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Long-term results of intravesical chemoprophylaxis of superficial bladder cancer: experience of the Japanese Urological Cancer Research Group for Adriamycin*

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Summary. Long-term results were analyzed in terms of tumor progression and survival in patients with superficial bladder cancer who were enrolled in the second intravesical chemoprophylactic study of the Japanese Urological Cancer Research Group for Adriamycin, which was started in July 1982. This study was a prospective, randomized, controlled trial conducted on primary tumors treated with a long-term instillation regimen that involved control versus intravesical instillations of Adriamycin or mitomycin C given once a week for the first 2 weeks, once every other week for 14 weeks, once a month for 8 months, and once every 3 months for 1 year, for a total of 21 instillations in 2 years. An analysis of the prophylactic effects of such treatment on bladder tumors after TUR has previously been performed, and the results have been published elsewhere. The present study represents a follow-up of the above trial. Of the 671 cases previously analyzed with regard to tumor prophylaxis, 158 cases (23.5%) were eligible to be followed for tumor progression and survival. A detailed comparison of the background factors between these 158 patients and the other 513 cases revealed no statistically significant difference. Thus, the 158 evaluable cases might reasonably be considered to represent all patients enrolled in the second study, and the results were thought to be reasonable enough to reflect the long-term efficacy of the long-term instillation regimen adopted in this study. The median follow-up for these 158 cases was 6.6 years. Tumor progression in terms of the disease stage and/or grade occurred in 43 of 127 patients who received prophylactic instillations and in 12 of 31 control cases. No significant difference in the incidence of tumor progression was found between the treatment and the control groups. In addition, no difference in survival was observed between the treatment group and the control group. Survival was also compared between patients who showed tumor progression and those who did not. All patients whose tumors did not progress survived, whereas the 7-year survival of those exhibiting tumor progression was <90%.

Introduction

Intravesical instillation of anticancer agents for the treatment of superficial bladder cancer has been practiced for nearly 40 years. Initially, this therapy was performed by the empirical method of trial and error. At this point, the efficacy and the limitations of intravesical instillation treatment should be elucidated.

Can intravesical instillation treatment alter the original biological characteristics of superficial bladder cancer? Can it extend the survival of patients with superficial bladder cancer? These two questions must be answered. The Japanese Urological Cancer Research Group for Adriamycin (JUCRGA) has performed collaborative studies on the efficacy of intravesical instillation treatment in preventing the recurrence of superficial bladder cancer [1, 3]. These collaborative studies have revealed that intravesical instillation of Adriamycin or mitomycin C is effective in delaying tumor recurrence after transurethral resection (TUR) of bladder tumors.

In the present paper, we report the results of a final follow-up study of patients who had undergone intravesical instillation treatment according to the protocol of the second JUCRGA study. All patients were followed for a

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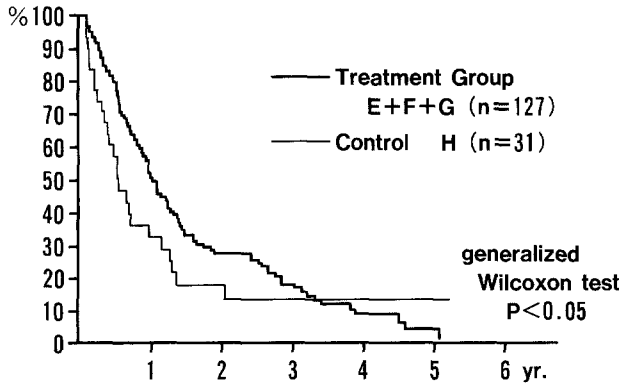

Fig. 1. Recurrence-free rate for the 158 evaluable patients

Table 1. Regimen adopted in the second JUCRGA study

Description:				
Long-term prophylactic intravesical chemoprophylaxis of superficial bladder cancer after TUR-Bt (prospective, randomized, controlled study)				
Regimen:				
Group	E	Adriamycin	30 mg/30 ml saline	Treatment groups
	F	Adriamycin	20 mg/40 ml saline	
	G	Mitomycin C	20 mg/40 ml saline	
	H	Control		
Schedule:				
Once weekly for 2 weeks, then once every 2 weeks for 14 weeks, then once monthly for 8 months, then once every 3 months for 1 year, i.e., a total of 21 doses given over 2 years				

