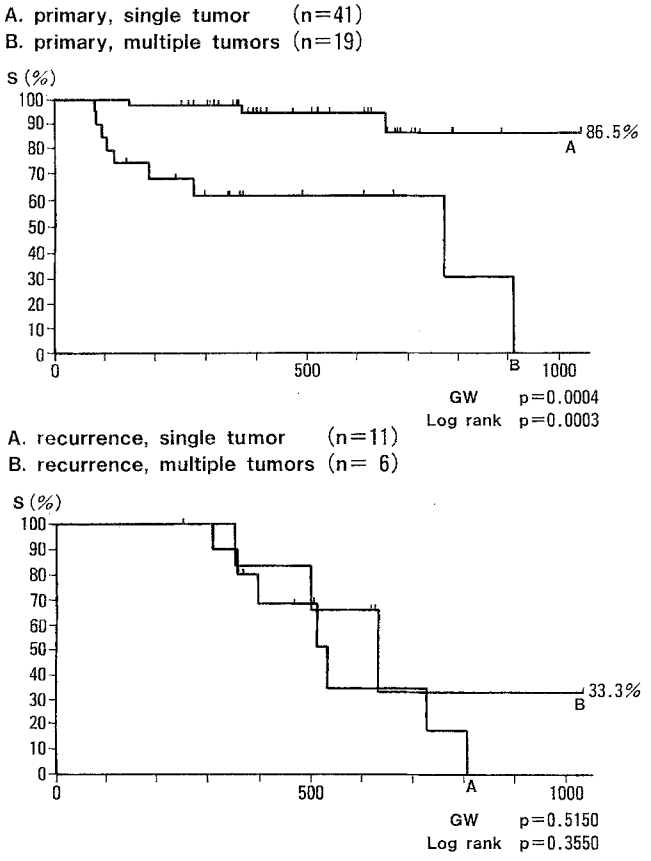


Fig. 7 Nonrecurrence rates determined according to type of disease and tumor multiplicity

Discussion

The principal approach to the treatment of superficial bladder cancer is bladder-preserving surgery, which is usually performed by TUR. However, TUR entails such a serious problem that there is a high incidence of recurrence, variously reported to be in the range of 30%–70% [8, 12], after the operation. Accordingly, it can be said that the most important purpose is to prevent tumor recurrence after TUR. Since Veenema et al. [15] first reported the efficacy of thio-TEPA given as an anticancer agent by intravesical instillation, there have been numerous reports of the efficacy of various other anticancer drugs, including bleomycin, mitomycin C (MMC), and Adriamycin, among others [2, 9, 13].

The following characteristics have been noted as being necessary for an anticancer drug to be suitable for application in intravesical instillation to prevent bladder cancer recurrence: (1) to exert its cytotoxic action against transitional-cell carcinoma, (2) to exert active cytotoxic action even when the duration of exposure of the target cancer to the drug is short, and (3) to cause no irritation to the normal mucosa and other tissues. ADM is rated as being excellent in terms of the first two of these characteristics. However, with regard to the third feature, it is said that ADM causes a high incidence of bladder-irritation symptoms in comparison with other anticancer drugs [9].

The anticancer drug that we employed in the present clinical trial, i.e., epirubicin, is a derivative of ADM, and it is said to provide anticancer efficacy that is equivalent to that of ADM, whereas its adverse reactions are said to be milder in severity than those caused by ADM [4, 5]. Tsushima et al. [14] carried out intravesical instillation using epirubicin at doses ranging from 50 to 80 mg dissolved in 30 ml physiological saline for a total of six instillations. They reported an efficacy rate of 55% and an incidence of adverse effects of 23% and noted that the efficacy was equivalent to that reported for ADM, whereas the adverse effects were lower in incidence and milder in degree than those caused by ADM [14].

In the present study, we set the concentration of epirubicin at a comparatively low level of 667 μg/ml (20 mg/30 ml saline) with the objective of reducing the severity of bladder-irritation symptoms. In this connection, Tsushima et al. [14] carried out a study on the potency of epirubicin in relation to human bladder-cancer cultured cell line T24 and reported that the dose that was lethal to 50% of the cells (LD_{50}) following an exposure period of 2 h was 0.006 μg/ml. In consideration of that finding, we surmised that the epirubicin concentration employed in the present clinical trial could be expected to show sufficient efficacy in the prohylaxis of tumor recurrence.

With regard to the time for which the instilled epirubicin was to be retained in the bladder by each patient, we decided that 30 min or more would be appropriate. The reason for this decision was that in a preliminary study carried out by analyzing the drug concentration in human bladder tissues biopsied at 30 min after intravesical instillation of an epirubicin solution (20 mg/30 ml saline) into bladder cancer patients, we had determined that no epirubicin was incorporated into the normal tissues but the drug was incorporated into the tumor. Accordingly, we surmised that a 30-min period of retention of epirubicin in the bladder would make it possible to achieve the objectives of prophylactic efficacy and reduced adverse effects.

The following factors have been indicated as the principal causes of tumor recurrence after TUR for bladder tumors: (1) incomplete resection of the tumor(s) by TUR, (2) tumor cell implantation at the time of TUR, and (3) polycentric tumor growth [1, 6]. Burnand et al. [3] had achieved statistically significant inhibition of recurrence of bladder cancer when they performed one intravesical instillation of thio-TEPA immediately after TUR. Similarly, on the basis of the theory of implantation of tumor cells released during resection, in the present study we also performed the first intravesical instillation of epirubicin immediately after TUR. Although the present trial was not a controlled study, our analysis of the data indicated that the efficacy of epirubicin was equivalent to that reported for various other anticancer agents. For example, Prout et al. [11] reported a 1-year nonrecurrence rate of 50% for thio-TEPA, and Niijima et al. [9, 10] reported 1-year nonrecurrence rates of 67% and 70% for MMC and ADM, respectively.

As part of the present study, we also analyzed the patients' background characteristics and the clinical findings in an attempt to identify risk factors for tumor recurrence. To date, the number, size, and pathological stage of tumors and a history of recurrence have been reported to be risk factors. On the basis of the findings obtained in the present study, we concluded that multiplicity of the tumors and a history of recurrence were important risk factors. However, in our analysis of the relationship between recurrence and tumor multiplicity in patients with primary tumors, we found a significantly higher rate of recurrence in the multiple-tumor subgroup ($P < 0.001$). In contrast, for the patients with recurrent tumors, a comparison of the single-tumor and multiple-tumor subgroups did not reveal any statistically significant difference in the recurrence rate.

We think that this seeming discrepancy can be explained by the observation that recurrent-disease cases are intrinsically multiple-tumor cases. That is, whereas multiple tumors represent spatial multiplicity, recurrence can be understood as chronological multiplicity, and we surmise that they are – in effect – the same.

The authors think that in the future it will be necessary to perform intravesical instillation therapy with the objective of preventing recurrence of superficial bladder cancer after the risk factors have been taken into account. At present, the authors are carrying out a controlled clinical study on epirubicin.

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