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ORIGINAL ARTICLE

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Intravesical adjuvant chemotherapy for superficial transitional cell bladder carcinoma: results of a randomized trial with epirubicin comparing short-term versus long-term maintenance treatment

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Abstract *Purpose:* Intravesical instillation of epirubicin (EPI) is one of the most effective adjuvant therapies for non-muscle-invasive bladder cancer after transurethral resection. We evaluated the optimal duration of EPI instillation in a multi-institution prospective randomized clinical study. *Methods:* Between June 1995 and May 1998, a total of 125 patients with superficial bladder cancer (transitional cell carcinoma grade 1 or 2) were enrolled in this study, and 102 patients were fully evaluated for recurrence. Two protocols for intravesical therapy (arm A – 30 mg EPI/30 ml saline 19 times over 1 year; arm B – 30 mg EPI/30 ml 12 times over 5 months) were established. Instillations were given every week for 4 weeks and then every 2 weeks for 4 months in arm B. After 5 months of treatment, maintenance was performed with seven further instillations (one every month for 7 months) in arm A. The analyzed background factors were the therapeutic method, gender, history (primary or recurrent tumor), stage (T classification), grade, number of tumors, and tumor size. *Results:* There were no significant differences in the analyzed background factors between the two arms, and there were no serious side effects in the study. In an intent-to-treat analysis, the overall 3-year recurrence-free survival rates were 48.5% in arm A and 55.1% in arm B. The difference between the two groups was not significant. *Conclusions:* This analysis indicated that extended prophylactic maintenance instillation of EPI was not significantly effective in reducing bladder cancer recurrence.

Keywords Superficial bladder cancer · Intravesical chemotherapy · Maintenance · Epirubicin

This work is presented by the authors on behalf of the Nagasaki Clinical Research Group for Bladder Cancer.

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Introduction

Transitional cell carcinomas of the urinary bladder are either superficial or muscle-invading tumors. About 75–80% of bladder cancers are superficial at first presentation [13]. Superficial bladder cancer is usually treated by transurethral resection of the bladder tumor (TUR-Bt), and about 40–70% of patients experience recurrence within 6 to 12 months of surgery [7, 12, 17, 18].

The usefulness of adjuvant intravesical chemotherapy after TUR-Bt has been established for reducing the recurrence rate of superficial bladder cancer [7]. The most popular cytostatic agents used for intravesical treatment are mitomycin C, doxorubicin, and epirubicin (4′-epidoxorubicin, EPI) [2, 17, 18, 20, 21] . Bacillus Calmette-Guérin (BCG) is active as an intravesical immunotherapeutic agent not only for carcinoma in situ but for high-grade T1 tumors [5, 10]. Recently, maintenance BCG immunotherapy has been reported to be

more beneficial than standard induction therapy in some superficial bladder cancer patients [11].

There are many reports concerning effective intravesical prophylactic agents. EPI has been demonstrated to produce the same therapeutic response but to have a lower toxicity profile than the parent compound doxorubicin [3]. EPI has been shown to be effective and to cause a lower incidence of side effects in a patient group with Ta and T1 tumors [15]. Recently, EPI has shown better efficacy and lower toxicity than doxorubicin for pT1 tumors when used as an intravesical agent [1]. The protocol for these adjuvant treatments has been studied [4, 16]. However, many problems remain unresolved regarding the dose, frequency of instillation, and starting time [17, 19]. In this study, we examined the optimal duration and total dosage for intravesical chemotherapy using EPI.

Material and methods

We conducted a multi-institution prospective randomized study at Nagasaki University School of Medicine with a central pathological laboratory between June 1995 and May 1998. The study population consisted of patients with histologically proven transitional cell carcinoma of the bladder (stages Ta and T1, grades 1 and 2) [14]. All patients were registered for randomization within 14 days of TUR-Bt. Patients with an ECOG performance status 0 or 1 and aged between 20 and 80 years were included. The exclusion criteria were prior treatment with an anthracycline, uncontrollable urinary tract infection, prior muscle-invasive transitional cell carcinoma, concurrent malignancy of another organ, and pregnancy. Before intravesical therapy, the patients underwent TUR-Bt, and none showed any evidence of residual cancer as judged by cytological examination of the voided urine.

Two protocols of intravesical therapy (arm A – 30 mg EPI/30 ml saline 19 times over 1 year; arm B – 30 mg EPI/30 ml saline 12 times over 5 months) were established. Instillations were given every week for 4 weeks and then every 2 weeks for 4 months in arm B. After 5 months of treatment, maintenance was done with seven further instillations (once per month for 7 months) in arm A. After all patients had provided informed consent, they were randomized into two groups. The analyzed background factors were the therapeutic method, gender, history (primary or recurrent tumor), stage (T classification), grade, number of tumors, and tumor size.

The protocol called for cystoscopic examination every 3 months after TUR-Bt. The first postoperative recurrence after randomization that was confirmed by cystoscopy and pathology was considered to be an event. Patients in whom no recurrence was detected at the final cystoscopic examination were also considered. The non-recurrence rates were evaluated using the Kaplan-Meier method for both groups.