The second study was initiated in July 1982. Registration of patients was terminated in July 1984, and final follow-up examinations were conducted in May 1990

Table 2. Summary of the patients' eligibility

Number of evaluable patients:		
Patients enrolled in the second study	→ 671	
(607 patients had been analyzed for tumor prophylaxis; median follow-up, 3.5 years [1])		
Number of patients eligible for the long-term study:		
Requests for follow-up records	→ 671	
Complete (collected full data)	158[a] (23.5%)	→ 322
Incomplete (collected data without tumor progression or survival)	→ 164	→ 671
Lost to follow-up	→ 134	→ 349
No response to the request	→ 215	

Median follow-up, 2,366 days (6.6 years); range, 480–2,817 days

[a] Evaluable for long-term tumor progression and survival

long period and were evaluated for the rate of tumor recurrence, the stage and/or grade of recurrent tumors, and the efficacy of the treatment in terms of survival.

Patients and methods

The subjects of this trial were patients who were included in the second JUCRGA study. That study was started in July of 1982, and recruitment of subjects was terminated in July of 1984. The subjects selected for the present study were patients for whom the total number of recurrences, the presence/absence of tumor progression, and the outcome (survival or death) were clear as of May of 1990.

The subjects included in the second JUCRGA study were patients with transitional-cell carcinoma pathologically staged as Ta or T1 and histologically graded as G2 or less [7] who had no previous history of bladder cancer. As shown in Table 1, intravesical instillation treatment was performed over a period of 2 years. Therefore, the subjects of the second JUCRGA study were considered to be very suitable for the objectives of the present trial.

In the second JUCRGA study, the rate of first tumor recurrence as of May of 1986 was mainly analyzed by the Kaplan-Meier method. The analysis revealed that the rate of first recurrence was significantly lower in the treatment group than in the control group; the regimen was thus found to be efficacious in suppressing tumor recurrence [1]. That analysis covered 607 of the 671 subjects enrolled. In the present study, we followed the 671 registered subjects by sending investigation cards directly to each investigator.

Results

Table 2 summarizes the state of recovery of the investigation cards and the data recorded therein. Of the 671 subjects answers were obtained for 456, whereas no answers could be obtained for the remaining 215 cases. Of the 456 cases for which answers were obtained, the investigators had failed to perform follow-up examinations in 134 cases and no histopathological data regarding tumor progression had been recorded for 164 cases, although some other data were recorded. Accordingly, 158 cases for which all of the requested data had been recorded were eligible for analysis of the long-term results; they accounted for 23.5% of the 671 subjects originally enrolled. The median follow-up from the day of performance of TUR for these 158 cases was 2,366 days (6.6 years), with the range being 480–2,817 days.

Background factors of 158 analyzed cases

To examine whether the 158 cases included in the patient analysis would adequately represent all of the subjects investigated in the second JUCRGA study, the background factors, which had been input to a computer at the time of registration, were compared between the 158 evaluable patients and the remaining 513 patients who were not included in the present analysis.

The major background factors of the 158 patients were: sex: M, 134; F, 24; age: ≦50 years, 21; ≦60 years, 28; <70 years, 56; ≧70 years, 53; tumor morphology: papillary, 126; nonpapillary, 32; pathological stage: pTis, 2; pTa, 70; pT1, 64; pTa or pT1, 22; histological grade: G1, 77; G2, 72; G1 or G2, 9; tumor size: <1 cm, 48; 1–3 cm, 85; 3–5 cm, 16; ≧5 cm, 9; and number of tumors: 1, 65; 2–4, 61; ≧5, 32. The distribution of each background factor was compared between the 158 evaluable patients and the remaining ineligible patients. The analyses did not detect any significant difference in the distribution of any

Table 3. Recurrence index and mean interval between recurrences

	Group					
	E	F	G	E+F+G	H	Totals
Number of cases	44	42	41	127	31	158
Σ recurrence	120	119	116	355	92	447
Σ duration (years)	253.6	232.5	245.9	732.0	180.3	912.3
Recurrence/year[a]	0.473	0.512	0.472	0.485	0.510	0.490
Mean time between recurrences (years)	2.11	1.95	2.12	2.06	1.96	2.04

[a] Recurrence index

of the background factors between the two groups. Thus, the 158 patients were judged to be representative of the total patient population of the second JUCRGA study.

