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Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced urothelial cancer*

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Summary. A series of 31 patients with advanced urothelial cancer were treated with combination chemotherapy consisting of 1–4 cycles of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC). Of the 31 patients, 29 had measurable and evaluable lesions. A complete remission was achieved by 4 of these 29 patients (14%) for 1–46 months. A partial remission was observed in 14 of the 29 patients (48%) for 1–9 months. Whereas bony and hepatic metastatic lesions did not respond, some nodal (7/12), pulmonary (4/8), and pelvic lesions (2/3) as well as primary bladder tumors (4/6) and a tumor marker (1/2) responded. Complete tumor remission was observed in nodal (2/12) and pulmonary (1/8) metastatic lesions, in invasive lesions to the prostate and seminal vesicle (1/1), and in primary lesions in the bladder (2/6), ureter (1/1), and urethra (1/1). Two of three patients with non-transitional cell tumors attained a partial remission for 1–7 months. Complete remission of the pulmonary lesions was obtained in a case of squamous cell cancer of the bladder with pulmonary metastases. The toxicity of this regimen was generally tolerable and included moderate to severe myelosuppression, mild to moderate nausea and vomiting, renal toxicity, and mucositis. These results suggest that the M-VAC regimen holds promise for the treatment of advanced metastatic transitional cell cancer as well as non-transitional cell cancer of the urothelium.

Introduction

Combination chemotherapy consisting of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) was reported by Sternberg and associates in 1985 [6]; these investigators obtained a complete remission rate of 50% in 25 patients with advanced urothelial cancer. In a subsequent trial, a response rate of 69% was obtained in 83 patients [7]. In Japan, there have been a few studies on the use of M-VAC to treat urothelial cancer, with response rates ranging from 43% to 69% [1–3, 5, 8]. The present report summarizes our experience with M-VAC in 31 patients with advanced urothelial cancer.

Patients and methods

From January 1986 to August 1990, 31 patients with advanced urothelial cancer were treated at Kanazawa University Hospital and 5 associated hospitals. The treatment schedule followed the original protocol described by Sternberg and associates [6]. On day 1, 30 mg/m^2 methotrexate was generally given, and 3 mg/m^2 vinblastine, 30 mg/m^2 doxorubicin, and 70 mg/m^2 cisplatin were given approximately 24 h later under proper hydration conditions. On days 15 and 22, the same doses of methotrexate and vinblastine were repeated as long as permitted by the blood cell counts. The patients were hydrated with 2–4.5 l physiological saline or 5% glucose in the presence or absence of 500 ml 15% mannitol and/or furosemide on day 2. The antiemetic regimen consisted of 10–100 mg metoclopramide hydrochloride and/or 240–300 mg hydrocortisone sodium succinate or methylprednisolone sodium succinate. The doses of the drugs were reduced according to the patients' condition. The doses given to our series of patients are shown in Table 1. Median doses of 28.0 mg/m^2 methotrexate, 2.8 mg/m^2 vinblastine, 27.2 mg/m^2 doxorubicin, and 66.7 mg/m^2 cisplatin were given, and a median of 2 cycles/patient were completed (range, 1–4).

The 31 patients included 25 men and 6 women aged between 46 and 82 years (median, 67 years). Twenty-one patients had the primary carcinoma originated in the bladder in 21 patients, in the renal pelvis in 4 subjects, in the ureter and bladder in 4 cases, and in the ureter and the urethra in 1 patient each (Table 2). Of 31 patients, 28 had transitional cell carcinoma or transitional cell carcinoma with squamous cell carcinoma; 1 patient each had squamous cell carcinoma, adenocarcinoma, and undifferentiated carcinoma (Table 3).

The response criteria proposed by the Japan Society for Cancer Therapy were used [4]. Tumor-related biochemical and biological markers were also evaluated. The duration of the response was measured from the time at which a complete or partial remission was first achieved. The duration of survival was measured from the time of initiation of the regimen. The cumulative survival was estimated by Kaplan-Meier's method. Statistical analyses were performed using the generalized Wilcoxon test.

