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Factors Related to the Outcome of M-VAC in 101 Patients with Advanced Urothelial Cancer

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ABSTRACT

The objective of this study is to identify factors related to the results of intravenous methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) for 101 patients with advanced urothelial cancer. The effects of various factors on response and survival were evaluated using univariate and multivariate analyses. The factors included in the analyses were sex, age, performance status (PS), primary site, histological type, grade, T category, N category, M category, prior chemotherapy, prior radiotherapy, and dose of chemotherapeutic drugs. Univariate analysis revealed that M category and prior chemotherapy had a significant correlation with the response, and that factors significantly related to survival were PS, primary site, N category, M category, prior chemotherapy and prior radiotherapy. A multiple logistic regression model showed that N category, M category and prior chemotherapy were related to response. The response rates of patients with N1-4 or M1 or prior chemotherapy were lower than those with N0 or M0 or without prior chemotherapy. A Cox regression model demonstrated that PS and M category independently contributed to survival. Patients with high grade PS or distant metastases showed a lower survival rate than those with low grade PS or localized diseases. M category was the most important factor related to response and survival. These results seem to indicate the low effectiveness of M-VAC for distant metastases, and the inability of this regimen to improve the outcome of patients with advanced urothelial cancer.

Key words: *Multivariate analysis, Response, Survival, M-VAC, Advanced urothelial cancer*

Although the present role of chemotherapy in patients with transitional cell carcinoma of the bladder is unclear, therapy for disseminated disease must be directed at eradication of all tumor foci, which can only be achieved at present by systemic chemotherapy[9]. Presently, cis-diamminedichloride platinum (CDDP) is considered to be the most active agent in the treatment of metastatic transitional cell carcinoma of the urothelial tract[17], and the results of multidrug regimens containing CDDP have been reported[3,6,13]. Among these multidrug regimens, excellent results have been reported with M-VAC chemotherapy consisting of methotrexate (MTX), vinblastine (VLB), doxorubicin (ADM) and CDDP[7,14]. However, it is unclear whether a favorable response to chemotherapy induces survival benefit or whether responding tumors have an inherently more favorable course[5]. Furthermore, the ability of M-VAC to prolong survival remains in question in the long-term followup. We attempted to identify patients who might benefit from the M-VAC regimen by evaluating background factors related to response and survival.

PATIENTS AND METHODS

From 1986 to 1994, 112 patients with advanced urothelial cancer were treated with systemic M-VAC chemotherapy, of whom 11 were ineligible because of the absence of a measurable lesion. Thus, 101 patients with invasive or metastatic urothelial cancer were selected for this study. The background characteristics of the patients are shown in Table 1. The performance status (PS) was assessed in accordance with the scale of the World Health Organization[16]. The tumor was graded according to the criteria of the International Union Against Cancer[4]. All of the patients

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Table 1. Patients' background characteristics

Number of patients	101
Sex (M:F)	78 : 23
Age	–50, 10; 51–60, 18; 61–70, 38; 71–80, 30; 81–, 5
Performance status (PS)	0, 43; 1, 25; 2, 21; 3, 10; 4, 2
Primary site	Bladder, 75; upper tract, 26
Histological type	Transitional cell carcinoma, 94; others, 7
Grade	G2, 34; G3, 67
T category	T1, 9; T2, 22; T3, 49; T4, 21
N category	N0, 66; N1, 7; N2, 4; N3, 7; N4, 17
M category	M0, 68; M1, 33
Prior chemotherapy	Yes, 30; no, 71
Prior radiotherapy	Yes, 18; no, 83
Dose of drugs	Full, 49; reduced, 52

underwent chest X-rays, bone scans, sonography, and computerized tomography (CT). Patients with bladder cancer were evaluated by cystoscopy with biopsy (or TUR-biopsy). These diagnostic studies were performed before each cycle of the chemotherapy, and the responses were evaluated according to the World Health Organization[16]. Complete response (CR) was defined as the disappearance of all known disease. Partial response (PR) was defined as the decrease by 50% or more in the total tumor size. No change (NC) was the condition when a 50% decrease in total tumor size could not be established or when a 25% increase in the size of one or more measurable lesions could not be demonstrated. Progressive disease (PD) was defined as an increase of 25% or more in the size of one or more measurable lesions, or the appearance of new lesions. The chemotherapy was administered intravenously in accordance with the regimen of Sternberg et al.[14] as follows: MTX (30 mg/m^2) was given on day 1 and approximately 24 h later VLB (3 mg/m^2), ADM (30 mg/m^2) and CDDP (70 mg/m^2) were administered with additional intravenous fluids to maintain a sufficient urinary output until oral intake was adequate. MTX and VLB were given on days 15 and 22 if the blood count permitted and no mucositis was present.