On the basis of the instillation regimen, the 158 patients consisted of 44 group E patients, 42 group F patients, 41 group G patients, 127 group E+F+G (treatment group; i.e., the sum of individuals who underwent intravesical instillation treatment) patients, and 31 group H (control group; i.e., no treatment) patients (Table 1).

Rate of first recurrence as analyzed by the Kaplan-Meier method

Figure 1 shows the changes in the rate of first tumor recurrence as analyzed by the Kaplan-Meier method in the treatment group and the control group and plotted as non-recurrence curves. As had been observed in the analysis of 607 cases as of May of 1986, significant suppression of the rate of first recurrence was found in the treatment group as compared with the control group.

Recurrence index and mean time between recurrences

With the objective of investigating the effects of the instillation treatment on the ultimate course of the tumor, comparisons were made between groups for the recurrence index, i.e., the quotient of the number of recurrences divided by the total observation period, and the mean time between recurrences, i.e., the reciprocal of the recurrence index. As shown in Table 3, the instillation therapy had no significant effect on the treatment group as compared with the control group during the 6.6-year clinical course (median) in terms of the recurrence index or the mean time between recurrences.

Tumor progression

When a recurrent tumor showed an increase in pathological stage and/or histological grade, that state was defined as tumor progression. The number of patients in each group who showed tumor progression during the follow-up period are listed in Table 4.

Progression in the pathological stage was seen in 5 E group cases, 1 F group case, 3 G group cases, and 1 H group case, and progression in the histological grade was observed in 7 E group cases, 5 F group cases, 5 G group cases, and 6 H group cases. Progression in both stage and grade was seen in 7 E group cases, 7 F group cases, 3 G group cases, and 5 H group cases. Thus, in the treatment group (E+F+G groups), tumor progression in the stage, the grade, or both occurred in 43 (33.9%) of 127 cases during the 6.6-year follow-up period, whereas tumor progression of the same category occurred in 12 (38.7%) of the 31 patients in the control group (H group) during the same period. No statistically significant difference in the frequency of tumor progression was found between the E, F, G, or H groups and the all treatment group (E+F+G group). When tumor progression was analyzed as a function of the number of recurrences, tumor progression was

Table 4. Tumor progression according to the stage and/or grade of the recurrent tumor

	Group					
	E	F	G	E+F+G	H	Total
Number of cases	44	42	41	127	31	158
Progression in						
Stage	5	1	3	9	1	10
Grade	7	5	5	17	6	23
Both	7	7	3	17	5	22
Total	19 (43.2%)	13 (31.0%)	11 (26.8%)	43 (33.9%)	12 (38.7%)	55 (34.8%)
No progression	25	29	30	84	19	103

Statistics: no difference

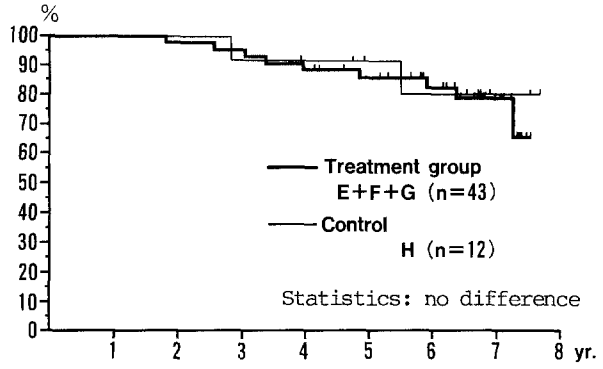

Fig. 2. Survival of patients showing tumor progression plotted as a function of treatment

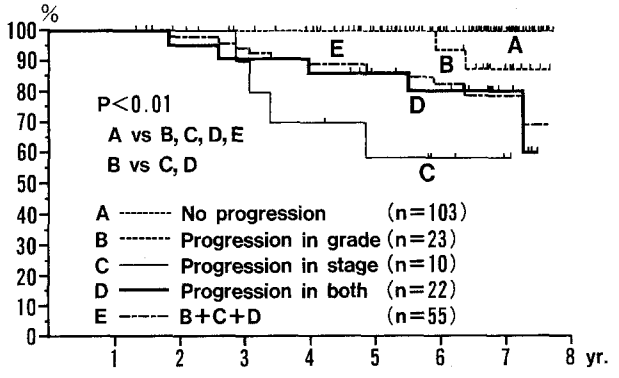

Fig. 3. Survival plotted as a function of tumor progression

seen in the first recurrence in 20 (46.5%) of the 43 cases in the treatment group and in 5 (41.7%) of the 12 cases in the control group. Tumor progression was observed for the first time in the second tumor recurrence in 10 patients (23.3%) in the treatment group and in 5 (41.7%) in the control group.