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Table 1. M-VAC doses

Drug	Dose (mg/m²)	
	Median	Range
Methotrexate	28.0	14.1–30.6
Vinblastine	2.8	1.3– 3.1
Doxorubicin[a]	27.2	12.5–30.3
Cisplatin	66.7	37.9–73.0

[a] One patient received Farmorubicin instead of doxorubicin

Table 2. Sites of primary lesions

	Number of patients
Bladder	21
Renal pelvis	4
Ureter and bladder	4
Ureter	1
Urethra	1
Total	31

Table 3. Histology of primary lesions

	Number of patients
TCC	27
TCC+SCC	1
SCC	1
AC	1
UC	1
Total	31

TCC, Transitional cell carcinoma; SCC, squamous cell carcinoma; AC, adenocarcinoma; UC, undifferentiated carcinoma

Table 4. Responses and survival

Response	Number of patients	Median duration of response (months)[a]	Survival (%)		
			1-year	2-year	3-year
CR	4 (14%)	17 (1–46)	100	100	100
PR	14 (48%)	4 (1– 9)	46	18	18
NC	5 (17%)		50	0	
PD	6 (21%)		20	0	
Total	29		48[b]	24[b]	24[b]

[a] Data in parentheses represent ranges
[b] Mean survival values

Table 5. Response rate for each disease site

Tumor site	Number of patients	Response	
		CR	PR
Lymph nodes	12	2 (17%)	5 (42%)
Lung	8	1 (13%)	3 (38%)
Bladder	6	2 (33%)	2 (33%)
Pelvic masses	3	0	2 (67%)
Renal pelvis	2	0	2 (100%)
Tumor marker	2	0	1 (50%)
Ureter	1	1 (100%)	0
Prostate and seminal vesicle	1	1 (100%)	0
Urethra	1	1 (100%)	0
Bone	1	0	0
Liver	1	0	0
Totals	38	8 (21%)	15 (39%)

Results

Of 31 patients, 2 received M-VAC as adjuvant chemotherapy and the other 29 had measurable and evaluable lesions. Of these 29 patients, 4 (14%) achieved a complete remission (CR) and 14 (48%) achieved a partial remission (PR), for an overall objective response rate of 62%. The median duration of response was 17 months (range, 1–46 months) in the CR group and 4 months (range, 1–9 months) in the PR group. In all, 2 of 3 (67%) patients who had previously received radiation therapy responded, as did 16 of 26 (62%) who had not undergone prior irradiation. The 1-year cumulative survival was 100%, 46%, 50%, and 20% in the CR, PR, no change (NC), and progressive disease (PD) group, respectively. The 3-year cumulative survival was 100%, 18%, 0, and 0 in the CR, PR, NC, and PD group, respectively (Table 4).

Measurable and evaluable disease sites totaled 38, and they showed a response rate of 60%. Whereas bony and hepatic lesions did not respond, responses were achieved in 4 of 8 pulmonary lesions, in 7 of 12 nodal lesions, in 2 of 3 pelvic masses, in 4 of 6 bladder tumors, and in 1 of 2 tumor-marker cases. All of the renal pelvic masses, the urethral tumor, the ureteral tumor, and the invasive lesion to the prostate and seminal vesicle responded (Table 5). Two of three patients with non-transitional cell tumors attained a PR for 1–7 months.

Among the 29 patients with measurable disease, 3 of 4 who achieved a CR showed no relapse during the subsequent follow-up period. Of the 14 patients in the PR group, 11 (79%) experienced a relapse. In 3 of these 11 (27%) patients, the relapse occurred in the liver, although none had shown any evidence of disease in the liver prior to their treatment with M-VAC; 6 others (55%) developed local recurrence in the lung, pelvis, or bladder (Table 6).

A total of 75 cycles of M-VAC were given. The median interval between cycles was 35 days between the 1st and 2nd courses and 34 days between cycles 2 and 3. During the first cycle, 42% of the patients completed a full course, as did 41% during the 2nd cycle and 29% during the 3rd cycle.

Hematological toxicity was significant. The median WBC reached nadirs of 2100 cells/mm³ (range, 800–5700/mm³) during the 1st cycle, 2500 cells/mm³ (range, 1600–3400/mm³) during the 2nd course, and 1900 cells/mm³ (range, 900–4100/mm³) during the 3rd cycle. The median platelet count reached nadirs of 150×10^3 cells/mm³ (range, $36–309 \times 10^3$/mm³) during the 1st cy-

Table 6. Data on CR and PR groups

Patient	Disease site	Histology	Response	Relapse site[a]	Survival (months)
1	Urethral tumor	TCC	CR	– (46)	48+
2	Lymph nodes	TCC	CR	– (1)	1+
3	Lymph nodes	TCC+SCC	CR	– (25)	27+
4	Ureter	TCC	CR	Ureter (8)	11+
5	Lymph nodes	TCC	PR	Liver (9)	12
6	Lymph nodes	TCC	PR	Liver (7)	10
7	Pelvic masses	TCC	PR	Liver (7)	9
8	Tumor marker	TCC	PR	Tumor marker (4)	41+
9	Bladder tumor, lung	SCC	PR	Prostate (7)	30+
10	Lung	TCC	PR	Lung (4)	9+
11	Lymph nodes, pelvic masses	TCC	PR	Pelvic masses (2)	12
12	Renal pelvic tumor	TCC	PR	– (2)	4+
13	Renal pelvic tumor, lymph nodes	TCC	PR	– (1)	2+
14	Bladder tumor	AC	PR	– (1)	4+
15	Bladder tumor, lymph nodes	TCC	PR	Bladder (4)	11
16	Lung	TCC	PR	Lung (4)	16
17	Bladder tumor, prostate and seminal vesicle	TCC	PR	Pelvic masses (15)	16
18	Lymph nodes, pelvic masses	TCC	PR	Pelvic masses (9)	16

