Cancer Chemother Pharmacol (1992) 30 (Suppl): S 77–S 80

Cancer Chemotherapy and Pharmacology

Factors affecting the outcome of patients with advanced urothelial cancer following chemotherapy with methotrexate, vinblastine, Adriamycin, and cisplatin*

Mikio Igawa, Taisuke Ohkuchi, Mitsutaka Ueda, and Tsuguru Usui

Department of Urology, Hiroshima University School of Medicine, Hiroshima 734, Japan

Summary. Attempts were made to identify factors related to the response of patients treated with intravenous methotrexate, vinblastine, Adriamycin, and cisplatin (M-VAC). The subjects consisted of 54 patients with advanced urothelial cancer whose histological type was transitional-cell carcinoma. The effects of various factors on the response were studied using univariate analysis and a multiple logistic regression model. The following factors were included in the anlayses: (1) age, (2) sex, (3) performance status (PS), (4) primary site, (5) histological grade, (6) T category, (7) N category, (8) M category, (9) tumor status, and (10) dose of drugs. In all, 9 patients achieved a complete response and 23 showed a partial response, for an overall response rate of 59% (95% confidence limits, 46%–72%). Univariate analysis revealed that the PS, M category, and dose of drugs were related to the response, and there was a significant correlation among these three factors. In the multiple logistic regression model, the absolute value of t was high for the M category. The presence of distant metastases is an important factor in predicting poor efficacy for the present regimen. The management of metastatic disease will be the subject of further study in the treatment of advanced urothelial cancer.

Introduction

Systemic chemotherapy is an important treatment modality for advanced urothelial cancer, particularly in patients with distant metastases. Among multidrug regimens, a combination of methotrexate, vinblastine, Adriamycin, and cisplatin (M-VAC) has been reported to be effective, and its efficacy against distant metastases is also recognized [7, 8]. However, quite a few patients do not respond to the present regimen, and its toxicity is serious [3]. Therefore, we must avoid unnecessary toxicity in patients who fail to respond to this treatment. We attempted to clarify the background factors related to the response so as to facilitate the selection of candidates who would be likely to benefit from the present regimen.

Patients and methods

Patients. From September 1986 through March 1989, 54 patients with advanced urothelial cancer were selected for this study. The histological type of all of the cancers was transitional-cell carcinoma, and all were treated with intravenous M-VAC. The background characteristics of the patients are summarized in Table 1. There were 40 men and 14 women aged a median of 64 years (range, 41–81 years). Based on the scale of the World Health Organization [10], the performance status (PS) ranged between 0 and 2 in most cases. The bladder was the most common primary site. The histological grade of most of the tumors was grade 3. In terms of the clinical stage, all patients had distant metastases or locally extensive disease. Two patients with T1 tumors had distant metastases. The doses of the chemotherapeutic agents were reduced in patients exhibiting a poor PS or renal impairment or undergoing episodes of radiotherapy.

Assessment and treatment. Laboratory investigations included a complete blood cell count; determinations of electrolytes, blood urea nitrogen, and serum creatinine; and liver-function tests. All of the patients underwent chest X-rays, bone scans, sonography, and computerized tomography (CT). Patients with bladder cancer were evaluated by cystoscopy with biopsy (or transurethral resection of the bladder) and urinary cytology. These diagnostic studies were performed before each cycle of the present chemotherapy, and the responses were evaluated according to the criteria of the World Health Organization [10]. Patients were treated with intravenous M-VAC chemotherapy in accordance with the regimen of Sternberg et al. [7, 8]. Methotrexate was given on day 1 at a dose of 30 mg/m^2, and 3 mg/m^2 vinblastine, 30 mg/m^2 Adriamycin, and 70 mg/m^2 cisplatin were given approximately 24 h later (day 2). Intravenous fluids were given before and after cisplatin to maintain sufficient urinary output. Methotrexate and vinblastine were given on

