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SESSION I

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M-VEC (methotrexate, vinblastine, epirubicin, and cisplatin) with granulocyte colony-stimulating factor for the treatment of urothelial cancer: an effective and safe chemotherapy regimen

Abstract The toxicity of combination chemotherapy is significant, with the most prominent side effect being myelosuppression. To reduce the toxicity, we used a recombinant human granulocyte colony-stimulating factor (rhG-CSF). A total of 52 patients were enrolled in this study. The sites of tumor involvement included the urinary bladder in 24 patients, the renal pelvis in 5, the ureter in 4, lymph nodes in 11, bone in 4, the lung in 1, and miscellaneous sites in 4 patients. The chemotherapy was given in 21-day cycles as follows: 30 mg/m^2 methotrexate was given intravenously on day 1, and approximately 24 h later, 3 mg/m^2 vinblastine, 30 mg/m^2 epirubicin, and 70 mg/m^2 cisplatin were given intravenously. The rhG-CSF (2 μg/kg per day) was injected subcutaneously on days 3–16 of each cycle. All patients received full doses of the antineoplastic agents on time according to the protocol design. The response rates were 61% for primary sites, 55% for lymph nodes, 0 for bone, and 67% for miscellaneous sites. Of 42 patients evaluated, 5 (12%) achieved a complete response and 20 (48%) achieved a partial response, for an overall response rate of 60%. Of the 42 patients, 27 (64%) are alive, and the median duration of survival is 14 months. The mean nadir white blood count was more than 5,600 cells/mm^3. The incidence of mucositis in the total toxic symptoms was low. There was no cardiac toxicity or drug-related death. These results indicate that the present combination chemotherapy with coadministration of rhG-CSF is an effective and safe regimen for the treatment of urothelial cancer.

Key words Urothelial cancer · M-VEC · G-CSF

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Introduction

Cisplatin-based multiple-drug chemotherapy is currently considered to be the most effective treatment for advanced and metastatic urothelial cancers [2]. Whereas the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) is one of the most effective regimens among multiple-drug chemotherapies, its myelosuppression is significant, with not a few cases of sepsis and drug-related death being reported [15]. Coadministration of hematopoietic growth factors has been shown to reduce the toxicities associated with combination chemotherapy [13], and granulocyte colony-stimulating factor (G-CSF) has been reported to enhance the cytotoxic effects of methotrexate on bladder cancer cells in vitro [10]. The present chemotherapy was composed of methotrexate, vinblastine, epirubicin, and cisplatin (M-VEC), whereby doxorubicin was replaced by its less toxic derivative epiribicin because of the reported association of doxorubicin cardiotoxicity with the cumulative dose [11]. We evaluated the response and toxicity of M-VEC with coadministration of G-CSF.

Patients and methods

From February 1991 to April 1993, 52 patients were enrolled in this study. All patients were evaluable for toxicity and 42 were evaluable for response. The 10 patients who were excluded from the evaluation of response received the present regimen in an adjuvant setting. The patients were assessed by abdominal and pelvic computerized tomography, sonograms, cystoscopy with biopsy (or transurethral resection of the bladder), urinary cytology, a chest radiograph, a radionuclide bone scan, and retrograde urography with brush biopsy for patients with renal pelvic or ureteral cancer. Evaluation of response was performed before each cycle, and the patients were followed every 3 months after the treatment. The response criteria applied were those of the World Health Organization (WHO) [17]. The duration of response and survival were measured from the initiation of treatment. The last day of observation was September 10, 1993. Toxic symptoms were graded according to WHO criteria [17].

The 42 patients evaluated consisted of 30 men and 12 women aged 39–83 years (mean age 63.9 years). With regard to the performance

Table 1 Extent of disease and response (*CR* Complete response, *PR* partial response, *NC* no change, *PD* progressive disease)

Tumor site	Number of patients	Response				CR + PR (%)
		CR	PR	NC	PD	
Primary site	31	5	14	12		19 (61)
Lymph node	11	2	4	3	2	6 (55)
Bone	4			4		0 (0)
Lung	1		1			1 (100)
Miscellaneous	3		2	1		2 (67)

Table 2 Overall response

Primary site	Number of patients	Response				% CR + PR
		CR	PR	NC	PD	
Bladder	30	5	11	13	1	53 (36–71)[a]
Renal pelvis or ureter	12		9	2	1	75 (48–94)
Totals	42	5	20	15	2	60 (44–74)