[a] Data in parentheses represent the duration of the response (in months) prior to relapse

Table 7. Hematological toxicity of M-VAC

	1st cycle	2nd cycle	3rd cycle
Number of patients	31	27	14
WBC count (/mm^3):			
Median nadir (range)	2100 (800–5700)	2500 (1600–3400)	1900 (900–4100)
Median day (range)	15 (2–49)	13 (3–20)	17 (7–30)
Toxicity grade:			
0 (>4000/mm^3)	9	0	7
1 (3000–3900/mm^3)	23	15	0
2 (2000–2900/mm^3)	23	63	36
3 (1000–1900/mm^3)	39	22	43
4 (<900/mm^3)	6	0	14
Platelet count ($\times 10^3$/mm^3):			
Median nadir (range)	150 (36–309)	165 (45–292)	103 (14–229)
Median day (range)	13 (4–21)	12 (7–40)	17 (7–30)
Toxicity grade:			
0 (>100 $\times 10^3$/mm^3)	78	85	50
1 (70–99 $\times 10^3$/mm^3)	19	4	22
2 (50–69 $\times 10^3$/mm^3)	0	7	7
3 (30–49 $\times 10^3$/mm^3)	3	4	7
4 (<29 $\times 10^3$/mm^3)	0	0	14
Median interval between cycles in days (range)	35 (27–142)	34 (22–151)	

Table 8. General toxicity of M-VAC

	Number of patients
Nausea, vomiting	30 (97%)
Fever	12 (39%)
Diarrhea	10 (32%)
Mucositis	8 (26%)
Hepatic toxicity	3 (10%)
Renal toxicity:	
1st cycle	7 (23%)
2nd cycle	3 (11%)
3rd cycle	2 (14%)

cle, 165×10^3 cells/mm^3 (range, $45-292 \times 10^3$/mm^3) during the 2nd course, and 103×10^3 cells/mm^3 (range, $14-229 \times 10^3$/mm^3) during the 3rd cycle (Table 7).

Whereas 30 (97%) patients complained of nausea and vomiting, the severity of such toxicity was not significant because of the antiemetic regimen used. Diarrhea occurred in 10 patients (32%) and mucositis, in 8 (26%), but these toxic symptoms were not severe. Transient hepatic toxicity was noted in 3 subjects (10%). Although renal toxicity was noted in 7 (23%), 3 (11%), and 2 (14%) patients during cycles 1, 2, and 3, respectively, the serum creatinine levels were lower than 1.5 mg/dl in all cases (Table 8).

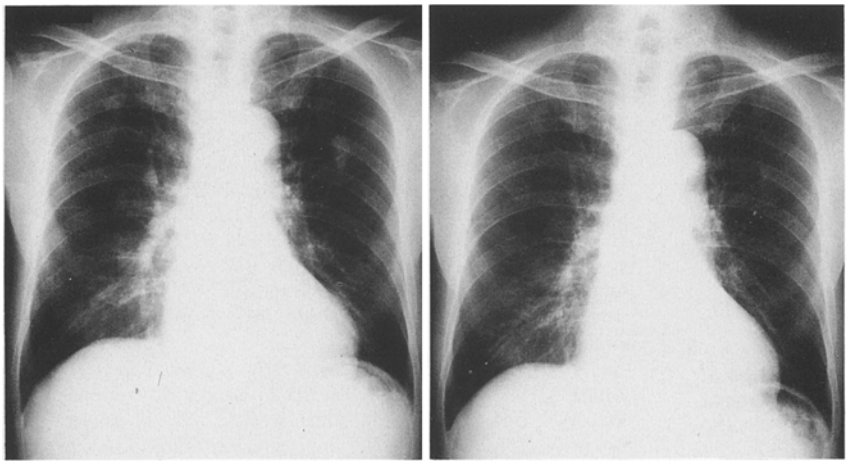

Fig. 1. Patient 9, a 75-year-old man, presented with pulmonary metastases originating from squamous-cell carcinoma of the bladder. *Left*, Multiple pulmonary metastases; *right*, disappearance of the pulmonary lesions after 3 cycles of M-VAC

