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SESSION I

Hiroaki Kobayashi · Koji Obata

Results of adjuvant chemotherapy for invasive urothelial cancer with lymph-node metastasis

Abstract From 1980 to 1991, 59 patients with advanced urothelial cancer (pathological stage, >pT3) underwent radical operations. Of these 59 patients, 33 had nodal involvement. This study focused on those 33 patients with nodal involvement. The primary site was the urinary bladder in 20 patients and the upper urinary tract (renal pelvis and/or ureter) in 13. In all, 13 patients underwent adjuvant chemotherapy with an M-VAC or M-VEC [methotrexate (M), vinblastine, doxorubicin (ADM) or epirubicin, and cisplatin (CDDP)] regimen, and another 8 patients were treated with other insufficient chemotherapies [CDDP + ADM or CDDP + ADM + etoposide (VP-16)]. A group of 12 patients did not receive any additional treatment. Most of the patients in the M-VAC and M-VEC groups received more than 2 cycles of the regimen (median, 3.2 cycles; range, 1–9 cycles). The overall 5-year survival rate of the M-VAC and M-VEC group was 31%, whereas the rate was 0 for the other insufficient-chemotherapy groups and the no-chemotherapy group. Of the 13 patients in the M-VAC group, 4 (31%) patients were alive without disease progression and 9 (69%) were dead due to progressive disease. In the other groups, only 1 patient was alive without progression. Our results suggest that adjuvant M-VAC or M-VEC chemotherapy may extend the median survival of patients with advanced urothelial cancer, but it failed to reduce the rate of cancer death.

Key words Adjuvant chemotherapy · M-VAC · Invasive urothelial cancer

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

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Introduction

Since Sternberg et al. [6] reported the effectiveness of M-VAC [methotrexate (M), vinblastine, doxorubicin (ADM), and cisplatin (CDDP)] chemotherapy in 1985, there have been many studies on the use of M-VAC to treat urothelial cancer [1, 2, 7, 8]. If nodal involvement was present, the 5-year survival rate was under 10% [3, 4]. Recently, there have been some studies on the usefulness of M-VAC for adjuvant chemotherapy of invasive urothelial cancer [5, 9–11]. Since 1987 in our hospital, patients with invasive urothelial cancer who have undergone radical operations have received postoperative adjuvant chemotherapy using M-VAC or M-VEC (M, vinblastine, ADM or epirubicin, and CDDP). This study summarizes our experience with adjuvant chemotherapy with or without M-VAC treatment for patients who underwent complete resection of their disease.

Patients and methods

This study included 33 patients who underwent radical operations. The pathological stage was >pT3, with nodal involvement. In all, 20 patients had bladder cancer, and 13 had renal pelvis and/or ureteral cancer (Table 1). There were 14 men and 6 women with urinary bladder cancer, and their median age was 64.6 years. Of those 20 patients with bladder cancer, 18 had transitional-cell carcinoma and 2 had squamous-cell carcinoma. The pathological grade was G2 in 5 patients and G3 in 9. The pathological stage was pT3 in 14 patients

Table 1 Invasive urothelial cancer (pT3< n = 59)[a]

		Primary site	
		Bladder	Renal pelvis and/or ureter
Nodal involvement	N–	21	5
	N+	20	13
Total		41	18

