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Randomized clinical trial on chemoprophylaxis of recurrence in cases of superficial bladder cancer

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Summary. *Several postoperative adjuvant therapeutic modalities have been adopted in attempts to reduce the recurrence rate of superficial bladder cancer. However, no definite conclusions on the effectiveness of intravesical chemoprophylaxis have been reached.*

A randomized clinical study on intravesical chemoprophylaxis was conducted by the Japanese Urological Cancer Research Group for Adriamycin to compare the recurrence rates among 575 patients with superficial transitional cell carcinoma of the urinary bladder. Group A received 30 mg/30 ml Adriamycin; group B received 20 mg/40 ml Adriamycin; group C received 20 mg/40 ml mitomycin C, and group D, no treatment (for control). Instillation was performed twice a week for 4 weeks after surgery. The postoperative observation period was 18 months. The overall recurrence rate in group D was 61.5%, which was statistically higher than in the other groups. The Adriamycin and Mitomycin C groups showed recurrence rates of 43%–48% and 57%, respectively.

Intravesical Adriamycin and Mitomycin C appeared to be effective in the prophylaxis of recurrence during this observation period. The main side-effect was cystitis syndrome, which was observed in 10%–20% of the patients. There were no life-threatening adverse effects in this series of patients.

Introduction

There are many modes of treatment for bladder cancer. Superficial bladder cancer (Ta and T1 in the 1978 UICC TNM classification [19]) has been treated mainly with transurethral surgery. The results were not satisfactory because of high local recurrence rates [6, 12]. Several adjuvant modalities have been adopted to reduce local recurrence, including thio-TEPA, alkylating agents, and other cytotoxic drugs. However, controversies concerning chemoprophylaxis still persist [1, 5, 15].

The object of this study is to compare the recurrence rates among patients treated with postsurgical intravesical chemotherapy for the prophylaxis of recurrence of superficial bladder cancer.

Patients and methods

1. Organization

Table 1 shows the members of the Japanese Urological Cancer Research Group for Adriamycin, chaired by Prof. Tadao Niijima, MD of the University of Tokyo, Japan, which organized this randomized clinical trial.

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Table 1. Japanese Urological Cancer Research Group

Chairman: Tadao Niijima, MD (University of Tokyo, Tokyo)	
Participating treatment centers	
Hokkaido University	(T. Koyanagi, MD)
Akita University	(S. Tsuchida, MD)
Iwate Medical University	(T. Ohori, MD)
Fukushima Medical College	(Y. Shiraiwa, MD)
Chiba Cancer Center Hospital	(T. Nagayama, MD)
Niigata University	(S. Sato, MD)
Tokyo University	(T. Niijima, MD)
Jikei University School of Medicine	(T. Machida, MD)
Tokyo Medical and Dental University	(M. Yokokawa, MD)
Cancer Institute Hospital	(T. Kawai, MD)
Nippon Medical College	(M. Akimoto, MD)
Tokyo Medical College	(T. Ooi, MD)
Yokohama City University	(R. Nishimura, MD)
Showa University	(Y. Kai, MD)
Kanagawa Center, Hospital for Adult Diseases	(I. Kondo, MD)
Hamamatsu University School of Medicine	(Y. Aso, MD)
Nagoya 2nd Red Cross Hospital	(K. Obata, MD)
Nagoya University	(H. Mitsuya, MD)
Osaka University	(T. Sonoda, MD)
Osaka City University	(M. Maekawa, MD)
Osaka Center Hospital for Adult Diseases	(T. Kotake, MD)
Wakayama Medical College	(T. Ōkawa, MD)
Kyoto Prefectural University of Medicine	(H. Watanabe, MD)
Nara Medical University	(E. Okajima, MD)
Kanazawa University	(H. Hisazumi, MD)
Kobe University	(J. Ishigami, MD)
Okayama University	(H. Omori, MD)
Shikoku Cancer Center Hospital	(T. Uyama, MD)
Hiroshima University	(H. Nihira, MD)
Yamaguchi University	(J. Sakatoku, MD)
Kyushu University	(S. Momose, MD)
Kurume University	(K. Eto, MD)
Kagoshima University	(K. Okamoto, MD)

2. Selection of the patients

A) Criteria for admission

1) Histologically proven primary or recurrent superficial bladder cancer (Ta, or T1)

2) All cases considered tumor-free after surgery

3) Diagnosis of superficial bladder tumor by routine methods.
B) Criteria for exclusion
1) TIS superficial bladder cancer
2) Other therapeutic modalities, such as systemic chemotherapy, immunotherapy, and radiotherapy, performed within 3 weeks after surgery
3) Presence of cardiovascular, renal, hepatic, or hematopoietic disturbances
4) Other complications
5) Existence of another cancer or previous history of another cancer.