Evaluation of the response was performed before each cycle and the survival was calculated from the date of the initiation of the treatment with M-VAC using the method of Kaplan and Meier[8]. Differences in survival were compared by the logrank test. The effects of factors on the response were evaluated using a chi-square test. The relative effect of factors on response was studied using a multiple logistic regression model[10], and the independent contribution of each factor to survival was analyzed with a Cox regression model[1]. The factors included in the analyses were sex, age, PS, primary site, histological type, grade, T category, N category, M category, prior chemotherapy, prior radiotherapy, and dose of chemotherapeutic drugs. Of the factors evaluated, PS, T category and N category were subdivided into two categories each in the statistical analyses, as follows: PS, grade 0-1 vs. grade 2-4; T1-2 vs. T3-4; N0 vs. N1-4. The content of prior chemotherapy is the combination of cyclophosphamide, ADM and CDDP. A p value of less than 0.05 was considered to be significant.

RESULTS

Of the 101 patients, 16 (16%) showed a complete response and 41 (40%) had a partial response for an overall response rate of 56% (95% confidence limits ranged from 46 to 66%, Table 2).

Using the chi-square test, we analyzed the relationship between the factors and the response. Among the factors evaluated, M category and prior chemotherapy showed a significant correlation with the response (p=0.016, p=0.030, respectively, Table 3). The response rates of patients with distant metastases or prior chemotherapy were lower than those with localized disease or without prior chemotherapy. The contribution of histological type to response was unclear because the number of histologies other than transitional cell carcinoma was small. Analysis by a multiple logistic regression model showed that N category, M category and prior chemotherapy independently contributed to the response (Table 4).

Table 2. Overall response

Number of patients	Response				CR+PR/Total
	CR	PR	NC	PD	%
101	16	41	28	16	57/101
					56% (46% – 66%)*

Abbreviations: CR, complete response; PR, partial response; NC, no change; PD, progressive disease.
* 95% confidence limits

Table 3. Response as a function of each factor

Factor	Category		CR+PR/Total (%)	p-value*
Sex	M	0	45/78 (58)	0.639
	F	1	12/23 (52)	
Age	<66	0	28/50 (56)	0.930
	≧66	1	29/51 (57)	
PS	0 - 1	0	40/68 (59)	0.630
	2 - 4	1	17/33 (52)	
Primary site	Bladder	0	43/75 (57)	0.757
	Upper tract	1	14/26 (54)	
Histological type	TCC	0	54/94 (57)	0.453
	Others	1	3/7 (43)	
Grade	G2	0	22/34 (65)	0.232
	G3	1	35/67 (52)	
T category	T1-2	0	19/31 (61)	0.661
	T3-4	1	38/70 (54)	
N category	N0	0	36/66 (55)	0.752
	N1-4	1	21/35 (60)	
M category	M0	0	44/68 (65)	0.016
	M1	1	13/33 (39)	
Prior chemotherapy	Yes	0	12/30 (40)	0.030
	No	1	45/71 (63)	
Prior radiotherapy	Yes	0	10/18 (56)	0.934
	No	1	47/83 (56)	
Dose of drugs	Full	0	31/49 (63)	0.179
	Reduced	1	26/52 (50)	

*Chi-square test, TCC=transitional cell carcinoma

Table 4. Results obtained by multiple logistic regression model

Factor	Parameter	p-value
Sex	–0.1098	0.8449
Age	–0.0067	0.7498
PS	0.0293	0.9560
Primary site	–0.2731	0.6330
Histological type	–1.0449	0.2493
Grade	–0.8442	0.0903
T category	0.1362	0.7866
N category	1.1792	0.0437*
M category	–1.3447	0.0122*
Prior chemotherapy	1.0514	0.0497*
Prior radiotherapy	–0.2571	0.6915
Dose of drugs	–0.5372	0.2492

*$p<0.05$

Of the 101 patients, 30 (30%) are still alive. The 1-, 3- and 5-year survival rates of all patients were 68, 32 and 21%, respectively. The logrank test showed that factors related to survival were PS, primary site, N category, M category, prior chemotherapy and prior radiotherapy. The survival rate of patients with high grade PS was lower than that of those with low grade PS (p=0.001, Fig. 1). The survival rate of patients who had an upper tract tumor was lower than that of those with bladder cancer (p=0.014). Patients with lymph node metastasis, prior chemotherapy or prior radiotherapy showed lower survival rates compared to those without (p=0.001, p=0.012, p=0.021, respectively). Patients with distant metastases demonstrated a lower survival rate than those with localized disease (p=0.001, Fig. 2). With multivariate analysis of factors in the Cox regression model, our study revealed that PS and M category were independently significant factors in the prediction of survival (p=0.008, p=0.001, respectively, Table 5).

