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Intra-arterial administration of methotrexate, Adriamycin, and cisplatin as neoadjuvant chemotherapy for bladder cancer

Manabu Kuriyama, Yoshito Takahashi, Yukihiro Nagatani, Ikuo Shinoda, Naoki Yamamoto, Tsukasa Nagai, Kazuya Ueno, Toshimi Takeuchi, Shinichi Maeda, Kazutoshi Isogai, and Yukimichi Kawada

Department of Urology, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu 500, Japan

Summary. As neoadjuvant chemotherapy for advanced bladder cancer, the intra-arterial administration of methotrexate (MTX), Adriamycin (ADM), and cisplatin (CDDP; IA-MAC) was evaluated. A total of 48 patients with bladder cancer (≧T2 or CIS) were selected and received 30.1 mg MTX, 34.5 mg ADM, and 89.1 mg CDDP as an average course. The mean tumor-regression rate after 2 or 3 weeks was 52.3%, and patients with grade 3 transitional-cell carcinoma showed the best results, achieving a 69.6% regression rate. In 30 cases (63%), downstaging was observed. Among the 46 patients who underwent subsequent surgical therapy, the bladder could be preserved in 26 cases by transurethral resection or segmental resection. According to the criteria of the Japanese Association of Cancer Therapy, a histological effect of GIII or better was obtained in 15 cases (29%). The histological effect correlated well with the tumor-regression rate. As compared with intravenous therapy with MTX, vinblastine, ADM, and CDDP (M-VAC), IA-MAC treatment was well tolerated due to its lower degree of bone marrow suppression, and it resulted in a longer disease-free interval and better survival. In addition, the period prior to surgical therapy was shortened in this study. These results suggest that IA-MAC chemotherapy can be useful as an arm of multidisciplinary treatment of advanced bladder tumors.

Introduction

Chemotherapy for bladder cancer has made considerable progress since the introduction of the M-VAC (methotrexate, vinblastine, Adriamycin, and cisplatin) regimen by Sternberg et al. [7], and preservation of the bladder has been possible in some cases [1, 3]. This paper presents our data on the intra-arterial administration of methotrexate, Adriamycin, and cisplatin (MAC) as neoadjuvant chemotherapy.

Patients and methods

A total of 48 patients with bladder cancer (T factor, >T2 or CIS) involving transitional-cell carcinoma (TCC) or squamous-cell carcinoma (SCC) were enrolled in this study beginning in 1985. Overall, 69% of the cases were newly diagnosed, and 30 patients had a performance status (PS) of 0. The CIS case was categorized as grade 3, and the classification of two patients with SCC was T4. For purposes of comparison, ten patients who were treated with intravenous M-VAC (IV-M-VAC) during the same period served as controls (Table 1).

The anticancer agents selected were methotrexate (MTX), Adriamycin (ADM), and cisplatin (CDDP), which were given on the 1st day at doses of 30, 30, and 70 mg/m^2, respectively. Each course lasted 3 weeks and was repeated (Table 2). Evaluation was carried out at the end of each course using the same medical diagnostic imaging procedure, such as computed tomography (CT) or ultrasonography. The pathological effects were evaluated in surgical specimens according to the criteria of Shimosato et al. [6].

Results

The doses delivered per course and the interval in days until the next course are presented in Table 3. Overall, 67%–85% of the planned dose was actually given, and the mean interval between courses was 19.9 days. A total of 71 courses of IA-MAC were given for an average of 1.48 courses per patient.

In 47 cases (excluding the 1 CIS patient), the mean rate of tumor regression was 52.3% (Table 4). No statistically significant difference in the regression rates was found between the newly diagnosed and the previously treated groups. The same tendencies were noted for T factors and PS. Although the drug doses given were the same, patients with grade 3 TCC achieved the best statistical results, showing a 69.6% regression rate. Figure 1 presents the

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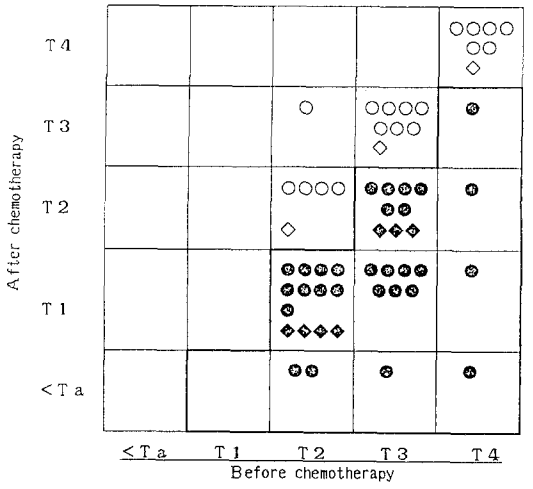
Correspondence to: M. Kuriyama, Department of Urology, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu 500, Japan

