Cancer Chemother Pharmacol (1994) 35 (Suppl): S 88–S 92

SESSION III

Koji Obata · Yasuo Ohashi · Hideyuki Akaza · Shigeo Isaka
Susumu Kagawa · Kenkichi Koiso · Toshihiko Kotake
Toyohei Machida · Yosuke Matsumura · Tadao Niijima
Hiroshi Ohe · Yoshitada Ohi · Jun Shimazaki
Kazuya Tashiro · Toyofumi Ueda · The Japanese Urological Cancer Research Group for Adriamycin

Prophylactic chemotherapy with intravesical instillation of Adriamycin and oral administration of 5-fluorouracil after surgery for superficial bladder cancer

K. Obata (✉)
Department of Urology, Japanese Red Cross Nagoya Second Hospital, 2-9 Myoken-cho, Showa-ku, Nagoya 466, Japan

Y. Ohashi
Department of Epidemiology and Biostatistics, School of Health Sciences and Nursing, Faculty of Medicine, University of Tokyo, Tokyo, Japan

H. Akaza · K. Koiso
Department of Urology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan

S. Isaka · J. Shimazaki
Department of Urology, School of Medicine, Chiba University, Chiba, Japan

S. Kagawa
Department of Urology, School of Medicine, University of Tokushima, Tokushima, Japan

T. Kotake
Department of Urology, The Center for Adult Diseases, Osaka, Japan

T. Machida
Department of Urology, Jikei University School of Medicine, Tokyo, Japan

Y. Matsumura
Department of Urology, Kobe West City Hospital, Kobe, Japan

T. Niijima
President, Tokyo Seamen's Insurance Hospital, Tokyo, Japan

H. Ohe
Department of Urology, Kyoto Second Red Cross Hospital, Kyoto, Japan

Y. Ohi
Department of Urology, School of Medicine, Kagoshima University, Kagoshima, Japan

K. Tashiro
Department of Urology, Atsugi Prefectural Hospital, Atsugi, Japan

T. Ueda
Department of Urology, National Beppu Hospital, Beppu, Japan

Paper presented at the 5th International Conference on Treatment of Urinary Tract Tumors with Adriamycin/Farmorubicin, 24–25 September 1993, Hakone, Japan

Abstract The Japanese Urological Cancer Research Group for Adriamycin has conducted a series of clinical trials to investigate the efficacy and safety of prophylactic intravesical chemotherapy for superficial bladder cancer. In the third trial, reported herein, patients with recurrent bladder cancer or multiple primary cancer were selected and randomized to one of four groups using the envelope method after complete resection of the original tumors. Group A was given Adriamycin alone, group B received oral 5-fluorouracil (5-FU), group C was given Adriamycin and oral 5-FU, and group D served as the control group. Of the 544 patients registered, 331 were evaluable for the purpose of this study. The administration of 5-FU (group B) failed to prevent the recurrence of bladder tumors. Although group C (both Adriamycin and 5-FU) did not fare better than group A (Adriamycin only), Adriamycin was effective in preventing the recurrence of tumors, especially in high-risk patients with recurrent and multiple tumors. The risk of recurrence was reduced to 0.21 (95% confidence interval, 0.10–0.44) relative to the control group. There was no indication of a synergistic effect between 5-FU and Adriamycin. As side effects, cystitis syndrome was observed in 23%–30% of the patients in the Adriamycin groups and mild myelosuppression was observed in the 5-FU groups.

