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Preoperative doxorubicin instillation in recurrent superficial bladder cancer

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Summary. Further recurrence of superficial bladder cancer after transurethral resection is frequent in patients who have already experienced recurrence. In an attempt to prevent or delay further recurrences in such patients, the effect of preoperative doxorubicin instillation was investigated. A total of 51 patients with recurrent superficial bladder cancer were randomized to receive either TUR alone or TUR with preoperative doxorubicin instillation. Doxorubicin was administered twice a week for 3 weeks before TUR surgery. An objective response (CR + PR) of the tumors was observed at operation in 12 of 25 (48%) evaluable doxorubicin-treated patients. Chemical cystitis was seen in 32% of the patients. Further recurrence after TUR was observed in 13 of 25 (52%) patients in the doxorubicin group, as against 15 of 23 (65%) evaluable patients in the control group. The mean disease-free interval was significantly longer (11.8 as against 7.1 months) in the doxorubicin group. These preliminary results suggest that preoperative doxorubicin instillation might be effective for prolongation of the disease-free interval in patients with recurrent bladder cancer.

Introduction

One of the common problems encountered in superficial bladder cancer is the high incidence of recurrence after initial management by transurethral resection (TUR). Among the patients undergoing TUR for this condition, 40%–85% can be expected to have recurrence after complete resection of all visible lesions [3, 8, 9]. Although the recurrent tumors are usually superficial, difficult clinical problems have arisen, offering unique opportunities for study. Once recurrence has been observed after therapy, further recurrences are the rule, and about 10% of the patients affected may develop infiltrative tumors in the course of further recurrences [3].

Intravesical chemotherapy with cytotoxic drugs has been advocated as a means of reducing the incidence of recurrence. The drugs most commonly used for this purpose are thio-TEPA, mitomycin C, epodyl, and doxorubicin. Although these drugs appear both to lower the recurrence rate and to extend the disease-free interval, neither their optimal schedule of administration nor their effectiveness in the prevention of recurrences has been established [4, 5, 8, 9].

For this reason, we attempted to prevent or delay further recurrence in patients with recurrent tumors by preoperative instillation of doxorubicin and started randomized prospective trials to compare the effect of preoperative doxorubicin instillation followed by TUR with standard TUR alone in these patients.

We report here the current status of our study, in which the median follow-up period is now 18 months.

Materials and methods

Fifty-one patients with recurrent superficial bladder cancer were entered in the trial. All had one or more TUR treatment, histologically proved recurrent transitional cell carcinoma with no evidence of muscle invasion. They were randomized to treatment with TUR only (control group)

Table 1. Patient characteristics

Characteristics	Doxorubicin + TUR	TUR only (control)
Age (years)		
Range	33–86	37–84
Median	66	70
Sex[a]		
Male	19	22
Female	6	4
Number of recurrence before study[a]	1.8	2.3
Tumor size		
Ø 1 cm >	19	23
Ø 1 cm <	6	3
Number of recurrent tumor		
Single	8	8
Multiple	17	18
Tumor stage		
T_1	25	26
T_2	0	0
Tumor grade		
G_1	15	16
G_2	6	7
Unknown	4	3

[a] Figures show no. of patients

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or with doxorubicin instillation followed by TUR (doxorubicin group). The background characteristics of the two groups are shown in Table 1.

In the doxorubicin group, doxorubicin was given intravesically (40 mg or 60 mg in 30 ml saline through a No. 8 urethral catheter) and retained in the bladder for 2 h. This doxorubicin instillation was repeated twice weekly for 3 weeks. One week after the final instillation the patients underwent cystoscopy to assess the response, and then underwent TUR of all residual tumors in the bladder. After the operation the patients in both groups were examined cystoscopically every 3 months for 2 years or more without undergoing any other form of anticancer treatment.

Response to doxorubicin instillation was evaluated macroscopically and by biopsy. Complete response (CR) was recorded when there was 100% disappearance of all tumors and negative histology. Partial response (PR) is defined as 50% disappearance of tumors, and minimal response (MR), as less than 50% disappearance of tumors. The terms no change (NC) and progression of disease (PD) are self-explanatory. For the assessment of the efficiency of recurrence prophylaxis by doxorubicin instillation, the recurrences and the tumor-free interval, i. e., time to first recurrence after TUR, in each patient were evaluated. The method of Kaplan and Meier was used for the evaluation of time to recurrence.