* Presented at the 4th International Conference on Treatment of Urinary Tract Tumors with Adriamycin/Farmorubicin, 16–17 November 1990, Osaka, Japan

Correspondence to: T. Usui, Department of Urology, Hiroshima University School of Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734, Japan

Table 1. Patients' background characteristics

Number of patients	54
Sex (M:F)	40:14
Median age (range)	64 (41–81) years
Performance status (PS)	0,18; 1,12; 2,16; 3,6; 4,2
Primary site	Bladder, 35; upper tract, 19
Grade	G2,14; G3,33; Gx,7
T category	T1,2; T2,8; T3,22; T4,14; Tx,8
N category	N0,26; N1,3; N2,1; N3,4; N4,13; Nx,7
M category	M0,32; M1,22
Tumor status	Primary, 17; recurrent, 37
Dose of drugs (1st cycle)	Full, 37; reduced, 17

Table 2. Coding of variables

Sex	M = 1; F = 2
Age (years)	<70 = 1; ≧70 = 2
PS	0–2 = 1; 3,4 = 2
Primary site	Bladder = 1; upper tract = 2
Grade	G2 = 2; G3 = 3
T category	T1–3 = 1; T4 = 2
N category	N0 = 0; N1–4 = 1
M category	M0 = 0; M1 = 1
Tumor status	Primary = 1; recurrent = 2
Dose	Full = 1; reduced = 2

Table 3. Extent of disease and response

Disease site	Number of patients	Response				Response rate
		CR	PR	NC	PD	
Primary	31	7	15	5	4	71%
Bladder	22	4	11	3	4	68%
Upper tract	9	3	4	2	0	78%
Lymph nodes	20	7	7	5	1	70%
Lung	9	3	2	1	3	56%
Liver	7	1	0	3	3	14%
Bone	12	0	3	5	4	25%

NC, No change; PD, progressive disease

Table 4. Overall response

Number of patients	Response				Response rate
	CR	PR	NC	PD	
54	9	23	10	12	59% (46%–72%)[a]

[a] 95% confidence limits

days 15 and 22 if the blood count permitted and no mucositis was present.

Statistical methods. Survival was estimated by the method of Kaplan and Meier [4]. The effects of variables on the response were studied using univariate analysis, and their relative effects were evaluated by a multiple logistic regression model [5]. The following variables were included in the analyses: (1) age, (2) sex, (3) PS, (4) primary site, (5) histological grade, (6) T category, (7) N category, (8) M category, (9) tumor status, and (10) dose of drugs during the first cycle. The coding for these variables is shown in Table 2.

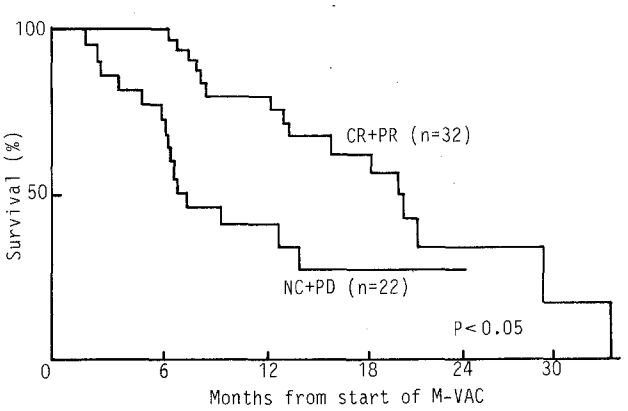

Fig. 1. Comparison of the survival of patients achieving a response (*CR+PR*) and those failing to respond (*NC+PD*) to M-VAC chemotherapy

Results

Response

A total of 79 sites were evaluated for treatment response. The objective response rates, defined as complete response (CR) plus partial response (PR) were 71% for the primary organs (68% for the bladder and 78% for the upper urinary tract), 70% for the lymph nodes, 56% for the lung, 14% for the liver, and 25% for bone (Table 3). Overall, 9 patients (17%) achieved a CR and 23 (42%) showed a PR, for an overall response rate of 59% (95% confidence limits, 46%–72%; Table 4). The median duration of response was 10 months for complete responders and 7 months for partial responders.