[a] 1980–1991, Japanese Red Cross Nagoya Second Hospital

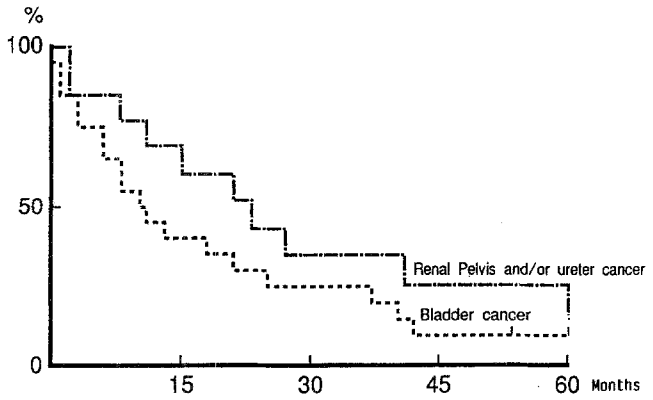

Fig. 1 Survival according to disease

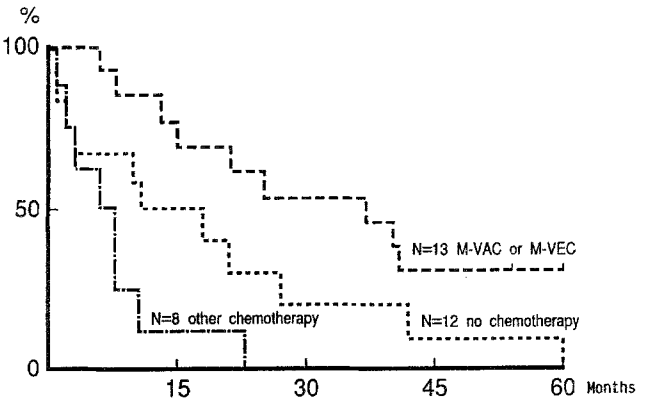

Fig. 2 Survival according to adjuvant chemotherapy

and pT4 in 6. There were 11 men and 2 women in the 13-member group with upper-urinary-tract cancer, and their median age was 63.5 years. Of the 13 patients with renal pelvis or ureteral cancer, 11 had transitional-cell carcinoma and 2 had squamous-cell carcinoma. The pathological stage of the renal pelvis and/or ureteral cancers was pT3 in 11 cases and pT4 in 2, whereas the pathological grade was G2 in 4 cases and G3 in 9 (Table 2).

In all, 13 of the 33 patients underwent adjuvant chemotherapy with an M-VAC (11 patients) or M-VEC regimen (2 patients) and 8 patients received other insufficient chemotherapies [CDDP + ADM or CDDP + ADM + etoposide (VP-16)]. A group of 12 patients did not receive any additional treatment. Most of the patients in the M-VAC and M-VEC groups received more than 2 cycles of the regimen (median, 3.2 cycles; range, 1–9 cycles). The median dose of CDDP was 60.2 mg/m^2 (86%) in the M-VAC and M-VEC groups, but it was 40.4 or 37.5 mg/m^2 in the other insufficient-chemotherapy groups (Table 3).

Table 2 Characteristics of patients with nodal involvement (n = 33)

	Primary site	
	Bladder	Renal pelvis and/or ureter
Number of patients	20	13
Sex:		
M	14	11
F	6	2
Age (mean ± SD, years)	64.6 ± 9.6	63.5 ± 9.9
Histological findings:		
Transitional-cell carcinoma	18	12
Squamous-cell carcinoma	2	1
Pathological stage:		
pT3	14	11
pT4	6	2
Pathological grade:		
G2	5	4
G3	15	9

Table 3 Regimen of adjuvant chemotherapy and the dose of CDDP

Regimen	Number of patients	Median dose of CDDP (mg/m^2)
M-VAC or M-VEC	13	60.2
CDDP + ADM	7	40.4
CDDP + ADM + VP-16	1	37.5
None	12	0

Results

Clinical effects

The overall 5-year survival rate of the 33 patients with nodal involvement was 14%. The overall 5-year survival rate of the invasive bladder-cancer cases with nodal involvement was 10%, and that of the invasive upper-urinary-tract cancers was 17%. There was no significant difference between the two curves (Fig. 1). In terms of the patients' characteristics, there was no significant difference between the M-VAC or M-VEC group, the other-chemotherapy group, and the no-chemotherapy group (Table 4).

The overall 5-year survival rate of the M-VAC and M-VEC group was 31%, whereas that of the other-insufficient-chemotherapy group and no-chemotherapy group was 0 as determined by Kaplan-Meier's method (Fig. 2). The survival of the M-VAC and M-VEC group was better than that of the other groups. The median survival was 32.5 months in the M-VAC and M-VEC group and 8 months in the other-chemotherapy group. The median survival of the no-treatment group was 12 months (Table 5). Of the 13 patients in the M-VAC group, 4 (31%) are alive without disease progression and 9 (69%) have died of tumor progression. All of the 8 patients in the other-chemotherapy group (100%) have died of tumor progression. Of the 12 patients in the no-chemotherapy group, 1 (8%) patient is alive without progression, 10 (83%) have died of their disease, and 1 (8%) has died without any evidence of tumor (Table 6). Local recurrence and/or metastasis occurred in 27 patients (17 with bladder cancer and 10 with renal pelvis and/or ureteral cancer). Various sites were involved in the local recurrence and/or metastasis. One patient in the M-VAC and M-VEC group had brain metastasis (Table 7).

Toxicity

The most common complications encountered (Table 8) were hair loss and gastrointestinal symptoms, e.g., nausea, vomiting, and anorexia, due to the administration of CDDP.