Results

Distribution of patients

There were 25 patients in the doxorubicin arm and 26 in the control arm. Table 1 summarizes the age, sex, and previous recurrence history of patients and the size, multicentricity, stage and grade of their tumors. No significant differences were observed between the two groups in these variables as they related to prognosis.

Anti-tumor effects

All 25 patients in the doxorubicin-treated group are evaluable for the response of tumors to doxorubicin instillation (Table 2): 15 patients received 40 mg doxorubicin in each instillation and 10 patients, 60 mg doxorubicin. CR/PR was achieved in 4 of 15 (27%) patients with 40 mg doxorubicin and 8 of 10 (80%) patients with 60mg doxorubicin. The overall response rate was 48% in all 25 patients treated with doxorubicin.

Prophylactic effects

Three years elapsed between the beginning of the study and the cut-off time. All 25 patients in the doxorubicin group and 23 of the 26 control patients were evaluable for further recurrence. The overall recurrence rates in the doxorubicin group and controls were 52% (13/25 patients) and 65% (15/23 patients), respectively (Table 3). Curves for the time to first recurrence were estimated by the Kaplan and Meier method and are shown in Fig. 1. The time from entry to recurrence was significantly longer in the doxorubicin-treated patients ($P < 0.05$: log-rank test). The median times to recurrence were 11.8 and 7.1 months in the doxorubicin group and the controls, respectively.

The observation period is now over 2 years in 10 patients in the doxorubicin group and 8 patients in the control group (Table 4). Although no significant difference in recurrence rate was detected between the two groups (60%

Table 2. Effect of doxorubicin: response to doxorubicin instillation in recurrent bladder cancer

Dose	No. of cases	Tumor response					Response rate	
		CR	PR	MR	NC	PD	CR+PR	Total (%)
40 mg	15	1	3	1	10	0	4/15	(27%)
60 mg	10	3	5	1	1	0	8/10	(80%)
Total	25	4	8	2	11	0	12/25	(48%)

Table 3. Recurrence in all patients entered in the study

Group	No. of cases	Recurrence			Recurrence rate	
		Recurrence	Without recurrence	Unknown (drop-out)	No. of recurrent cases	No. of cases evaluable (%)
Doxorubicin	25	13	12	0	13/25	(52%)
Control	26	15	8	3	15/23	(65%)

Table 4. Recurrence of patients with more than 2 years observation

Group	No. of cases	Recurrence		Recurrence rate	Average disease-free interval (months)	Average recurrence frequency (times/2 years)
		Recurrence	Without recurrence	No. of recurrent cases/ Total cases		
Doxorubicin	10	6	4	60%	12.2	1.1
Control	8	6	2	75%	5.5	2.0

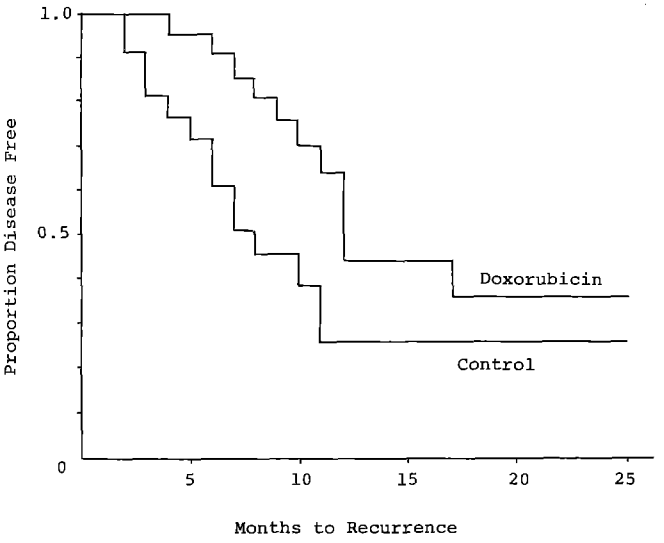

Fig. 1. Disease-free intervals for patients treated with TUR only (control) vs patients treated with doxorubicin and TUR (doxorubicin). Recurrence is significantly delayed in the doxorubicin group. (Kaplan and Meier method)