Table 1. Patients' characteristics

	IA-MAC	IV-M-VAC
Number of patients	48	10
Sex (M/F)	37/11	8/2
Mean age (years)	65.0±11.9	64.6±10.9
Previous treatment:		
None	33 (69%)	8 (80%)
Yes	15 (31%)	2 (20%)
TUR	11 (23%)	1 (10%)
SR	4 (8%)	1 (10%)
Performance status:		
0	30 (62%)	8 (80%)
1	8 (17%)	2 (20%)
2	8 (17%)	0
3	2 (4%)	0
T factor:		
2	17 (35%)	5 (50%)
3	20 (42%)	3 (30%)
4	10 (21%)	2 (20%)
CIS	1 (2%)	0
Histology and grade:		
TCC G1	3 (6%)	1 (10%)
G2	25 (52%)	4 (40%)
G3	18 (38%)	5 (50%)
SCC	2 (4%)	0

TUR, Transurethral resection; SR, segmental resection



○&●: IA-MAC (n=47, One case of CIS was excluded)
◇&◆: IV-M-VAC (n=10)

	IA-MAC	IV-M-VAC	p value
Improvement	62%	70%	N.S.
Improvement ≧2 factors	28%	0%	0.096

Fig. 1. Improvement in T factor after neoadjuvant chemotherapy. *N. S.*, Not significant

patients who showed downstaging. No statistically significant difference in the rate of downstaging was observed between the IA-MAC group and the IV-M-VAC control group. However, marked improvement was seen only in the IA-MAC group.

A pathological response of grade III or better was obtained in 15 patients, including the 1 CIS case. The pathological response correlated well with the tumor-regression rate (Table 5). Table 6 presents a summary of the adverse reactions to IA-MAC therapy. Although no statistically significant difference was found between the two groups, the IA-MAC group showed a tendency to develop mild side effects, especially bone marrow suppression.

After the chemotherapy, 46 patients underwent surgical treatment. Preservation of the bladder was accomplished in 26 cases (54%), and this rate was significantly superior to that obtained in the IV-M-VAC group (Table 7). The nonrecurrence rates following neoadjuvant chemotherapy and surgery revealed no significant difference between the groups, although the IA-MAC group achieved better results. The survival of patients treated with IA-MAC was 90%, 82%, and 82% at 1, 2, and 3 years, respectively (Fig. 2). The patients who received IA-MAC survived

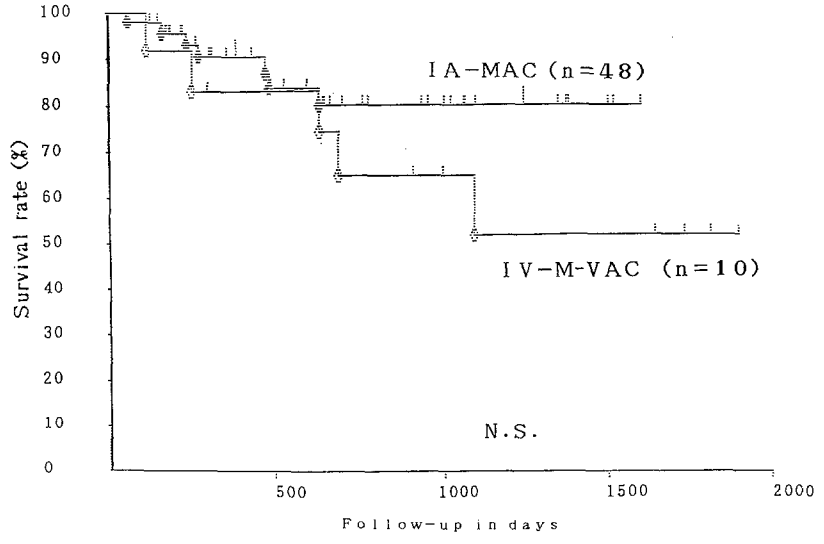


Fig. 2. Survival of patients after treatment

Table 2. Schedule of administration

	IA-MAC			IV-M-VAC		
Drugs and doses (mg/m^2)	Day 1	MTX	30	Day 1	MTX	30
		ADM	30	Day 2	VLB	3
		CDDP	70		ADM	30
					CDDP	70
				Day 15	MTX	30
					VLB	3
				Day 22	MTX	30
					VLB	3
Interval between courses	3 weeks			4 weeks		

Table 3. Doses given in one course and interval until the next course

Drug	IA-MAC		IV-M-VAC	
	Number of courses	Mean ± SD (mg/body)	Number of courses	Mean ± SD (mg/body)
MTX	68	30.1±11.4	10	35.6±13.4
ADM	71	34.5± 9.5	14	37.1±15.8
CDDP	71	89.1±29.9	14	98.4±58.7
VLB			10	6.7± 4.6
	Number of courses	Mean ± SD (days)	Number of courses	Mean ± SD (days)
Interval	37	19.9± 8.5	8	31.2± 7.2

Table 4. Tumor regression after neoadjuvant IA-MAC

		Number of patients	Mean regression (%)	Statistics
Total cases		47	52.3±30.4	
Previous treatment	None	32	53.3±30.3	N. S.
	Yes	15	50.1±30.8	
T factor	2	17	47.8±32.5	
	3	20	53.2±30.5	N. S.
	4	10	59.0±27.9	
Cell grade	1	3	46.6±23.0	
	2	25	47.6±33.0	P <0.05 G3 vs others
	3	17	69.6±27.2	
	SCC	2	35.6±26.8	
Performance status	0	29	53.5±33.6	
	1	8	43.0±30.4	N. S.
	2	8	54.0±26.7	
	3	2	54.0±10.6	

N. S., Not significant

longer, although there was no statistically significant difference between the two groups.