Table 4 Patients' characteristics and adjuvant chemotherapy of invasive urothelial cancer (pT3< $n + N = 33$)

	Primary site and chemotherapy					
	Bladder			Renal pelvis and/or ureter		
	M-VAC or M-VEC	Other	None	M-VAC or M-VEC	Other	None
Number of patients	8	4	8	5	4	4
Pathological stage:						
T3	5	2	7	5	3	3
T4	3	2	1	0	1	1
Pathological grade:						
G2	1	3	1	0	1	1
G3	7	1	7	3	3	3

Table 5 Median survival according to adjuvant chemotherapy

	Number of patients	Median survival (months)
M-VAC or M-VEC	13	32.5 (range, 7–81)
Other chemotherapy	8	8.0 (range, 2–24)
None	12	12.0 (range, 1–64)

Table 6 Follow-up results obtained in patients with tumors and lymph-node involvement (pT3< $n = 33$)

	M-VAC or M-VEC	Other chemo-therapy	None
Alive without progression	4/13 (31%)	0	1/12 (8%)
Alive with progression	0	0	0
Dead with progression	9/13 (69%)	8/8 (100%)	10/12 (83%)
Dead without tumor	0	0	1/12 (6%)

Table 7 Details of patients with local recurrence and/or metastasis

Site of recurrence or metastasis	Chemotherapy		
	M-VAC or M-VEC ($n = 9$)	Other chemotherapy ($n = 8$)	None ($n = 12$)
Local recurrence	3	3	8
Lymph node	3	6	3
Lung	3	1	3
Liver	1	3	5
Bone	2	2	3
Brain	1	0	0

Table 8 Side effects of M-VAC or M-VEC chemotherapy

Toxicity	Number of patients (%)
Hair loss	13/13 (100%)
Nausea/vomiting	12/13 (92%)
Leukopenia (<3000/mm^3)	12/13 (92%)
Stomatitis	4/13 (31%)
Thrombocytopenia (<10 × 10^4/mm^3)	3/13 (23%)
Renal toxicity	0/13 (0)

Leukopenia (WBC, <3000/mm^3) was seen in all 33 patients (94%). Recently, we have become more successful in reducing severe toxic side effects using antiemetic regimens and recombinant granulocyte colony-stimulating factor (rG-CSF), but these supporting drugs are nonetheless incapable of freeing most patients from the unpleasant effects.

Discussion

M-VAC chemotherapy has been used to treat measurable metastatic disease and local advanced urothelial tumors with encouraging results [2, 3, 4, 7]. When patients who undergo radical operations have nodal involvement, more than 50% of them do not survive for 5 years without adjuvant chemotherapy [1, 5]. Adjuvant chemotherapy reduces the rate of cancer death and improves the survival rate. Recently, the M-VAC regimen has been applied as adjuvant chemotherapy for invasive urethral cancer [5, 9–11]. Stockle et al. [9] reported on 49 bladder cancer patients with tumors of stage pT3–pT4 and/or pelvic lymph-node involvement who were randomized into 2 comparative groups (adjuvant chemotherapy with M-VAC and no therapy). Their results indicated that the survival of patients after radical operations can be prolonged considerably by adjuvant chemotherapy, especially in patients with lymph-node involvement.

Although our study was not randomized, similar results were obtained. Of the 13 patients in the M-VAC group, 4 (39%) are alive without disease progression at this writing, whereas only 1 (8%) of the 12 patients in the no-chemotherapy group is alive without progression. The median survival was 32.5 months in the M-VAC group and 12 months in the no-chemotherapy group. This result shows the usefulness of adjuvant chemotherapy with the M-VAC regimen.

Our results suggest that adjuvant M-VAC chemotherapy may extend the median survival of patients with advanced urothelial cancer, but it did not seem to reduce the rate of cancer death. A clearer answer must await further follow-up of this adjuvant chemotherapy. Another question is how many cycles are needed for effective adjuvant chemother-

apy. Stockle et al. [9] started adjuvant chemotherapy with three cycles of M-VAC or M-VEC. In the present study, we gave an average of 3.2 cycles of M-VAC as adjuvant chemotherapy. In our series, three patients who received the M-VAC adjuvant chemotherapy experienced recurrence with tumor progression at 6 months after the last adjuvant chemotherapy. The question remains as to how long we should continue the adjuvant chemotherapy for maintenance to improve the nonrecurrence rate. A study of this aspect would probably require a larger number of patients and seems possible only in a multicenter setting.

The problem of toxicity remains. Decreased kidney function and severe leukopenia can be limiting factors for M-VAC adjuvant chemotherapy. Most Japanese studies of M-VAC therapy have not used the full dose of M-VAC chemotherapy because of side effects [11]. Recently, we have become more successful in reducing severe toxic side effects using antiemetic regimens and rG-CSF. Without these supporting agents, we have not been capable of giving a complete dose of M-VAC therapy. The present adjuvant chemotherapy with M-VAC was considered to be useful. However, before M-VAC adjuvant chemotherapy is accepted as a golden standard, data from larger prospective trials are needed.

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