Key words Superficial bladder cancer · Chemoprophylaxis · Adriamycin

Introduction

Since 1980, the Japanese Urological Cancer Research Group for Adriamycin has implemented five randomized trials of prophylactic intravesical chemotherapy after complete resection of superficial bladder cancer [1, 3]. In the first and second studies, Adriamycin had a clear beneficial effect in preventing the recurrence of tumors in patients with superficial bladder cancer [1]. Oral administration of

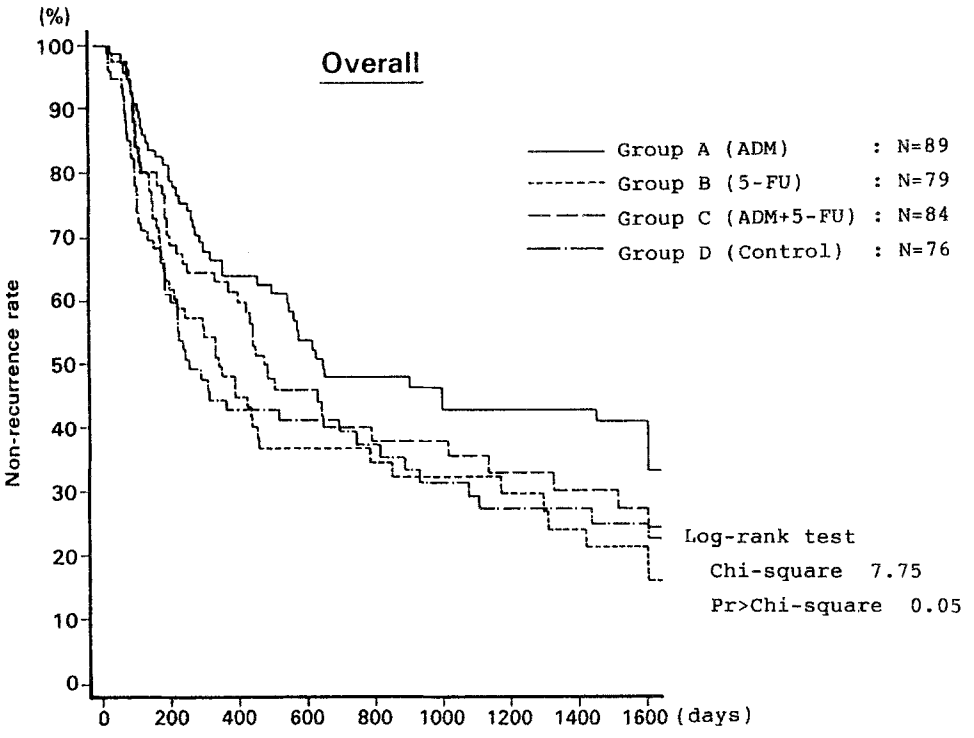

Fig. 1 Nonrecurrence curves (overall)

5-fluorouracil (5-FU) was reported to induce some clinical response against bladder cancer [4, 5]. Long-term oral administration of a 5-FU derivative, tegafur, was reported to be useful in preventing the intravesical recurrence of bladder cancer [2].

The aim of this trial was to investigate whether Adriamycin and 5-FU show a synergistic effect in the prevention of tumor recurrence after complete resection of superficial bladder cancer. Our previous studies revealed that both the recurrence pattern (previous tumor history) and the multiplicity of tumors are significant determining factors for tumor recurrence. On the basis of those findings, patients with recurrent tumors or multiple primary tumors (Ta and T1) were selected as the target population for this third trial.

Materials and methods

The patients enrolled in this trial were randomly assigned to one of four treatments by the envelope method with stratification by institution and a randomized block design (block size, 4). The basic design of this trial was the 2-by-2 factorial design [6]. Group A was given 20 mg Adriamycin in 40 ml physiological saline twice a week for 4 weeks and then once a month for 11 months. Group B received 150 or 200 mg 5-FU p.o. daily for 1 year. Group C was given Adriamycin and 5-FU according to the above-mentioned dosing schedule. Group D did not receive any treatment and served as the control. Patients were followed until the first recurrence, and the primary end point of this trial was defined as the time to the first recurrence. The treatment after recurrence was left to the discretion of each investigator.

The distributions of demographic/prognostic factors were summarized for each treatment group, and the homogeneity among groups was tested by the chi-square test and the generalized Mantel (Cochran-Mantel-Haenszel, CMH) test.