Discussion

Since the introduction of the M-VAC regimen by Sternberg et al. [7], chemotherapy of bladder cancer has made considerable progress. These authors have obtained a mean response rate (complete + partial responses) of 69% ± 10% in measurable and evaluable patients with advanced-stage transitional-cell urothelial cancer [8]. These results have encouraged the use of these anticancer agents as neoadjuvant chemotherapy [5, 9]. Furthermore, to obtain a higher concentration of the drugs in the tumor tissues and to reduce the resultant toxicity, intra-arterial injection has been attempted [1–4]. This paper represents our preliminary clinical report on intra-arterial MTX, ADM, and CDDP injection.

As Yagoda [9] has noted, the objectives of neoadjuvant treatment of bladder cancer are to debulk or downstage the tumor and to destroy micrometastases as well. To achieve these objectives, further investigation is necessary to determine the agents and doses to be used and the number of cycles to be given. From the M-VAC regimen, we selected MTX, ADM, and CDDP, and the intra-arterial route of administration was chosen to reduce bone marrow suppression and to shorten the time to subsequent surgical treatment. Indeed, as compared with the IV-M-VAC group, bone marrow suppression was milder in patients receiving IA-MAC, and the intervals between cycles were shorter, i.e., 20 days. Igawa et al. [2] have also reported that the use of intra-arterial M-VAC results in a longer time to the nadir of bone marrow suppression and in milder gastrointestinal symptoms. At present, the number of cycles needed to obtain the maximal effect remains uncertain. Yagoda [9] has noted that if given by the intravenous route, three courses of M-VAC might be required.

The effects in terms of both tumor regression and histological response were promising. Downstaging was observed in 62% of patients, which was almost equal to the

Table 5. Correlation between pathological response and tumor regression

Shimosato-Oboshi's criteria		IA-MAC			IV-M-VAC		
		Number of specimens examined	% Regression		Number of specimens examined	% Regression	
			Range	Mean ± SD		Range	Mean ± SD
Grade	0	3 (6%)	−4 − 41	13.7 ± 24.0	0		
	I	7 (15%)	−5 − 87	33.9 ± 25.6	1 (10%)	15	15
	II	23 (49%)	32 − 83	58.3 ± 18.1	5 (50%)	0 − 91	45.8 ± 38.4
	III	4 (8%)	43 − 98	63.4 ± 8.7	4 (40%)	50 − 86	63.0 ± 14.7
	IV	10 (21%)	40 − 100	83.8 ± 17.2	0		
Totals		47[a]	−4 − 100	52.3 ± 30.4	10	0 − 91	39.7 ± 21.5

[a] One case of CIS (TCC G3) was excluded because the percentage of regression could not be evaluated; however, this patient showed a good pathological response corresponding to grade III of Shimosato-Oboshi's criteria

Table 6. Adverse reactions to neoadjuvant chemotherapy

	IA-MAC	IV-M-VAC
Number of patients	48	10
Anorexia	28 (58%)	7 (70%)
Nausea	46 (96%)	8 (80%)
Vomiting	42 (88%)	7 (70%)
Alopecia (>grade II)	24 (50%)	6 (60%)
Leukopenia (<3,000/mm^3)	34 (71%)	8 (80%)
Thrombocytopenia (<5 × 10^4/mm^3)	17 (35%)	5 (50%)

No significant difference in the frequency of adverse reactions was observed between these two groups

Table 7. Number of patients who underwent surgery after chemotherapy

Type of surgery	IA-MAC	IV-M-VAC
TUR	21 (44%)	2 (20%)
SR	5 (10%)	0
Total cystectomy	20 (46%)	8 (80%)

results obtained using M-VAC [5, 9] and to those obtained in another study of intra-arterial M-VAC [2]. Our finding that the histological response correlated significantly with the tumor-regression rate was interesting; calculation of the regression rate can thus estimate the histological response. Moreover, in 54% of the patients who might have been treated by total cystectomy, it was possible to preserve the bladder, whereby no significant difference was observed between the non-recurrence rates obtained in the two groups and a tendency toward longer survival was noted for the IA-MAC group as compared with the IV-M-VAC group.

In conclusion, the IA-MAC regimen showed almost the same efficacy as did M-VAC therapy, with the interval until surgery being shorter and the toxicity, lower. Bladder preservation was possible in 54% of patients. Of course, although further studies are necessary to clarify the time for evaluation and the number of treatment courses needed, this intra-arterial regimen can be useful as an arm of multidisciplinary treatment of advanced bladder cancers.

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