All histological analyses were performed on hematoxylin-eosin-stained sections. Each specimen was histologically re-examined by a special pathologist of the central laboratory.

Results

A total of 138 patients were enrolled and randomly assigned to either the long-term treatment arm (arm A) or the short-term treatment arm (arm B). Of the enrolled patients, 13 (9 from arm A and 4 from arm B) were subsequently found not to meet the eligibility criteria. Of the remaining 125 patients (55 in arm A and 70 in arm B), 8 had protocol violations, 7 did not complete the treatments because of adverse reactions or other reasons, and 8 refused follow-up. The remaining 102 patients (44 in arm A and 58 in arm B) were evaluable (Fig. 1). The median duration of follow-up was 18.1 months (2.1–54.4 months).

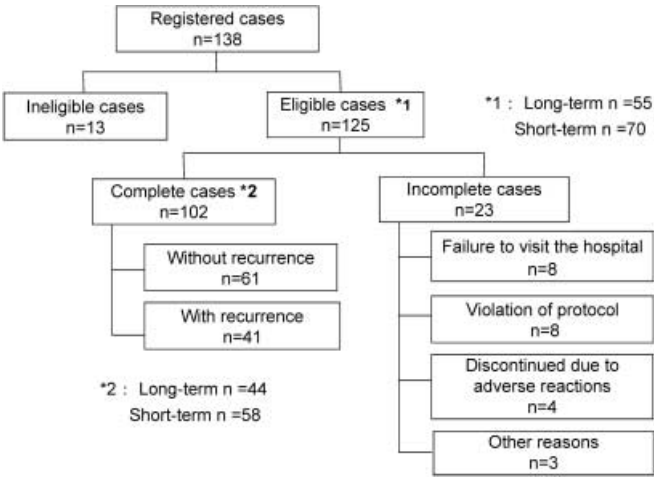


Fig. 1. Trial flow diagram

Table 1. Patient characteristics (*n.s.* not significant)

	Arm A	Arm B	χ^2 analysis
Sex			
Male	44	60	n.s.
Female	11	10	
Primary or recurrent			
Primary	43	54	
Recurrent	9	15	n.s.
Not recorded	3	1	
Number of tumors			
1	27	41	n.s
2 to 4	14	21	
5 or more	10	6	
Covering surface	2	1	
Not recorded	2	1	
Size of tumor (cm)			
< 1	11	18	n.s.
1–3	36	44	
3–5	4	6	
> 5	1	0	
Not recorded	3	2	
Morphological features of tumor			
Papillary, pedunculated	34	50	n.s.
Papillary, sessile	13	15	
Non-papillary, pedunculated	2	2	
Non-papillary, sessile	3	4	
Velvetinous	1	3	
Not recorded	3	2	
Histological grade			
1	27	37	n.s.
2	28	33	
Pathological stage			
pTa	28	42	n.s.
pT1	25	26	
pTx	2	2	

Table 2. Adverse reactions in eligible cases (*n.s.* not significant)

	Grade[a]	Arm A	Arm B	χ^2 analysis (*P* value)
Pollakisuria	0	37	59	$P=0.05$
	1	13	8	
	2	2	3	
	3	3	0	
Micturition pain	0	38	55	n.s.
	1	12	12	
	2	3	3	
	3	2	0	
Macroscopic hematuria	0	32	45	n.s.
	1	9	9	
	2	6	7	
	3	8	9	

[a]ECOG Common Toxicity Criteria

Patient characteristics

Table 1 shows the patients' characteristics and tumor characteristics, including the distributions of the T category and grade, as well as the number and size of tumors at entry. Of the 125 patients analyzed, 18% were retrospectively found to be ineligible mainly because they were not followed up. There were no significant differences in the analyzed background factors between the two treatment groups.