[a] Numbers in parentheses are the 95% confidence limits

status based on the WHO performance score [17], there were 36 patients with grade 0 or 1 and 6 patients with grade 2 or 3. Of the patients evaluated, 30 had primary carcinoma originating in the bladder; 8, in the renal pelvis; and 4, in the ureter. The staging of the tumor was performed according to the criteria of the International Union Against Cancer [5]. The tumor stage was T1 or T2 in 11 patients, T3 or T4 in 23 subjects, and TX in 8 patients. The sites of tumor involvement included the bladder in 23 patients, the renal pelvis in 5, the ureter in 3, lymph nodes in 11, bone in 4, the lung in 1, and miscellaneous in 4. In all, 33 patients had transitional-cell carcinoma, 1 had transitional-cell carcinoma combined with squamous-cell carcinoma, and 2 had transitional-cell carcinoma with adenocarcinoma. Of the patients evaluated, 19 had undergone prior surgery, 4 had received prior radiation therapy, and 5 had been given prior systemic chemotherapy.

The chemotherapy consisted of methotrexate (30 mg/m^2) given intravenously on day 1, followed by vinblastine (3 mg/m^2), epirubicin (30 mg/m^2), and cisplatin (70 mg/m^2) given intravenously on day 2. rhG-CSF (Chugai Co., Japan) was given by subcutaneous injection at 2 μg/kg per day on days 3–16. The cycle length was 21 days.

Results

An average of 2.0 cycles of treatment were given (range, 1–6 cycles). We evaluated 42 patients for response, and a total of 50 sites were evaluated in these patients. The response rate was 61% for primary sites, 55% for lymph nodes, and 67% for miscellaneous sites. No response was noted in bone lesions (Table 1). The overall response rates by site were 53% in patients with bladder cancer and 75% in those with renal pelvic or ureteral cancer. Of the 42 patients evaluated, 5 (12%) achieved a complete response and 20 (48%) achieved a partial response, for an overall response rate of 60%, with the 95% confidence limits being 44%–74% (Table 2). There was no statistically significant difference in the overall response rate as judged by the presence or absence of prior radiotherapy or chemotherapy. The median duration of response was 20 months for the complete responders and 11 months for the partial responders. The complete responders had no recurrence, whereas 6 (30%) of the 20 partial responders experienced progression at a median of 7 months (Table 3). Of those 6 partial responders who suffered progression, 2 had regrowth of the primary lesion and 4 had regrowth of a tumor in a metastatic site.

Table 3 Duration of response

Response	Number of patients	Median duration (months)	Number with progressive disease (%)
CR	5	20	0
PR	20	11	6 (30)

Of the 42 patients evaluated, 27 (64%) are alive, and the median duration of survival is 14 months. In all, 5 patients with a complete response, 12 of the 20 (60%) with a partial response, 9 of 15 (60%) with no change, and 1 of the 2 subjects with progressive disease are alive, their median survival times being 20, 20, 14, and 2 months, respectively. As estimated by the method of Kaplan and Meier [7], there was no significant difference in survival between the responders and the nonresponders.

A total of 52 patients were evaluated for toxicity. The hematological side effects are shown in Table 4. The mean nadir white blood cell count and platelet count exceeded 5,600 and 125,000 cells/mm^3, respectively. No significant difference was observed in the mean nadir white blood cell count or platelet count as a function of the treatment cycle or the presence or absence of prior radiotherapy or chemotherapy. The number of days taken for the platelet count to reach the nadir was significantly shorter than that required for the white blood cell count. The main toxic symptoms encountered are shown in Table 5. No patient suffered from mucositis during cycle 1, and grade 1 mucositis was noted in only one patient during cycles 2 and 3, respectively. Nausea and vomiting showed a downward tendency in grade as the number of cycles increased. The frequency and grade of hair loss increased as the number of cycles increased. Grade 1 dermatitis was noted in one patient in

Table 4 Hematological toxicity

	Cycle 1	Cycle 2	Cycle 3
Number of patients	52	40	15
White blood cell count nadir (cells/mm^3):			
Mean	6,303	5,627	5,708
Range	1,030–20,800	1,800–16,700	400–11,500
Mean days to nadir	11.2	13.2	14.4
Platelet nadir ($\times 10^4$/mm^3)			
Mean	13.1	14.8	12.5
Range	0.9–32.1	2.3–33.0	1.7–25.3
Mean days to nadir	8.4	10.8	10.7