Survival

In relation to the response category, the 1- and 2-year survival values were 80% and 37% for responders and 40% and 27% for nonresponders, respectively. The survival of responders was significantly greater than that of nonresponders as judged by the generalized Wilcoxon test ($P < 0.05$, Fig. 1). This result suggests that the survival rate is greatly influenced by the response. Therefore, the effects of variables on the response were studied in the following tests.

Factors affecting the response

Using the Pearson chi-square test, we analyzed the relationship between each variable and the response. Among the ten variables evaluated, the PS, M category, and dose of drugs showed a significant correlation with the response (Table 5). Specifically, the response rates of patients exhibiting a low-grade PS and an M category of MO who

Table 5. Response as a function of each variable

Variable		CR+PR/Total	*P* value[a]
Sex	M	24/40 (60%)	0.85
	F	8/14 (57%)	
Age (years)	<70	23/38 (61%)	0.77
	≧70	9/16 (56%)	
PS	0–2	30/46 (65%)	0.03
	3,4	2/8 (25%)	
Primary	Bladder	21/35 (60%)	0.88
	Upper tract	11/19 (58%)	
Grade	G2	8/14 (57%)	0.68
	G3	21/33 (64%)	
T category	T1–3	18/33 (55%)	0.28
	T4	10/14 (71%)	
N category	N0	15/26 (58%)	0.33
	N1–4	15/21 (71%)	
M category	M0	24/32 (75%)	0.005
	M1	8/22 (36%)	
Tumor status	Primary	13/17 (77%)	0.08
	Recurrent	19/37 (51%)	
Dose	Full	27/37 (73%)	0.003
	Reduced	5/17 (29%)	

[a] Pearson chi-square test

Table 6. Relationships between the dose, M category and PS and the response

Dose	M category	PS	CR+PR/Total
Full	M0	0–2	20/25 (80%)
		3,4	
	M1	0–2	6/10 (60%)
		3,4	1/2 (50%)
Reduced	M0	0–2	3/6 (50%)
		3,4	1/1 (100%)
	M1	0–2	1/5 (20%)
		3,4	0/5

received a full dose of drugs were higher than those of subjects showing a high-grade PS and an M category of M1 who were given a reduced dose of drugs. The response rates calculated for various combinations of the dose of drugs, the M category, and the PS are shown in Table 6. The best response rate was achieved for a combination of a full dose of drugs, an M category of MO, and a low-grade PS. Conversely, the poorest response was obtained for the combination of a reduced drug dose, an M category of M1, and a high-grade PS. Significant relationships were found between the dose of drugs, the M category, and the PS (Table 7). The relative effects of these variables on the response were studied using a multiple logistic regression model. The *t* value (coefficient/SE) was 1.90 for the M category, which was the highest obtained among the variables tested, whereas the *P* value was 0.068 (Table 8).

Table 7. Relationships between three variables

		PS		*P* value[a]
		0–2	3,4	
M category	M0	31	1	0.004
	M1	15	7	
Dose	Full	35	2	0.004
	Reduced	11	6	

[a] Pearson chi-square test

Table 8. Results obtained by multiple logistic regression

Variable	Coefficient	SE	Coefficient/SE	*P* value
Sex	–1.16	1.44	–0.81	0.425
Age	0.04	0.05	0.89	0.383
PS	–1.23	1.59	–0.77	0.446
Primary site	1.77	1.30	1.36	0.186
Grade	0.57	1.18	0.48	0.633
T category	–1.02	1.14	–0.89	0.380
N category	–2.49	1.35	–1.86	0.075
M category	2.08	1.10	1.90	0.068
Tumor status	1.06	1.15	0.93	0.362
Dose	2.44	1.35	1.81	0.082

Discussion

Cisplatin-based combination chemotherapy is well known to be the most effective treatment available for advanced and metastatic urothelial cancers [1]. The results obtained using M-VAC chemotherapy at Memorial Sloan-Kettering Cancer Center (MSKCC) [8] appear to be superior to those achieved using other combination regimens such as cyclophosphamide, doxorubicin, and cisplatin (CAP) [6, 9]. Encouraged by the success at MSKCC, we used M-VAC to treat 54 patients with advanced urothelial cancer. As compared with the findings in the MSKCC report [8], our results indicated poor efficacy against distant metastases, especially bone and liver lesions.