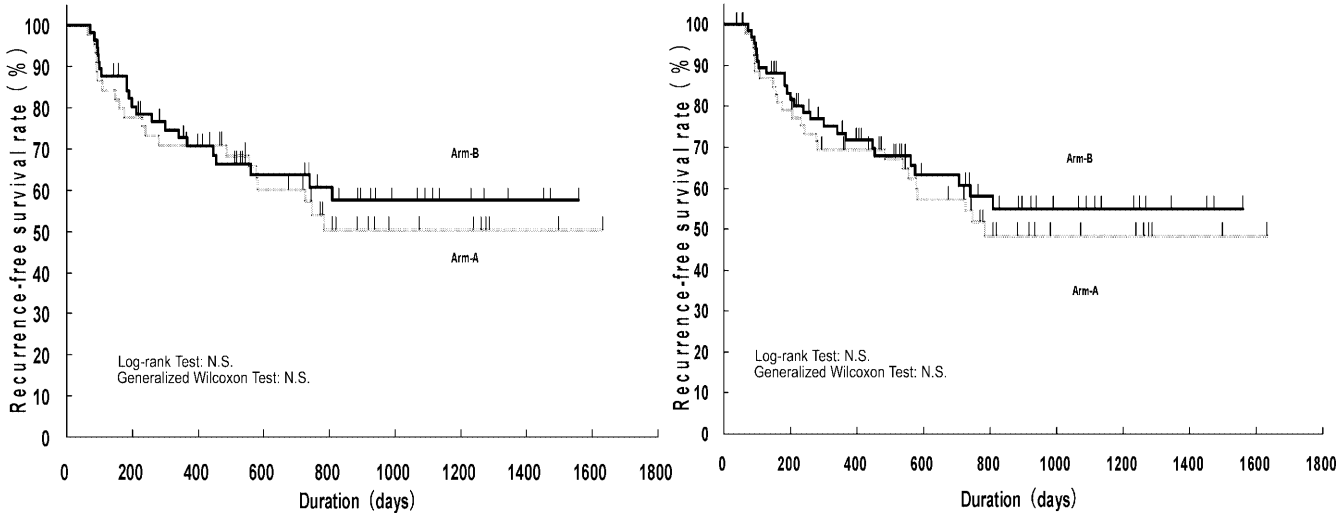
Toxicity

Table 2 shows the incidence of toxicity in each treatment arm. Pollakisuria, micturition pain, and macroscopic hematuria occurred in both arms. The incidence of pollakisuria in arm A was significantly different from that in arm B ($P=0.05$). However, there were no serious side effects requiring discontinuation of the instillations in either arm.

Disease-free interval

At 3 years after treatment, among the intent-to-treat patients ($n=125$), 48.5% in arm A and 55.1% in arm B were recurrence-free, and among the evaluable patients ($n=102$), 50.0% in arm A and 57.5% in arm B were recurrence-free. Kaplan-Meier analysis of recurrence in both the intent-to-treat group and the evaluable group showed no significant differences between arm A and arm B (Fig. 2). For grade 2 superficial bladder cancers in the evaluable group, the 3-year recurrence-free survival rate was 53.5% in arm A (28 patients) and 59.8% in arm B (33 patients). The difference was not statistically significant (data not shown).

Fig. 2a, b. Treatment outcome in the intent-to-treat patients (**a**) and the evaluable patients (**b**). At 3 years after treatment, 48.5% of the patients in arm A and 55.1% of the patients in arm B were recurrence-free among the intent-to-treat patients ($n=125$). At 3 years after treatment, 50.0% of the patients in arm A and 57.5% of the patients in arm B were recurrence-free among the evaluable patients ($n=102$)



Discussion

Our results indicate that the EPI maintenance therapy administered after 5 months treatment (arm A) was not valuable for extending the disease-free interval of the patients. There have been few reports on the optimal

duration of intravesical adjuvant chemotherapy for superficial bladder cancer [4]. Okamura et al. reported no significant difference in the recurrence-free interval between 6 instillations and 17 instillations using EPI [16]. In this study, the majority of the patients were at low risk, and the number of patients included was insufficient to demonstrate a small difference. However, ten patients with G3 tumors were included. Bouffioux et al. reported that in a randomized trial of intravesical adjuvant chemotherapy with doxorubicin and mitomycin C, comparing short-term (6 months) and long-term (12 months) treatment, there was no significant difference in recurrence rate between the two groups [4]. However, their study differed from ours in regard to the agent and patient selection. G3 tumor patients were about 13% in their study, and intravesical chemotherapy with anthracycline is not a good option for prophylactic purposes after TUR of G3 superficial bladder cancer [2]. In the present study, we focused on G1 and G2 superficial bladder cancers to investigate adjuvant therapy with EPI.

The 1998 WHO and the International Society of Urological Pathology consensus classification divides noninvasive papillary bladder tumors into three subgroups with different clinical behaviors, which seemed to be superior to the classification which we adopted [6]. However, even in our grade 2 urothelial cancer patients, there was no difference between the two treatment arms, and the recurrence-free rate might be superior compared with TUR without adjuvant therapy [9]. Ali-El-Dein reported that EPI has efficacy and lower toxicity than doxorubicin for pT1 bladder cancer when used as an adjuvant intravesical agent [1]. These results suggest that 5 months adjuvant intravesical EPI chemotherapy may be a treatment option after endoscopic removal of superficial bladder cancer except for in the high-risk group.

Hinotsu et al. reported that there are two phases of tumor recurrence in superficial bladder carcinoma after TUR [8]. The early phase is up to about 100–120 days after TUR. The late phase is up to about 500 days after TUR. Intravesical chemotherapy may be effective mainly in reducing the hazard for recurrence in the early phase. In our study, there was no significant difference between the 1-year treatment and the 5-month treatment. Therefore, 5 months treatment may be sufficient to reduce the risk of recurrence in the early phase. Systemic toxicity was rare and mild, while the occurrence of local reactions was consistent. This trial showed that the frequency and severity of side effects did not increase in proportion to the number of instillations of EPI. On the basis of these results, we suggest 5 months intravesical EPI treatment as adjuvant therapy of superficial bladder cancer in patients who are not at high risk since this will reduce the economic and psychological burdens on them.

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