Table 5 Toxic symptoms

Toxic symptom	Grade[a]	Number of patients (%)		
		Cycle 1 (52 patients)	Cycle 2 (40 patients)	Cycle 3 (15 patients)
Mucositis	0	52 (100)	39 (97.5)	14 (93.3)
	1	–	1 (2.5)	1 (6.7)
	2	–	–	–
Nausea/vomiting	0	16 (30.8)	16 (40.0)	6 (40.0)
	1	15 (28.8)	7 (17.5)	5 (33.3)
	2	14 (26.9)	11 (27.5)	2 (13.3)
	3	7 (13.5)	6 (15.0)	2 (13.3)
	4	–	–	–
Hair loss	0	26 (50.0)	9 (22.5)	2 (13.3)
	1	13 (25.0)	6 (15.0)	3 (20.0)
	2	11 (21.2)	18 (45.0)	7 (46.7)
	3	2 (3.8)	7 (17.5)	3 (20.0)
	4	–	–	–

[a] WHO criteria

cycles 2 and 3, respectively. There was no sepsis, cardiotoxicity, or drug-related death.

Discussion

In this study, the response rate was 61% for primary sites, 55% for lymph nodes, and 0 for bone. The poor effect on bone lesions, which we had observed with the M-VAC regimen [6], was thus also seen with this regimen. The overall response rate of 60% was slightly lower than the 72.3% response rate obtained with the original M-VEC regimen [12] but almost equal to those achieved with the M-VAC [6, 15] and cisplatin/methotrexate/vinblastine (CMV) regimens [4]. As shown by the lack of effectiveness of the present regimen against bone lesions, it has been reported on the basis of work in the treatment of metastatic disease that a considerable number of tumors (30%–40%) are totally insensitive to chemotherapy [1].

Dose escalation of agents is considered to be one of the treatment modalities to enhance tumor sensitivity to chemotherapeutic agents. Recent trials using hematopoietic growth factors provide hope for decreasing the side effects and possibly improving the outcome by using a higher dose intensity [16]. The results of intensified M-VAC therapy with coadministration of G-CSF [14] or GM-CSF [8, 9] have been reported, but it does not appear that the dose escalations that are clinically achievable within acceptable toxicity ranges are likely to improve the outcome significantly [13]. We did not attempt to increase the doses of the anticancer agents since the main objective of the present study was to give anticancer agents safely and on schedule. All of the patients in the present study received the full doses of the antineoplastic agents on schedule, and this seemed to shorten the hospital stay and to be significant in the neoadjuvant setting.

The frequencies of leukocytosis and mucositis were low in the present study. The myelotoxicity of M-VAC chemotherapy without G-CSF was significant, with the mean nadir white blood cell count being 1,900 cells/mm^3. Also, 20% of the patients experienced sepsis and the frequency of drug-related death was 4% for M-VAC without G-CSF [15]. In each of the three cycles of the present study, the mean nadir white blood cell count exceeded 5,600 cells/mm^3 and there was no sepsis. Prior radiation therapy is considered to be a risk factor for severe myelosuppression as dose reduction of doxorubicin is recommended in patients who have undergone radiotherapy of the whole pelvis or of two or more bone-marrow-containing sites [15]. Whereas we did not decrease the dose of epirubicin in four patients who had undergone prior radiotherapy, there was no significant difference in the mean nadir white blood cell count between patients with and those without prior radiotherapy. There was no cardiac toxicity related to the present regimen. A low incidence of mucositis was a characteristic of the

present regimen. Although we had encountered mucositis in 21%–32% of patients treated with M-VAC without G-CSF [6], the incidence of mucositis was reduced for the same regimen by coadministration of G-CSF [3]. This observation seems to have been confirmed in the present study.

In summary, the present 60% overall response rate was similar to that achieved with the M-VAC or CMV regimen. All patients were capable of receiving full doses of the antineoplastic agents on time according to the protocol design, thanks to the combined use of G-CSF. There was no sepsis or drug-related death, and the frequency of mucositis was very low. These results suggest that M-VEC chemotherapy with G-CSF is an effective and safe chemotherapy regimen.

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