3. Intravesical instillation

Within 1 week after surgery, patients giving informed consent were allocated to the following groups and the treatment was started:

Group A: The drug (Adriamycin 30 mg/30 ml physiological saline) was instilled into the bladder and retained for 1 h during which the patient's position was changed to obtain homogenous contact with the bladder mucosa. Drug instillation was performed twice a week for 4 weeks.

Group B: Adriamycin (20 mg/40 ml physiological saline) was instilled intravesically in the same manner as in group A.

Group C: Mitomycin C (20 mg/40 ml distilled water) was instilled in the manner described above.

Group D: The control group consisted of patients receiving no postsurgical treatment.

The use of agents considered to influence the prophylactic effects of Adriamycin and Mitomycin C was avoided. Other chemotherapeutic, anticancer, immunosuppressive, and radiomimetic substances were also excluded from this series. However, antibacterial antibiotic, analgesic, and antispasmodic agents were used as necessary.

4. Observation

Protocols

A) Previous history was checked carefully, with especial reference to whether tumors were primary or secondary. In cases of secondary tumors previous treatments were noted
B) Status praesens (localis)
1) Local status. Tumor characteristics, such as site, shape, number, size, and other local findings related to the malignancy were checked according to the *General Rules for Clinical and Pathological Studies on Bladder Cancer* (Japanese Urological Association and The Japanese Pathological Society).
2) General status
C) Urinary cytology. Pre-operative urinary cytology was performed at least twice. Classes IV and V were considered positive
D) Excretory urography, vesicography, bimanual palpation of the tumor, angiography, lymphangiography, and ultrasound sonography were performed and the findings recorded as necessary
E) Pathological findings. After TUR of superficial bladder tumors, the results of pathological examinations, including the cell type, grade, and mode of growth, etc., were recorded
F) Laboratory examinations
1) CBC. Hemoglobin, RBC, WBC, platelets, lymphocytes, hematocrit, and erythrocyte sedimentation rate were measured
2) Blood chemistry and liver function test. T.P., A/G, BUN, creatinine, electrolytes, GOT, GPT, γ-GTP, LDH, phosphatase, TTT, and zinc sulfate were measured
3) Urinalysis was performed
4) ECG.

These laboratory examinations were performed every 2 weeks.

5. Side-effects

Hematological and hepatic disturbances were checked routinely. If toxicity was suspected instillation was delayed until a return to normal levels was obtained. In cases of severe complications, such as drug-induced cystitis, the effects of chemoprophylaxis were also delayed.

In case of complications, the nature, the time of onset, duration, severity, and relief procedures were recorded. Description of adverse effects was performed as follows: (−), no side-effects; (+), slight, no therapeutic procedures needed; (++), moderate, recovery on treatment for adverse effects; (+++), instillation therapy stopped due to severe side-effects.

6. Evaluation of instillation therapy

Cystoscopy was repeated at 12-week intervals during the observation period (5 years). A diagnosis of recurrence was established by pathological examination of the biopsy specimens. Cytologic examinations were also performed.

The effectiveness of chemoprevention was evaluated according to the disease-free survival, average disease-free interval, and average recurrence rates per year. Disease-free interval was defined as the time interval between the operation and the data of first positive pathological findings by biopsy.

Statistical methods adopted here were the χ^2-test and the generalized Wilcoxon test.

Results

Seven hundred seven patients with superficial bladder cancer were entered on this protocol. However, only 575 patients were evaluable, the remainder being ineligible due to protocol violation, cessation of instillation, adverse effects, or other reasons (Table 2). The number of patients was approximately the same in all four groups, and no significant differences in age, sex, shape or type of tumor growth, grade, depth of invasion, size, number of tumors, and location, were found among these groups.

Overall disease-free survival rates were compared among these for groups (Table 3). After 450 days there were statistically significant differences among groups A, B, C, and D ($P < 0.05$). At day 540 only group A showed a superior result to the control.

In terms of tumor characteristics, primary or recurrent, it was clearly demonstrated that patients with recurrent tumors had shorter disease-free survival rates than those with primary tumors.

The tumors were classified morphologically as papillary pedunculated, papillary sessile, and non-papillary. Among these three types of tumor there were no statistical differences in disease-free survival rates.