At present, the ultimate objective of chemotherapy for advanced urothelial cancer is prolongation of the survival of patients. Our study showed that the survival of responders was significantly greater than that of nonresponders. Therefore, the likelihood of a response is an important indicator for the selection of candidates for treatment with the present M-VAC regimen. Univariate analysis revealed that the grade of PS, the M category, and the dose of drugs were significantly related to the response. With regard to the relationship between the PS and the M category, the number of sites (tumor burden) has been shown to correlate with a poor PS in breast cancer [2]. Furthermore, we tend to determine the dose of drugs on the basis of special consideration of the PS. The significant relationship found between the PS, the M category, and the dose of drugs in the present study indicate that methods of univariate analysis cannot be used to assess the importance of each factor. In contrast, multivariate analysis is an effective method for ranking the various prognostic factors in the order of their predicitive ability [2]. The multiple logis-

tic regression model used in our study revealed that the most important factors in predicting the response were the M category followed by the dose of drugs.

In conclusion, it is conceivable that the best candidates for treatment with the M-VAC regimen are patients with locally invasive cancers. At present, however, systemic chemotherapy is the only treatment modality for patients with disseminated metastases. In subsequent trials, favorable results in the treatment of metastatic urothelial cancer might be obtained using high-dose chemotherapy combined with recombinant human graunulocyte colony-stimulating factor.

References

1. Freiha F, Vries C de, Torti F (1988) Neoadjuvant and adjuvant chemotherapy of transitional cell carcinoma of the urothelium with cisplatin, methotrexate and vinblastine. World J Urol 6: 153
2. Hortobagyi GN, Smith TL, Legha SS, Swenerton KD, Gehan EA, Yap H-Y, Buzdar AU, Blumenschein GR (1983) Multivariate analysis of prognostic factors in metastatic breast cancer. J Clin Oncol 1: 776
3. Igawa M, Ohkuchi T, Ueki T, Ueda M, Okada K, Usui T (1990) Usefulness and limitations of methotrexate, vinblastine, doxorubicin and cisplatin for the treatment of advanced urothelial cancer. J Urol 144: 662
4. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53: 457
5. Lee E (1980) Identification of risk factor related dichotomous data. In: (eds) Statistical methods for survival data analysis. Lifetime Learning, California, p 338
6. Schwartz S, Yagoda A, Natale RB, Watson RC, Whitmore WF, Lesser M (1983) Phase II trial of sequentially administered cisplatin, cyclophosphamide and doxorubicin for urothelial tract tumors. J Urol 130: 681
7. Sternberg CN, Yagoda A, Scher HI, Watson RC, Ahmed T, Weiselberg LR, Geller N, Hollander PS, Herr HW, Sogani PC, Morse MJ, Whitmore WF (1985) Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. J Urol 133: 403
8. Sternberg CN, Yagoda A, Scher HI, Watson RC, Herr HW, Morse MJ, Sogani PC, Vaughan ED Jr, Bander N, Weiselberg LR, Geller N, Hollander PS, Lipperman R, Fair WR, Whitmore WF Jr (1988) M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. J Urol 139: 461
9. Troner MB, Hemstreet GP III (1981) Cyclophosphamide, doxorubicin and cisplatin (CAP) in the treatment of urothelial malignancy: a pilot study of the Southeastern Cancer Study Group. Cancer Treat Rep 65: 29
10. World Health Organization (1979) Handbook for reporting results of cancer treatment WHO, Geneva