Patients were stratified according to the combination of the recurrence pattern and the multiplicity of tumors into a primary-multiple group, a recurrent-solitary group, and a recurrent-multiple group. The Kaplan-Meier method was used for calculating the nonrecurrence rate (proportion), and a log-rank test was performed to test the difference in time to the first recurrence among the four treatment groups. Test statistics were calculated for each of the treatment groups and summarized into overall statistics. The risk ratios of the three treatment groups (groups A, B, and C) to the control group (group D) were calculated from log-rank test statistics with 95% confidence intervals. For recurrent-multiple patients in whom the effect of Adriamycin was highly significant, Cox regression analysis was performed to estimate the treatment effect after adjusting for the other prognostic factors: tumor stage, grade, cell type, and size. All statistical calculations were performed using SAS (FREQ, LIFETEST, and PHREG) procedures [7].

Results

From July 1985 to June 1987, 544 patients were enrolled in this trial from 62 institutions, and 331 patients were evaluated. The cases excluded from the evaluation con-

Table 1 Enrolled and evaluable patients

Enrolled	544
Ineligible:	155
Primary and solitary	122
Residual tumor	4
G3	11
Tis	1
T2	2
Double cancers	4
Benign tumor	4
Prior treatment within the past 3 weeks	7
Incomplete data	21
Protocol violation	37
Evaluable cases	331

sisted of 155 ineligible cases, 21 cases with incomplete data, and 37 cases of major protocol violation (Table 1). Among the evaluated patients, 90 had been randomized to receive Adriamycin (group A); 80, to receive 5-FU (group B); and 85, to receive Adriamycin and 5-FU (group C). The control group consisted of 76 patients (group D). The main characteristics of the 331 evaluated patients are shown in Table 1. Of these patients, 274 had multiple tumors at the initial surgery for bladder cancer and 185 had recurrent tumors. There was no significant difference in the grade, pathological stage, or number of tumors among the four groups, but the distribution of the size of the tumors was not uniform ($P = 0.03$, Table 2).

Patients without recurrence were followed until January 1991, and the overall 3-year nonrecurrence rates were 44% in group A, 33% in group B, 36% in group C, and 30% in group D (Fig. 1; chi-square = 7.75, *df*, 3; $P = 0.052$). The main contribution to this overall significance came from the difference in patients with recurrent (especially recurrent-multiple) tumors. The 3-year nonrecurrence rates determined for patients with primary tumors were 47% in group A, 52% in group B, 52% in group C, and 37% in group D (chi-square = 0.88, *df*, 3; $P = 0.83$), whereas those obtained in patients with recurrent tumors were 41% in group A, 23% in group B, 23% in group C, and 23% in group D (chi-square = 8.70, *df*, 3; $P = 0.034$). The difference was exaggerated in patients with recurrent-multiple tumors (Fig. 2), and the 3-year nonrecurrence rates determined for patients with primary tumors were 39% in group A, 8% in group B, 19% in group C, and 16% in group D (chi-square = 13.80, *df*, 3; $P = 0.003$). The estimates of risk ratios (relative risks) based on log-rank statistics are summarized in Table 3.

To adjust for possible bias in the estimation of the risk ratios due to imbalance of prognostic factors, Cox regression analysis was performed on all patients and those with

Table 2 Patients' characteristics (*NS* Not significant)