versus 75%), the average disease-free interval (time to first recurrence) was significantly longer in doxorubicin-treated patients ($P < 0.01$: Chi-square test). During the 2-year observation period, some of these patients experienced further (second plus) recurrences. According to the protocol, these recurrences were treated by TUR only. The average frequency of recurrence in the 2 years is also significantly lower in the doxorubicin group (1.1 vs 2.0; $P < 0.001$ by Chi-square test).

The need for total cystectomy in addition to periodic TUR at the time of recurrence was also monitored. This was necessary in 2 of 23 evaluable control patients (8.7%) because of multiple occurrence of lesions and development of invasive tumors at the time of recurrence. Cystectomy was not indicated for any of the 25 doxorubicin-treated patients.

Toxicity

Minor local adverse reactions were observed in some of the doxorubicin-treated patients, 8 (32%) of whom experienced frequency and urgency of urination after the instillation of doxorubicin. However, none of the patients had systemic side effects as evaluated clinically or by laboratory test values.

Discussion

In this preliminary report, we analyzed the results of preoperative intravesical doxorubicin treatment of recurrent superficial bladder cancer with regard to the prophylaxis of further recurrence.

Although several anticancer drugs have been administered intravesically to prevent the recurrence of superficial bladder cancer, only a few have proved effective [9]. Doxorubicin is one of these drugs, as confirmed by studies including a randomized prospective trial of more than 500 patients in Japan [7]. However, data that might indicate the optimal schedule of doxorubicin instillation and the merits of doxorubicin as a prophylactic agent in comparison with other drugs, such as thio-TEPA, are still limited [4, 9]. Also, there have been no reports on prophylactic effects of doxorubicin instillation given as preoperative adjuvant treatment.

Reports of doxorubicin instillation, particularly in patients with recurrent superficial tumors, have also been very few. Garnick et al. [2] selected 27 patients with multiple recurrent superficial transitional carcinoma of the bladder as high-risk patients for recurrence and performed intermittent intravesical doxorubicin after resection of tumors. They reported that 56% of patients were disease-free, with median follow-up periods of 12 months. In the study of the Blinst Italian Cooperative Group, the 50% periods to recurrence in patients treated for *recurrent* tumors with intermittent doxorubicin instillation after TUR was 480 days, as against 810 days in patients with *primary* tumors [1]. Their study, however, did not compare the values in controls treated by TUR only. On the other hand, the EORTC study group reported a significantly longer disease-free interval in patients with recurrent tumors treated with intermittent doxorubicin instillation after TUR than in patients treated with TUR only [6].

The study reported in the present paper is a prospectively controlled randomized trial of preoperative doxorubicin instillation to patients with recurrent tumors. Our results indicate that preoperative doxorubicin does prolong the disease-free interval and decreases the probability of recurrence, at least during the initial 2-year observation period.

A further important finding recorded in our study is that doxorubicin instillation before TUR may delay the need for more aggressive therapy, particularly cystectomy. Although reports vary, the published incidence of subsequent development of invasive tumor in superficial bladder cancer patients is 5%–10% [3, 9]. In our study, 2 of 23 patients (8.6%) who underwent TUR alone had invasive tumors requiring cystectomy at the time of subsequent recurrence. None of the patients receiving doxorubicin instillation and TUR required cystectomy. Obviously our results are preliminary and only tentative conclusions are possible at this stage.

Local and systemic side effects of instillation were remarkably few and mild. No serious problems were encountered in the performance of TUR.

Our trial suggests the superiority of adjuvant chemotherapy over TUR alone for recurrent superficial tumor. We are continuing the study to obtain a larger number of patients and a longer observation period to enable us to analyze the influence of several prognostic factors, such as tumor grade and multicentricity, on the occurrence of further recurrence.

We, however, could now conclude that preoperative intravesical application of doxorubicin is an effective and safe treatment prolonging the disease-free interval in patients with superficial recurrent bladder cancer.

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