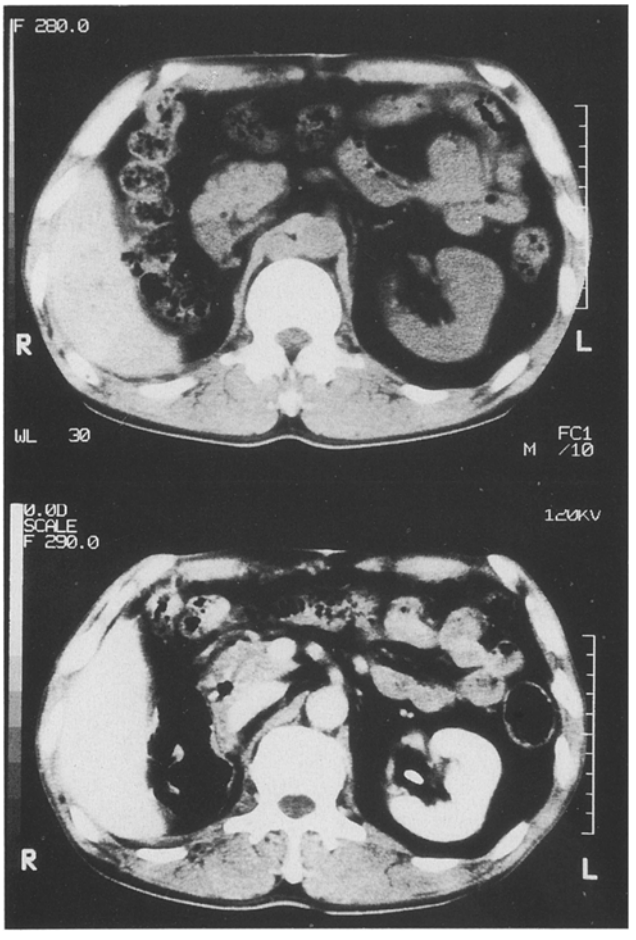

Fig. 2. Patient 3, a 57-year-old man, presented with para-aortic lymph-node metastasis originating from a right ureteral tumor. *Upper image*, para-aortic lymph-node metastasis; *lower image*, complete disappearance of lymph-node swelling

Discussion

M-VAC is one of the most effective chemotherapeutic regimens for advanced urothelial cancer. An overall objective response rate of 62% was attained in our series, which was almost the same as the 69% response rate reported by Sternberg and associates [7]. Whereas a CR rate of 37% was obtained in the latter series, 12% of the 83 patients treated achieved a CR after resection of their residual disease, and a clinical and pathological CR was attained by 25% of the subjects. In our series, patient 9 (Table 6), who had squamous cell carcinoma of the bladder with pulmonary metastases, achieved a CR of the pulmonary lesions after undergoing 3 cycles of M-VAC therapy (Fig. 1). Transurethral resection of the prostate, performed because of difficulty in urination at 7 months after the end of M-VAC treatment, revealed squamous cell carcinoma. Although this case was categorized as a PR, the patient achieved a CR for 30 months after this surgical intervention. It seems that surgical debulking of the residual disease contributes to a better response and/or improved survival.

Bony and hepatic lesions did not respond in our series, and other authors have also reported relatively low response rates for such lesions [1, 2, 5–7]. It seems that M-VAC shows limited activity against bony and hepatic metastases. Whereas Sternberg and associates [6, 7] have reported that this regimen exhibits only limited antitumor activity against non-transitional cell cancer, two of our three patients with non-transitional cell cancer attained a PR. The patient who presented with squamous cell cancer of the bladder with pulmonary metastases (patient 9) achieved a CR of the pulmonary lesions. Patient 3 (Table 6), who had metastatic nodal lesions from transitional cell carcinoma and squamous cell carcinoma of the ureter, maintained a CR for 25 months (Fig. 2). More patients with non-transitional cell cancer or mixed carcinoma must be treated to assess the effect of M-VAC on such diseases.

Although a high incidence of central nervous system (CNS) relapse has been reported in responders [6, 7], no CNS metastases were detected in our series. Instead, three patients had relapse in the liver. Patients treated with M-VAC should undergo careful follow-up with computer-assisted tomography of the brain as well as the abdomen.

In general, the toxicity of M-VAC was not significant. Nausea and vomiting were frequent, but myelosuppression was most important because it upset the schedule of drug administration. Only about 40% of the patients received the doses scheduled for days 15 and 22 because the WBC and platelet counts reached their nadirs between the 13th and 17th days. Although not all patients could tolerate all

of the cycles, long-term CRs and PRs were observed despite such unscheduled variations.

Our results suggest that not only transitional cell cancer but also non-transitional cell cancer of the urothelium is chemotherapeutically responsive to M-VAC and that this regimen should be given to patients with advanced disease. Its usefulness as adjuvant or neoadjuvant therapy should also be explored.

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