Characteristic	Arm				Total	χ^2 test P value (CMH P value)
	A	B	C	D		
Sex:						
M	70	65	66	62	263	NS
F	20	15	19	14	68	0.88
Age (years):						
≤49	10	7	2	6	25	
50–59	14	14	23	19	70	NS
60–69	36	33	27	25	121	0.30
≥70	30	26	33	26	115	(0.83)
History:						
Primary	41	25	41	39	146	NS
Recurrent	49	55	44	37	185	0.05
Cell type:						
TCC	78	73	78	72	310	NS
Other/unknown	3	7	7	4	21	0.45
Grade:						
G0	0	1	3	0	4	
G1	28	34	30	37	129	NS
G2	58	39	48	35	180	0.19
Gx	3	3	2	3	11	(0.11)
Stage:						
pTa	30	36	34	33	133	NS
pT1	47	32	40	32	151	0.49
pTx	11	9	5	9	34	(0.54)
Operation:						
TUC	5	5	2	4	6	NS
TUR	82	72	77	69	301	0.84
Other	3	2	4	3	12	
Size of tumor:						
<1 cm	46	60	40	44	190	
1–3 cm	33	14	39	25	111	0.03
>3 cm	8	3	6	4	21	(0.00)
Unknown	3	3	0	3	9	
Number of tumors:						
Single	15	23	10	9	57	
2–4	51	42	53	52	198	NS
≥5	22	14	21	14	71	0.22
All over surface	1	1	1	0	3	(0.10)
Unknown	1	0	0	1	2	

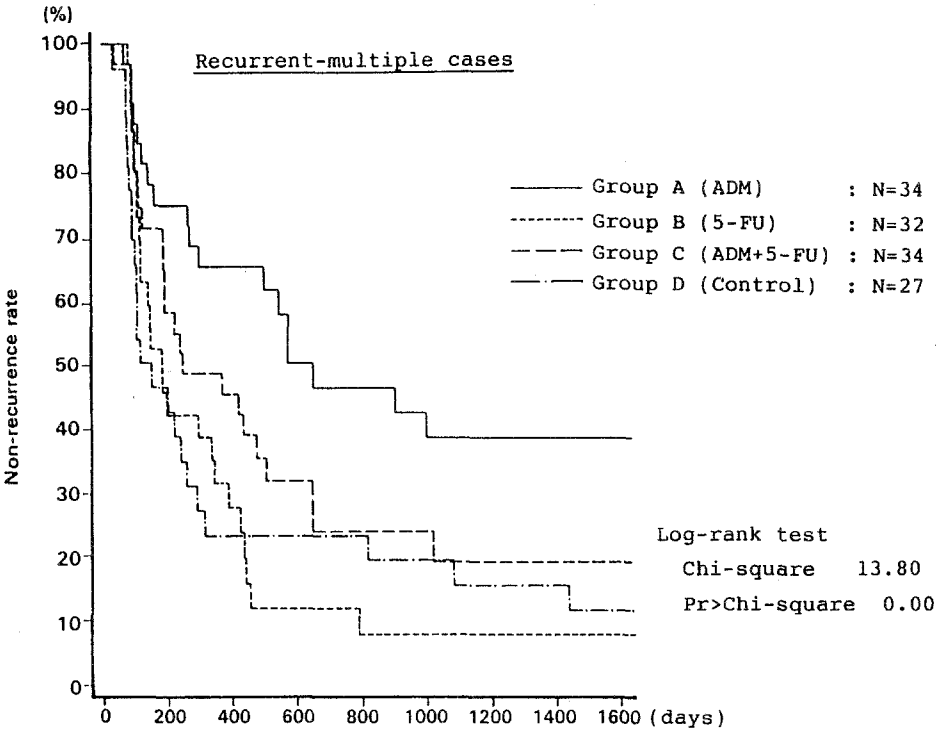

Fig. 2 Nonrecurrence curves (recurrent-multiple cases)

recurrent-multiple tumors. The stage, grade, cell type, and size of tumors as well as the pattern of recurrence and the number of tumors were selected as candidate variables for the model, and the size of tumors (< 1 cm, 1–3 cm, > 3 cm) was selected for the final model by stepwise regression and inspection of the results of model-fitting. The regression coefficients and estimates of risk ratios are summarized in Table 4 for patients with multiple-recurrent tumors. Both unadjusted analysis and adjusted analysis showed that the administration of Adriamycin reduced the risk of recurrence highly significantly by 60%–70% as compared with the control group in the high-risk patients with recurrent-multiple tumors, whereas there was no significant reduction due to the administration of 5-FU. There was no indication of a synergistic effect between Adriamycin and 5-FU.