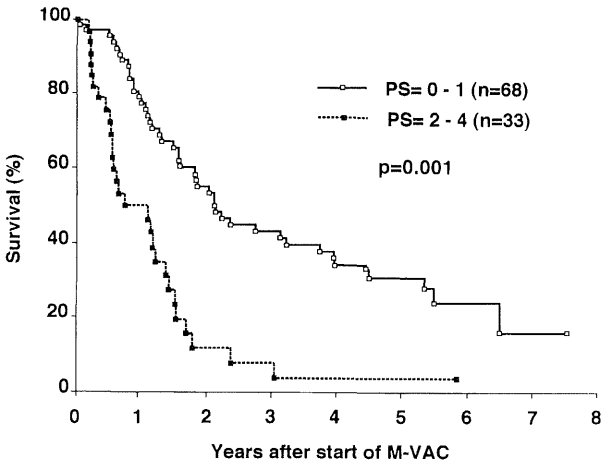

Fig. 1. Survival of patients with high-grade PS compared with those with low-grade PS.

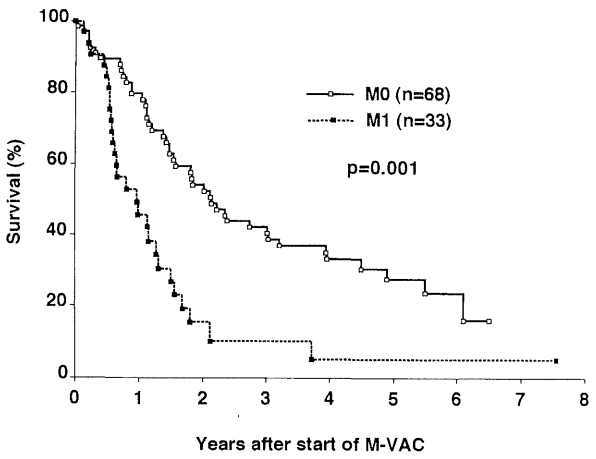

Fig. 2. Comparison of survival plots for patients with M0 and those with M1.

Table 5. Results of Cox regression model

Factor	Parameter	p-value
Sex	0.3253	0.2958
Age	–0.0021	0.8545
PS	0.7810	0.0083*
Primary site	0.3029	0.6149
Grade	0.4840	0.0994
T category	0.1582	0.6192
N category	0.4051	0.1916
M category	1.0207	0.0008*
Prior chemotherapy	–0.4365	0.1328
Prior radiotherapy	–0.5515	0.1026
Dose of drugs	0.1206	0.6555

*p<0.05

DISCUSSION

Analysis by the multiple logistic regression model demonstrated that factors independently related to the response were N category, M category and prior chemotherapy. Interestingly, the response rate of patients with N1-4 was higher than that of those with N0. This may suggest the characteristics of lymph node metastases which have a high response rate and a high relapse rate[7]. As to the M category, patients with M0 showed a higher response rate than those with M1. These results seem to indicate that patients with nodal disease only exhibit a greater response to M-VAC chemotherapy than those with metastatic disease. Of 21 patients with nodal disease 11 (52%) achieved a complete response with M-VAC in the Memorial series, compared to only 33 of 100 (33%) with visceral metastases[15]. Also, a comparison of response rates by site of metastases revealed that complete responses occurred more frequently among patients with only nodal metastases, whereas those patients with visceral metastases had a significantly lower response rate in the CISCA chemotherapy[11]. These differences in response to chemotherapy between nodal and visceral metastases may reflect innate differences between clones of cells with a metastatic capacity and clones with the ability for lymph node metastases only. Patients treated with prior chemotherapy demonstrated a lower response rate compared to those without chemotherapy. This influence of prior chemotherapy on response may indicate the presence of drug resistance in patients with prior history of chemotherapy. In a study at Memorial Sloan-Kettering, primary and metastatic tumors were assessed for P-glycoprotein expression using an avidin-biotin immunohistochemical technique[12]. The fact that the positive rate of P-glycoprotein increased in primary and metastatic tumors after M-VAC suggests that induction of the multidrug-resistance phenotype contributes to the resistance observed in the clinic[12]. Drug resistance is considered to be a significant therapeutic obstacle to improving the outcome of patients with advanced urothelial tumors.

The logrank test showed that PS, primary site, N category, M category, prior chemotherapy, and prior radiotherapy were significantly related to the survival rate. Since some of the factors are mutually correlated with, for example, the number of sites (tumor burden) being correlated with poor PS, methods of univariate analysis can not be employed to assess the relative prognostic value of each factor[5]. The Cox regression model used in our study revealed that PS and M category were independent prognostic factors. High grade PS was a prognostic factor indicating a poor prognosis. It is clear from the work in metastatic disease that there is a considerable number

of tumors (30-40%) that are totally insensitive to chemotherapy[2]. M category was the most important factor related to response and survival. Patients with high performance status and localized disease may benefit from the present regimen.

