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Evaluation of systemic chemotherapy with methotrexate, vinblastine, Adriamycin, and cisplatin for advanced bladder cancer*

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Summary. In a cooperative study of the Japanese Urological Cancer Research Group for Adriamycin, the usefulness of chemotherapy with methotrexate, vinblastine, Adriamycin, and cisplatin (M-VAC therapy) in treating advanced or recurrent bladder cancer was examined. Evaluation of the clinical responses obtained in 86 evaluable patients revealed 13 complete responses, 29 partial responses, 4 minor responses, 19 cases of no change, and 21 cases of progressive disease. The overall response rate was 48.8% (42/86). The rate of response to M-VAC therapy at each disease site was as low as 21.4% (3/14) in bone lesions but exceeded 40% in the primary lesion, the lymph nodes, the lung, the liver, and other lesions. The clinical response to M-VAC therapy was not significantly influenced by the performance status of the patients, the dose intensity, or previous therapy. The median duration of response for the 42 responders was 22.7 weeks (range, 8.1–134.1 weeks), and the median duration of survival for the 86 evaluable patients was 9.8 months. Side effects were frequently encountered; the patients experienced anorexia, nausea, vomiting, malaise, alopecia, and leukopenia, but all of these symptoms were tolerable.

Introduction

The Japanese Urological Cancer Research Group for Adriamycin (JUCRGA) has previously studied the usefulness of cyclophosphamide, Adriamycin, and cisplatin (CAP therapy) and cyclophosphamide, Adriamycin, and 5-fluorouracil (CAF therapy) in the treatment of advanced or recurrent bladder cancer in an open trial and reported overall response rates of 17% (16/96) and 13% (1/8), respectively [3]. In 1985, Sternberg et al. [5] published a noteworthy report that combination therapy with methotrexate, vinblastine, Adriamycin, and cisplatin (M-VAC therapy) produced a high response rate of 71% in advanced or recurrent cases of bladder cancer. We therefore investigated the usefulness of M-VAC therapy in Japan in the second study of the JUCRGA.

Patients and methods

The subjects of the study were patients with advanced or recurrent bladder cancer who had been treated at the 25 institutions listed in Table 1 during the 1-year period between July 1987 and July 1988. The registered cases numbered 100, and 94 of them, excluding 5 who had no evaluable lesions and 1 who died early, satisfied the protocol for eligibility. Of these 94 patients, 86 were evaluated following the exclusion of 4 who had been given intraarterial M-VAC therapy, 2 who had received Adriamycin and cisplatin derivatives, and 2 cases of incomplete observation.

Table 2 summarizes the characteristics of the 86 evaluable patients. They included 72 men and 14 women aged an average of 60.7 years (range, 42–82 years). Primary cases numbered 36 and recurrent cases, 50. A total of 46 patients had undergone prior therapy other than a surgical operation: 21 had received chemotherapy only; 6, radiation only; 16, chemotherapy plus radiation (including 2 who had received chemotherapy and radiation as well as other treatments); and 3, other treatments. The other 40 patients had undergone no prior therapy other than a surgical operation. The performance status (PS) at the initiation of M-VAC therapy was 0–2 in 65 patients and 3–4 in 21 subjects. The 86 evaluable patients had 22 primary lesions and 35 metastatic lesions in the lymph nodes, 34 in the lung, 21 in bones, and 12 in other organs.

The M-VAC regimen was given according to the original plan of Sternberg et al. [5] (Table 3). The dose of each drug could be reduced by 70% at the maximum, depending on the PS or the side effects encountered in each patient, and symptomatic treatment of side effects was allowed. Then, in an attempt to examine the influence of M-VAC dose reduction, drug withdrawal, or prolongation of the administration period on the response to treatment, the concept of dose intensity as expressed in milligrams per square meter of body-surface area per week was introduced [1, 2]. The patients were divided into a standard-dose group corresponding to a $\geq 70\%$ relative dose intensity (RDI) and a modified-

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Table 1. The Japanese Urological Cancer Research Group for Systemic Combination Chemotherapy (Chairman, Tadao Niijima)

Hokkaido University	T. Koyanagi
Iwate Medical University	T. Kubo
Fukushima Medical College	Y. Shiraiwa
Ohta General Hospital	H. Ishiwata
University of Tokyo	Y. Aso
Cancer Institute Hospital	T. Kawai
Yokohama City University	M. Hosaka
Fujigaoka Hospital, Showa University	Y. Kai
Chiba University	J. Shimazaki
National Nagoya Hospital	K. Yoshida
Gifu University	Y. Kawada
Toyama Medical and Pharmaceutical University	T. Katayama
Kanazawa University	H. Hisazumi
Center for Adult Diseases, Osaka	T. Kotake
Yao City Hospital	T. Yamaguchi
Osaka Prefectural Hospital	K. Ito
Kawasaki Medical School	H. Tanaka
Hiroshima University	T. Usui
Onomichi City Hospital	N. Akazawa
Ehime University	M. Takeuchi
Matsuyama Red Cross Hospital	T. Shiraishi
Kochi Medical School	Y. Fujita
National Shikoku Cancer Center	Y. Sumiyoshi
Medical College of Oita	J. Ogata
Kagoshima University	Y. Ohi