The side effects of the treatments are listed in Table 5. Pollakisuria occurred in 19%–21% of the patients receiving Adriamycin as compared with 6% of the patients receiving 5-FU. Pain on urination occurred in 22%–24% of the patients receiving Adriamycin as compared with 8% of the 5-FU group. Mild myelosuppression (WBC, < 4000/μl) was observed in 11% of the patients in group A, in 20% of those in group B, and in 11% of those in group C.

Table 3 Stratified log-rank test for treatment effects (*ADM* Adriamycin)

Patient group	Log-rank	χ^2 (*P* value)	Risk ratio (vs D)		
			A (ADM)	B (5-FU)	C (ADM+5-FU)
Primary-multiple (n = 145)[a]	0.68	(0.88)	0.81	0.88	0.79
Recurrent-solitary (n = 57)	0.40	(0.94)	1.09	1.34	1.17
Recurrent-multiple (n = 127)[a]	13.80	(0.003)	0.40	1.02	0.62
Overall	8.98	(0.030)	0.61	1.02	0.75

[a] The number of tumors in 2 patients with multiple tumors was unknown

Table 4 Prognostic factors and adjusted effects in recurrent multiple cases (by Cox regression)

Factor	Estimate	SE	χ^2 (*P* value)	Risk ratio (95% confidence limit)
A vs D (ADM)	–1.25	0.34	13.9 (0.0002)	0.29 (0.15–0.55)
B vs D (5-FU)	–0.16	0.31	0.3 (0.59)	0.85 (0.47–1.54)
C vs D (ADM+5-FU)	–0.64	0.31	4.0 (0.046)	0.54 (0.29–0.99)
Size (1–3 cm)	0.29	0.26	1.1 (0.28)	1.33 (0.45–2.23)
Size (≥3 cm)	0.95	0.54	3.1 (0.077)	2.59 (0.90–7.41)

Table 5 Frequency of side effects

Side effect	A (n = 90)	B (n = 80)	C (n = 85)
Pollakisuria	17 (18.9%)	4 (5.5%)	18 (21.2%)
Pain on urination	20 (22.2%)	6 (7.5%)	20 (23.5%)
Dysuria	4 (4.4%)	0 (0)	3 (3.5%)
Hematuria	11 (12.2%)	4 (5.0%)	9 (10.6%)
Contracted bladder	1 (1.1%)	0 (0)	4 (4.7%)

Discussion

Intravesical chemotherapy is commonly recognized as preventing the recurrence of superficial bladder cancer. Since 1980, the Japanese Urological Cancer Research Group for Adriamycin has conducted clinical trials to investigate the preventive effect of Adriamycin on recurrence of superficial bladder cancer. The first and second trials demonstrated a significant reduction in the risk of first recurrence in groups treated with Adriamycin [1, 3]. 5-FU used in a single-drug treatment for patients with metastatic bladder carcinoma produced complete and partial remission in some patients [2]. Therapeutic responses to oral 5-FU were observed in two phase II studies performed in Japan [4, 5], and long-term oral administration of tegafur, a derivative of 5-FU, was reported to have a good prophylactic effect against the recurrence of bladder tumors [10]. One study also reported the effect of 5-FU against transitional cancer cells [8]. Those reports suggested that simultaneous oral administration of 5-FU with Adriamycin instillation might provide better results than administration of each drug alone for chemoprophylaxis of bladder cancer.

The present study reveals that 5-FU has no significant effect. The same result was reported for a randomized trial with early intravesical instillation of Adriamycin and long-term oral administration of 5-FU [9]. In conclusion, there is no indication of synergism between 5-FU and Adriamycin.