The grade of differentiation of the tumor was determined according to the UICC criteria. Overall recurrence rates of grade III tumors were higher than those of grade I and II

Table 2. Number of patients evaluable

Group	No. of patients entered into this protocol	No. of patients evaluable	No. of patients dropped out
A	192	149	43
B	176	148	28
C	185	139	46
D	154	139	15
Total	707	575	132

Table 3. Overall disease-free survival rates

Group	*n*	Disease-free survival rates					
		Day 90	180	270	360	450	540
A	149	94.5	80.8	72.9	69.9*	62.2*	56.6
B	148	93.1	83.4*	72.5	66.3	63.1*	52.0
C	139	94.8	81.3	74.5	66.6*	61.5*	42.4
D	139	92.5	72.9	66.2	54.1	45.6	38.5

Generalized Wilcoxon test A:D, B:D $P < 0.05$; C:D $P < 0.10$
* Significant vs control ($P < 0.05$)

Table 4. Frequency of side-effects

Group	*n*	No. of episodes during instillation			
		Frequency	Micturition pain	Hematuria	Cystitis syndrome
A	130	44 (33.8%)	48 (36.9%)	26 (20.0%)	31 (23.8%)
B	138	39 (28.3%)	38 (27.5%)	16 (11.6%)	27 (19.6%)
C	124	41 (33.1%)	34 (27.4%)	12 (9.7%)	11 (8.9%)

tumors, as other investigators have already pointed out. Nonetheless, it was pointed out that the instillation therapy of group A was more effective than the control group, especially in grade II tumors. No conclusions about the recurrence rates of other grades were drawn.

Invasion into the bladder wall was estimated according to the UICC pT classification. T_1 tumors showed superior results to T_2 tumors in terms of disease-free survival. No statistical differences pT classification were noted among the four groups of patients.

Most of the tumors were less than 3 cm in size. It was found that in group A tumors 1–3 cm in size responded well to the instillation therapy.

The number of tumors was said to be a prognostic factor in recurrence of superficial bladder cancer. The overall disease-free survival rates were examined to clarify this point. It was clearly shown that patients with solitary tumors had superior results to those with multiple tumors. Results in groups A and C were superior to the control in solitary tumors, while it was demonstrated that methods A and B were effective in multiple tumors.

Urinary frequency, pain on micturition, hematuria, and cystitis syndrome were prominent side-effects. Urinary frequency was found in almost 30% of the patients. No statistical differences were found among these chemoprophylactic methods. However, hematuria and micturition pain were much more prominent in group A than in group B, which suggested a dose-dependent effect (Table 4) [7, 10].

Discussion

In general the prognosis of superficial bladder cancer has been reported to be excellent irrespective of which of the various treatments available is applied. However, one of the most important aspects of treatment was the high recurrence rates after surgical intervention [14, 18].

Recurrence is now considered to have many causes: continuous exposure of the bladder epithelium to carcinogen, implantation of cancer cells during surgery, multicentric growth of bladder cancer and inadequate resection of the tumor [2, 9].

Several adjuvant treatments in addition to surgery of superficial bladder cancer have been adopted to prevent recurrence rates, lengthen the disease-free interval, and increase survival. Thio-TEPA has been used for this purpose [11]. Until recently its prophylatic value was uncertain. The National Bladder Cancer Co-operative Group A and the European Organization for Research on Treatment of Cancer demonstrated by a randomized study that thio-TEPA was useful for the chemoprophylaxis of superficial bladder cancer recurrence [8, 17]. The most serious problem with thio-TEPA was a high degree of bone marrow suppression, especially at higher dosages [3]. Other investigators, using VM 26, Epodyl, 5-FU, Bleomycin, Adriamycin, and Mitomycin C, have reported on their efficacy for the prevention of recurrence of superficial bladder cancer [4, 20]. However, there have been no reports of Adriamycin and Mitomycin C in a nation-wide randomized chemoprophylaxis clinical trial. For the purpose of tumor regression and reduction of bulk of tumor mass, intravesical instillation of Adriamycin and Mitomycin C have been used for superficial lesions, with encouraging results. On the basis of these facts these two agents were chosen for a trial on prevention of the rather high recurrence rates of superficial bladder cancer.

It was also pointed out that Adriamycin and Mitomycin C were effective in improving disease-free survival rates. However, no difference was obtained after 540 days in any instillation group. Either escalation of the dosage or prolongation of the period of administration of these agents could be considered to extent the disease-free period.

In terms of tumor characteristics, it was clearly shown that patients with primary tumors responded well to instillation therapy. The shapes of the tumors had no relationship with the disease-free interval. It goes without saying that grade III tumors recurred most frequently and soon after transurethral surgery in spite of instillation therapy. With reference to the depth of invasion, T_1 tumors responded well. The number and size of the superficial tumors were considered one of the prognostic factors in this study series [13, 16].

Urinary frequency, pain on micturition, hematuria, and cystitis syndrome were prominent side-effects in this study. No cardiotoxicity due to Adriamycin was observed.

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