Table 2. Patients' characteristics

Characteristic		Number of patients			χ^2 test
		Total	Standard dose	Modified dose	
Number of evaluable patients		86	46	40	
Sex:					
	M	72	39	33	NS
	F	14	7	7	
Age (years):					
	Mean	60.7	60.2	61.3	
	Range	42–82	42–77	44–82	
History:					
	Primary	36	20	16	NS
	Recurrent	50	26	24	
Prior treatment:					
	Chemotherapy	37	24	13	NS
	Radiation	22	11	11	
	Surgery	72	40	32	
	Others	5	2	3	
Performance status:					
	0–2	65	38	27	NS[a]
	3–4	21	8	13	
Sites of measurable disease:					
	Primary tumor	22	15	7	NS
	Lymph nodes	35	21	14	
	Lung	34	17	17	
	Liver	7	3	4	
	Bone	21	12	9	
	Others	12	4	8	

[a] *U*-test
NS, Not significant

Table 3. M-VAC regimen

Drugs	Dose	Schedule	
Methotrexate	30 mg/m² i. v.	Days 1, 15, 22	every 4 weeks
Vinblastine	3 mg/m² i. v.	Days 1, 15, 22	
Adriamycin	30 mg/m² i. v.	Day 2	
Cisplatin	70 mg/m² i. v.	Day 2	

dose corresponding to a <70% RDI, and the clinical response was compared between the two groups. The RDI was calculated using the following formula:

$$\text{RDI} = \frac{\text{Delivered dose (mg/m}^2\text{ weekly)}}{\text{Projected dose (mg/m}^2\text{ weekly)}}$$

The clinical response to M-VAC therapy was evaluated in accordance with the following criteria: complete response (CR), the complete disappearance of the tumor according to all clinical criteria for at least 4 weeks; partial response (PR), a reduction of ≥50% in the size of the tumor for at least 4 weeks; minor response (MR), a reduction of 25%–49% in the size of the tumor for at least 4 weeks; no change (NC), a decrease of <25% in the size of the tumor or stable disease; progressive disease (PD), an increase of >25% in the size of the tumor or the appearance of a new lesion(s).

Survival values were calculated according to the method of Kaplan-Meier. The background factors of the patients and the clinical responses were analyzed using the χ^2 test or the *U*-test.

Results

The evaluation of the clinical response to M-VAC therapy obtained in 86 evaluable patients revealed 13 CRs (15.1%), 29 PRs (33.7%), 4 MRs (4.7%), 19 NCs (22.1%), and 21 PDs (24.4%). The overall response rate was 48.8% (42/86) (Table 4). As shown in Table 5, the rate of response to M-VAC therapy at each site of disease was 40.9% for the primary lesion, and the values determined for metastatic lesions included 45.7% (16/35) for the lymph nodes, 47.1% (16/34) for the lung, 50.0% (3/6) for the liver, 21.4% (3/14) for bones, and 63.6% (7/11) for others (skin and pelvic cavity, among others). The response rate was similar for all lesions except those in bones.

Next, the influence of various factors on the clinical response to M-VAC therapy was investigated. A response rate of 53.8% (35/65) was obtained in patients with a PS of 0–2, and this value was higher than the 33.3% noted for patients with a PS of ≥3 (Table 6). The response rate in the standard-dose group (corresponding to an RDI of ≥70%) was 56.5% as compared with 40.0% in the modified-dose group (corresponding to an RDI of <70%). This tendency was recognized both in patients with a PS of 0–2 and in those with a PS of ≥3. The influence of prior therapy other than a surgical operation on the clinical response to M-VAC therapy is shown in Table 7. The response rate was 57.5% (23/40) in patients who had not received prior therapy, 47.6% in those who had been treated with chemotherapy only, 50.0% in those who had undergone irradiation alone, 31.3% in those who had received chemotherapy plus radiation, and 33.3% in those who had received other treatments.