EORTC (European Organization for Research and Treatment of Cancer) trials show that well-known prognostic factors such as the pathological (T) category, the histological (G) grade, the number of tumors, and the previous recurrence rate have significant importance for the recurrence of superficial tumors [11]. The present study also confirmed that the recurrence rate was higher in patients with recurrent tumors than in those with primary tumors. With regard to the number of tumors, patients with multiple tumors showed a high risk of recurrence as compared with those bearing a single tumor. To elucidate the beneficial effect of chemoprophylaxis in the high-risk group, the target population of this study was restricted to patients with primary-multiple and recurrent tumors. The results of this study showed that the effect of Adriamycin was much clearer in patients with recurrent-multiple tumors than in the other two groups (primary-multiple and recurrent-solitary) of patients. Another factor that influenced recurrence in the recurrent-multiple group was the size of the tumor. After adjustment for this factor, Adriamycin was found to reduce the risk of recurrence to 0.21 (95% confidence interval, 0.10–0.44) relative to the control group in these high-risk cases.

References

1. Akaza H, Isaka S, Koiso K, Kotake T, Machida T, Maru A, Matsumura Y, Niijima T, Obata K, Ohe H, Ohi Y, Shimazaki J, Tashiro K, Ueda T, Uyama T, the Japanese Urological Cancer Research Group for Adriamycin (1987) Comparative analysis of short-term and long-term prophylactic intravesical chemotherapy of superficial bladder cancer. Cancer Chemother Pharmacol 20 [Suppl]: S91
2. Fossa SD, Gudmundsen TE (1981) Single drug chemotherapy with 5-FU and Adriamycin in metastatic bladder carcinoma. Br J Urol 53: 320
3. Matsumura Y, Akaza H, Isaka S, Kagawa S, Koiso K, Kotake T, Machida T, Niijima T, Obata K, Ohashi Y, Ohe H, Ohi Y, Shimazaki J, Tashiro K, Ueda T, the Japanese Urological Cancer Research Group for Adriamycin (1992) The 4th study of prophylactic intravesical chemotherapy with Adriamycin in the treatment of superficial bladder cancer: the experience of the Japanese Urological Cancer Research Group for Adriamycin. Cancer Chemother Pharmacol 31 [Suppl]: S10
4. Nagamoto A, Kubota Y, Shuin T, Moriyama M, Satomi Y, Fukushima S, Fukuoka H, Ishizuka E, Furuhata A, Yoshimura S, Matsuura K, Kumagai H, Ida T, Hirokawa M, Nakahashi M, Misaki H, Hosaka M (1989) Phase II study of 5-FU tablets for bladder tumors. Jpn J Cancer Chemother 16: 845
5. Ohmori H, Matsumura Y, Yoshimoto J, Obama T, Hara M, Josen Y, Ishido N, Nasu Y, Tanahashi T, Asai T, Ike N, Akazawa N, Tsushima T, Tanaka H, Furukawa Y (1988) A phase II study of 5-FU tablets for bladder tumors. Jpn J Cancer Chemother 15: 3115
6. Pocock SJ (1983) Clinical trials. Wiley, New York London
7. SAS Institute Inc. (1989) SAS/STAT user's guide, version 6, 4th ed, vols 1–2. SAS Institute, Carry, North Carolina
8. Sekiguchi H (1983) Drug-sensitivity test of cultured human bladder cancer cells. Jpn J Urol 74: 25
9. Ueda T, Naito S, Iguchi A, Sagiyama K, Osada Y, Ariyoshi A, Omoto T, Kumazawa J, the Kyushu University Urological Oncology Group (1992) Adjuvant chemotherapy with early intravesical instillation of Adriamycin and long-term oral administration of 5-fluorouracil in superficial bladder cancer. Cancer Chemother Pharmacol 30 [Suppl]: S31
10. Uyama T, Yamamoto A, Aga Y, Sumiyoshi Y, Yonezawa M, Fujita J (1984) Prophylactic long-term treatment of bladder tumors with oral chemotherapy (tegafur). Urology 23: 367
11. Van der Meijden APM, Kurth KH, Oosterlink W, Debruyne FMJ, EORTC Genito-Urinary Group (1992) Intravesical therapy with Adriamycin and 4-epirubicin for superficial bladder cancer: the experience of the EORTC GU Group. Cancer Chemother Pharmacol 30 [Suppl]: S95