Survival of patients

The survival of patients who showed tumor progression was calculated by the Kaplan-Meier method and compared between the groups (generalized Wilcoxon test). However, no significant difference was detected. Figure 2 shows the survival curves constructed for patients in the treatment (E+F+G) and control (H) groups who showed tumor progression. Figure 3 illustrates the survival curves calculated by the Kaplan-Meier method for the 158 evaluable patients of the present study following their classification into a subgroup showing no tumor progression, a subgroup showing progression in the histological grade, a subgroup showing progression in the pathological stage, and a subgroup showing progression in both grade and stage. It was found that all 103 cases who showed no tumor progression were alive when the investigation cards were prepared, whereas the survival (calculated by the generalized Wilcoxon test) of the other subgroups showing some tumor progression was significantly shorter. The outcome was especially poor in the subgroup showing progression in the pathological stage. The 3-, 5-, and 7-year survival found for each of the above subgroups were: no tumor progression: 100% for each survival period; subgroup showing progression in grade: 100%, 100%, and 87.8%, respectively; subgroup showing progression in stage: 90.0%, 58.3%, and 58.3%, respectively; subgroup showing progression in grade and stage: 86.4%, 86.4%, and 60.5%, respectively.

Discussion

This study constituted part of the second JUCRGA study and was a prospective, randomized, controlled trial [1]. To prevent recurrence after TUR of bladder tumors that developed in patients with no previous history of bladder cancer, Adriamycin or mitomycin C was instilled into the bladder over a 2-year period. This study analyzed the long-term results of intravesical instillation treatments. Because the median follow-up was as long as 6.6 years and none of the patients enrolled in the second JUCRGA study had a previous history of malignancy, these conditions were judged to be appropriate for investigating the effects of intravesical instillation treatments on the ultimate course of the disease.

On the basis of the list of patients registered by the JUCRGA secretariat, investigation cards were mailed to each investigator at each medical institution to request collection of follow-up data. However, only 23.5% of the investigation cards were recovered with complete data. This poor result is thought to be due to the extremely long follow-up period and to the collaborative nature of the study, which involved numerous medical institutions. Thus, in the performance of such a collaborative study, it is important that the participating institutions be carefully selected and that each participating investigator be strictly educated to ensure full cooperation.

To investigate whether the evaluable 23.5% (158) of the patients would accurately represent the total number of patients (671) registered in the second JUCRGA study, various background factors were compared between these 158 patients and the remaining 513 subjects who were not included in the present analysis. No significant difference in the distribution of any of the background factors analyzed was found between the two populations. As part of the JUCRGA study, the efficacy of intravesical instillation treatment in suppressing the first tumor recurrence had been investigated as of 1986 in a total of 607 patients [1]. The present study was performed with the same objective and yielded the same results. On the basis of this as well, the 158 patients evaluated in the present study were thought to represent accurately the total patient population of the second JUCRGA study.

In the present study, however, intravesical instillation treatment did not show any significant efficacy in terms of the recurrence index or the mean time between recurrences when the ultimate course was analyzed and compared between the treatment group and the control group.

Tumor progression was seen in 33.9% of the treatment group, which was somewhat lower than the 38.7% value found for the control group, but the difference was not statistically significant. Other investigators have reported tumor-progression rates of 10%–20% [5, 6], which are somewhat lower than our results. This discrepancy is surmised to be due to our longer follow-up period. The rate of tumor progression found in the first recurrence in the present study was about half of each of the above values as calculated for all recurrences (27%–43% in the treatment group and 39% in the control group); the rates observed in the first recurrence are in agreement with the reported values [5, 6].

When survival was calculated only for patients who showed tumor progression, no significant difference was noted between the treatment group and the control group, indicating that intravesical instillation treatment had no effect on the survival of such patients. On the other hand, when patients showing tumor progression were compared with those showing no tumor progression, the survival of the former was significantly shorter. The outcome was especially poor in patients showing tumor progression in terms of the pathological stage. This result supports the conventional theory [4] that the prognosis of high-grade and/or high-stage bladder cancers is poor and simultaneously emphasizes the importance of prevention of recurrence in the treatment of bladder cancer.