Our results suggest the low effectiveness of M-VAC for distant metastases, and the inability of this regimen to prolong survival in patients with advanced urothelial cancer. New approaches and new agents are necessary to improve the outcome of patients with metastatic diseases.

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REFERENCES

1. **Cox, D.R.** 1972. Regression models and life tables. J. R. Stat. Soc. **34:** 248–275.
2. **De Vere White, R.W. and Meyers, F.J.** 1988. Impact of chemotherapy on the treatment of bladder cancer. Problem in Urology **2:** 413–418.
3. **Harker, W.G., Meyers, F.J., Freiha, F.S., Palmer, J.M., Shortliffe, L.D., Hannigan, J.F., McWhirter, K.M. and Torti, F.M.** 1985. Cisplatin, methotrexate, and vinblastine (CMV): an effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract. A Northern California oncology group study. J. Clin. Oncol. **3:** 1463–1470.
4. **Harmer, M.H.** 1978. TNM Classification of Malignant Tumours, 3rd edn, International Union Against Cancer, Geneva.
5. **Hortobagyi, G.N., Smith, T.L., Legha, S.S., Swenerton, K.D., Gehan, E.A., Yap, H.Y., Buzdar, A. U. and Blumenschein, G.R.** 1983. Multivariate analysis of prognostic factors in metastatic breast cancer. J. Clin. Oncol. **1:** 776–786.
6. **Igawa, M., Kadena, H., Tacho, T., Nakamoto, T. and Usui, T.** 1995. Preliminary results of methotrexate, etoposide and cisplatin in the treatment of urothelial cancer. Urol. Int. **54:** 80–84.
7. **Igawa, M., Ohkuchi, T., Ueki, T., Ueda, M., Okada, K. and Usui, T.** 1990. Usefulness and limitations of methotrexate, vinblastine, doxorubicin and cisplatin for the treatment of advanced urothelial cancer. J. Urol. **144:** 662–665.
8. **Kaplan, E.L. and Meier, P.** 1958. Nonparametric estimation from incomplete observations. J. Am. Stat. Ass. **53:** 457–481.
9. **Kedia, R.K., Gibbons, C. and Persky, L.** 1981. The management of advanced bladder carcinoma. J. Urol. **125:** 655–658.
10. **Lee, E.** 1980. Identification of risk factor related dichotomous data, p. 338–365. *In* E. Lee (ed.), Statistical methods for survival data analysis. Lifetime Learning, California.
11. **Logothetis, C.J.** 1988. The role of chemotherapy in the management of urothelial tumors: interpretation of the M.D. Anderson Cancer Center results. World J. Urol. **6:** 163–166.
12. **Petrylak, D.P., Scher, H., Reuter, V., O'Moore, P.V., Sheinfeld, J., O'Brien, J. and Cordon-Cardo, C.** 1992. P-glycoprotein (PGP) expression in invasive and metastatic urothelial tract cancer (UTC) [abstract]. Proc. Am. Soc. Clin. Oncol. **11:** 200.
13. **Schwartz, S., Yagoda, A., Natale, R.B., Watson, R.C., Whitmore, W.F. and Lesser, M.** 1983. Phase II trial of sequentially administered cisplatin, cyclophosphamide and doxorubicin for urothelial tract tumors. J. Urol. **130:** 681–684.
14. **Sternberg, C.N., Yagoda, A., Scher, H.I., Watson, R.C., Herr, H.W., Morse, M.J., Sogani, P.C., Vaughan, E.D., Jr., Bander, N., Weiselberg, L.R., Geller, N., Hollander, P.S., Lipperman, R., Fair, W.R. and Whitmore, W.F., Jr.** 1988. M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. J. Urol. **139:** 461–469.
15. **Sternberg, C.N., Yagoda, A., Scher, H.I., Watson, R.C., Geller, N., Herr, H.W., Morse, M.J., Sogani, P.C., Vaughan, E.D., Bander, N., Weiselberg, L., Rosado, K., Smart, T., Lin, S., Penenberg, D., Fair, W.R. and Whitmore, W.F., Jr.** 1989. Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. Cancer **64:** 2448–2458.
16. **World Health Organization.** 1979. Handbook for Reporting Results of Cancer Treatment. No. 48. WHO Offset Publication, Geneva.
17. **Yagoda, A.** 1980. Chemotherapy of metastatic bladder cancer. Cancer **45:** 1879–1888.