Table 4. Overall rate of response to M-VAC therapy

Number of patients	Response					Objective response (CR+PR)
	CR	PR	MR	NC	PD	
86 (100%)	13 (15.1%)	29 (33.7%)	4 (4.7%)	19 (22.1%)	21 (24.4%)	42/86 (48.8%)

Table 5. Response rate according to the disease site

Site of disease	Number of lesions	Response (CR+PR)	Objective response rate (CR+PR)
Primary lesion (bladder)	22	9	40.9%
Lymph node	35	16	45.7%
Lung	34	16	47.1%
Liver	6	3	50.0%
Bone	14	3	21.4%
Others	11	7	63.6%

Table 6. Influence of dose intensity and performance status on the response to M-VAC therapy

Performance status	Dose intensity	Number of patients	Response		Objective response rate (CR+PR)
			CR	PR	
0–2	Standard dose	38	4	19	60.5%
	Modified dose	27	5	7	44.4%
	Subtotals	65	9	26	53.8%[a]
3–4	Standard dose	8	1	2	37.5%
	Modified dose	13	3	1	30.8%
	Subtotals	21	4	3	33.3%[a]
0–4	Standard dose	46	5	21	56.5%
	Modified dose	40	8	8	40.0%
	Totals	86	13	29	48.8%[a]

[a] Mean values

Table 7. Influence of previous therapy on the response to M-VAC therapy

Prior therapy	Number of patients	Response		Objective response rate (CR+PR)
		CR	PR	
Chemotherapy only	21	3	7	47.6%
Radiation only	6	2	1	50.0%
Chemotherapy + radiation	16	1	4	31.3%
Others only	3	1	0	33.3%
No therapy	40	6	17	57.5%

Table 8. Time to response and response duration

	Response	Number of patients	Median (range)
Time to response	CR	13	61.1 days (25–148)
	PR	29	43.5 days (1–71)
	CR+PR	42	46.5 days (1–148)
Response duration	CR	13	22.7 weeks (8.1–134.1)
	PR	29	11.4 weeks (4.0– 64.7)
	CR+PR	42	12.6 weeks (4.0–134.1)

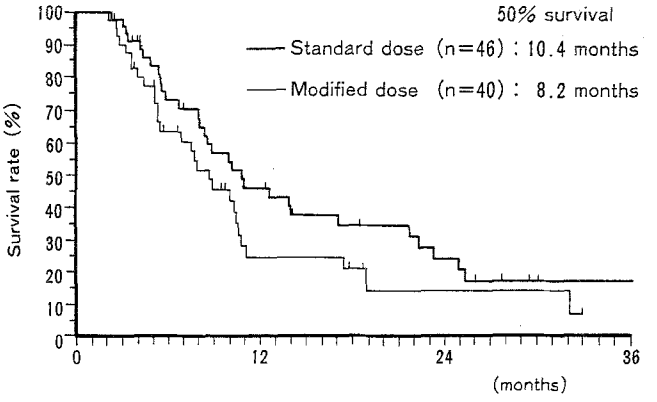

Fig. 1. Influence of dose intensity on the survival of patients receiving M-VAC therapy

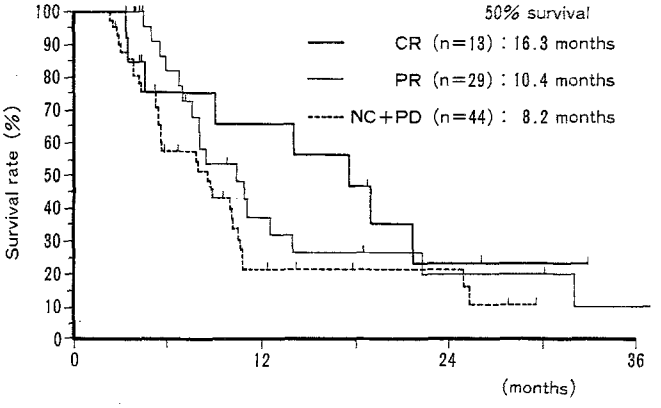

Fig. 2. Comparison of survival values as a function of the response category

The time to response and the response duration in the 42 responders to M-VAC therapy (i.e., 13 CRs and 29 PRs) are shown in Table 8. The median time to response was 46.5 days (range, 1–148 days), and the median duration of response was 22.7 weeks (range, 8.1–134.1 weeks) in patients who achieved a CR and 11.4 weeks (range, 4–64.7 weeks) in those who showed a PR. The median duration of survival for the 86 evaluable cases was 9.8 months. The influence of the dose intensity and the response category on the survival of these 86 patients is shown in Figs. 1 and 2, respectively. The median duration of survival for the standard-dose group was 10.4 months, whereas that noted for the modified-dose group (RDI, <70%) was 8.2 months. The median duration of survival for each response category was 16.3 months for the CR group, 10.4 months for the PR group, and 8.2 months for the NC+PD group.

Side effects related to the M-VAC therapy were frequently encountered. Anorexia occurred in 93.3% of patients; nausea and vomiting, in 97.3%; malaise, in 71.6%; alopecia, in 75.3%; leukopenia, in 93.8%; and anemia, in 84.4% (Table 9).