On the basis of the above findings, it can be concluded that the intravesical instillation treatments (E, F, and G) used in the second JUCRGA study are effective at least in extending the time to the first recurrence after TUR but are not capable of improving the ultimate course of superficial bladder cancer. In other words, this regimen cannot reduce the number of tumor recurrences or the malignant progression of the tumors after TUR.

Huland et al. [2] have recently obtained beneficial effects on the prevention of tumor progression by the instillation of Adriamycin or mitomycin C using a mean follow-up period of 28 months. However, their study did not include a control group of nontreated patients, and the duration of the follow-up was not sufficient to enable any definitive conclusion to be drawn. Accordingly, we think that more careful consideration is necessary before intravesical instillation of an anticancer agent is undertaken. On the other hand, further work is necessary for the development of new drugs or methods that are capable of preventing tumor recurrence after TUR.

Appendix 1

The Japanese Urological Cancer Research Group for Adriamycin (Chairman, T. Niijima)

Hokkaido University	(T. Koyanagi)
Asahikawa Medical College	(S. Yachiku)
Iwate Medical University	(T. Ohori)
Iwate Prefectural Central Hospital	(I. Yoshida)
Tohoku University	(S. Orikasa)
Sendai Municipal Hospital	(Y. Imai)
Fukushima Medical College	(Y. Shiraiwa)
Fukushima Rosai Hospital	(R. Chiba)
Akita University	(S. Tsuchida)
Niigata Cancer Center	(Y. Sakata)
Niigata University	(S. Sato)
Saitama Medical School	(K. Okada)
Mito Kyodo Hospital	(Y. Koizumi)
Mito Red Cross Hospital	(R. Suzuki)
University of Tsukuba	(K. Koiso)
Chiba University	(J. Shimazaki)
Chiba Cancer Center	(T. Nagayama)
Juntendo University	(R. Kitagawa)
Tokyo Medical and Dental University	(H. Oshima)
Nippon Medical School	(M. Akimoto)
Jikei University School of Medicine	(T. Machida)
University of Tokyo	(Y. Aso)
Tokyo Medical College	(M. Miki)
Cancer Research Hospital	(T. Kawai)
Showa University, Fujigaoka Hospital	(Y. Kai)
Yokohama City University	(M. Hosaka)
Toho University, Ohmori Hospital	(K. Ando)
Kanagawa Cancer Center	(I. Kondo)
Kawakita General Hospital	(K. Tannowa)
Hamamatsu University School of Medicine	(K. Kawabe)
National Nagoya Hospital	(K. Yoshida)
Nagoya City University	(K. Ohtaguro)
Nagoya University	(H. Mitsuya)
Japanese Red Cross Nagoya First Hospital	(T. Murase)
Japanese Red Cross Nagoya Second Hospital	(K. Obata)
Shakai Hoken Chukyo Hospital	(S. Ohshima)
Aichi Medical University	(A. Segawa)
Gifu University	(Y. Kawada)
Kyoto Prefectural University of Medicine	(H. Watanabe)
Nara Medical University	(E. Okajima)
Wakayama Medical College	(T. Ohkawa)
Osaka City University	(M. Maekawa)
Osaka University	(T. Sonoda)
Center for Adult Diseases, Osaka	(T. Kotake)
Osaka Medical College	(S. Miyazaki)
Kansai Denryoku Hospital	(H. Katamura)
Kanazawa University	(H. Hisazumi)
Kobe University	(S. Kamidono)
Kobe City General Hospital	(M. Matsuo)
Okayama University	(H. Omori)
Kawasaki Medical School	(H. Tanaka)
Tottori University	(H. Goto)
Hiroshima University	(H. Nihira)
Yamaguchi University	(J. Sakatoku)
Kochi Medical School	(Y. Fujita)
University of Tokushima	(S. Kagawa)
Shikoku Cancer Center	(Y. Sumiyoshi)
Matsuyama Red Cross Hospital	(T. Shiraishi)
Kyushu University	(J. Kumazawa)
Kurume University	(K. Eto)
Kumamoto University	(S. Ueda)
Nagasaki University	(Y. Saito)
Medical College of Oita	(J. Ogata)
Kagoshima University	(Y. Ohi)

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