Table 9. Incidence of side effects

Side effect	Incidence
Gastrointestinal:	
Anorexia	93.3% (70/75)
Nausea, vomiting	97.3% (73/75)
Stomatitis	38.7% (29/75)
Diarrhea	20.0% (15/75)
Constipation	8.0% (6/75)
General:	
Fever	40.5% (30/74)
Deafness	6.9% (5/72)
Malaise	71.6% (53/74)
Alopecia	75.3% (55/73)
Renal function:	
Creatinine (1.5 mg/dl)	17.9% (7/39)
BUN (25 mg/dl)	21.1% (8/38)
Creatinine clearance (70 ml/min)	52.6% (10/19)
Bone marrow suppression:	
Leukopenia (4,000 leukocytes/mm^3)	93.8% (45/48)
Thrombocytopenia (10×10^4 platelets/mm^3)	38.3% (18/47)
Anemia (Hb, 11.0 g/dl)	84.4% (38/45)
Others	14.6% (11/75)

Hb, Hemoglobin

Discussion

Bladder cancer is said to be a tumor that responds relatively well to anticancer drugs, and 5-fluorouracil, cyclophosphamide, Adriamycin, and cisplatin have been demonstrated to be effective antitumor agents. Recently, the combined use of these drugs (i.e., CAF therapy and CAP therapy) in treating advanced bladder cancer has been studied; these regimens yield a response rate of around 40% [4, 7], and they are now commonly applied. In 1985, Sternberg et al. [5] reported a noteworthy preliminary finding that the combination of methotrexate, vinblastine, Adriamycin, and cisplatin (M-VAC therapy) produced an objective response rate (CR+PR) of 71% in patients with advanced bladder cancer, and 50% of the subjects achieved a CR in response to this therapy.

The Japanese Urological Cancer Research Group for Adriamycin (JUCRGA) has previously evaluated the usefulness of CAF therapy ($n = 8$) and CAP therapy ($n = 96$) in 104 patients with advanced bladder cancer and obtained response rates of 13% and 17%, respectively [3]. In the present study, the usefulness of M-VAC therapy in the treatment of advanced bladder cancer was investigated in the second study of the JUCRGA.

The overall rate of response to M-VAC therapy in 86 evaluable patients with advanced bladder cancer was 48.8% (42/86), including a CR rate of 15.1% (13 cases). These values are considerably lower than those preliminarily reported by Sternberg et al. for 25 patients [5]. However, the latter authors subsequently increased the number of patients to 91 and obtained a lower overall response rate of 69% and a CR rate of 37% [6]; these values differ to a lesser extent from the present results.

Because we feared that the M-VAC regimen described by Sternberg et al. [5] would induce excessively severe side effects, a maximal dose reduction of 70% was allowed in the present study, depending on the patient's condition. In many cases, dose reduction, drug withdrawal, and other alterations were carried out; these changes would naturally have decreased the actual dose intensity and would have been reflected in the clinical response. Then, as a new trial, the clinical response was compared between the standard-dose group [corresponding to a $\geq 70\%$ relative dose intensity (RDI)] and the modified-dose group (corresponding to a <70% RDI). In the standard-dose group the CR rate was not improved, but the overall response rate increased to 56.5%, i.e., more closely approached the value reported by Sternberg et al. [6].

Sternberg et al. [6] reported that the median duration of survival for patients treated with M-VAC was 12 months overall and exceeded 30 months in subjects who achieved a CR. In the present study, the median duration of survival was 9.8 months overall, 10.4 months for the standard-dose group (RDI, $\geq 70\%$), and 16.3 months for complete responders. All of these values were lower than those reported by Sternberg et al. The discrepancies seem to be attributable to the decreased dose intensity used in our study as well as to the different background factors of the patients.

A detailed examination of the results of the present study in terms of each site of disease revealed that the response rate was 21.4% for bone lesions, which was lower than that noted for other lesions (>40%). This tendency was in agreement with the reports of other investigators. As for the influence of the PS on the clinical response of patients to M-VAC therapy, the response rate was lower in subjects with a PS of ≥ 3, and the PS aggravation tended to synchronize with a decrease in the RDI. Therefore, the decreased dose intensity caused by an aggravated systemic condition may have contributed greatly to the lower clinical response rates obtained in these patients.

As side effects of M-VAC therapy, anorexia, nausea and vomiting, malaise, alopecia, leukopenia, and anemia occurred frequently. Generally, they were made somewhat tolerable by drug withdrawal, dose reduction, and other alterations.

The above-described findings indicate that M-VAC therapy is a useful combination regimen that produces markedly improved response rates as compared with those previously reported for CAF or CAP therapy and that its side effects can be managed and made tolerable by dose reduction, drug withdrawal, and other manipulations. The usefulness of the M-VAC regimen in achieving a high response rate as neoadjuvant therapy should be further studied, and modification of the protocol on the basis of the present results must also be examined.

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