Cancer Chemother Pharmacol (1994) 35 (Suppl): S 5–S 8

SESSION I

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The effect of dose intensity on M-VAC therapy for advanced urothelial cancer

Abstract M-VAC therapy (methotrexate, vinblastine, Adriamycin, and cisplatin) has improved the treatment results of urothelial cancer patients. However, it is sometimes complicated by drug toxicities, including bone marrow suppression. We analyzed the relative dose intensity in each patient undergoing M-VAC chemotherapy in relation to the chemotherapeutic effect and survival. In addition, the role of granulocyte colony-stimulating factor (G-CSF) in the dose intensity of M-VAC therapy was analyzed. Between June 1988 and March 1993, 29 patients with advanced urothelial cancer were treated with M-VAC therapy in our institution. Of 18 patients with evaluable lesions, 2 (11.1%) showed a complete response (CR) and 7 (38.9%) showed a partial response (PR), and the overall response rate was 50.0%. The median follow-up period for these 18 patients was 14.6 months and the median survival was 8.7 months, with 12 of the 18 patients being alive at the time of analysis. The relative dose intensity (RDI) for these 18 patients was 0.81 for methotrexate, 0.80 for vinblastine, 0.92 for Adriamycin, and 0.91 for cisplatin, for a mean RDI of 0.87. There was no correlation between the chemotherapeutic effect and the RDI. When we calculated the RDI for all 29 patients who underwent M-VAC therapy, G-CSF increased the RDI of Adriamycin significantly. The results of this retrospective study indicate that a dose intensity for M-VAC therapy in the range of 0.61–1.00 is unlikely to correlate with the chemotherapeutic effect, although G-CSF contributes to increasing the RDI of Adriamycin.

Key words M-VAC · Urothelial cancer · Dose intensity · G-CSF

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Paper presented at the 5th International Conference on Treatment of Urinary Tract Tumors with Adriamycin/Farmorubicin, 24–25 September 1993, Hakone, Japan

Introduction

Sternberg et al. [16] demonstrated that the combination of methotrexate (MTX), vinblastine (VLB), Adriamycin (ADM), and cisplatin (CDDP) for advanced urothelial cancer was associated with a 72% response rate and a 55% 3-year survival rate [16]. However, M-VAC therapy in such patients is sometimes complicated by drug toxicities, including bone marrow suppression, which require modification of the dose and schedule and detract from the treatment results.

The dose intensity (DI), which is a useful index of the completeness of chemotherapy, is defined as the amount of drug given per unit of time. Analyses of the DI have shown that the amount of drug actually received by a patient has greater prognostic significance than does the amount that is planned in the protocol. This is particularly important in urothelial cancer, a disease of the elderly in whom impaired tolerance of combinations of agents with overlapping toxicities can prevent the administration of adequate drug doses.

The relative dose intensity (RDI) is the fraction of a drug given relative to the standard. The RDI can be calculated for each single agent or averaged for all of the drugs in a combination regimen [4]. The time unit is usually 1 week, and the DI is expressed in milligrams per square meter per week. It is assumed that there is no drug interaction. In the case of a multiagent regimen, the mean RDI is defined as the mean of the single-agent RDIs calculated for all the drugs in the combination with the assumption that they have equivalent activity.

In this study, we examined the effect of the RDI on the response rate and survival rate achieved with M-VAC therapy in advanced urothelial cancer patients. We also evaluated the efficacy of granulocyte colony-stimulating factor (G-CSF) in this regimen in relation to dose intensification.

Patients and methods

Patients

Between June 1988 and March 1993, 29 patients with advanced urothelial cancer were treated with the M-VAC regimen in our institute. The patients included 13 with renal pelvic and ureteral cancers, 12 with bladder cancers, 3 with coexistence of upper-urinary-tract and bladder cancer, and 1 with urethral cancer. The mean age was 63.8 (range, 44–77) years; there were 21 men and 8 women.

All of the patients were diagnosed as having advanced histologically proven urothelial cancer, no prior chemotherapy, no central nervous system metastasis, an absolute granulocyte count of $\geq$1,000/mm^3, a platelet count of $\geq$100,000/mm^3, and normal renal function, defined as a serum creatinine level of $\leq$1.2 mg/dl and creatinine clearance of $\geq$50 ml/min. In all, there were 27 cases of transitional-cell carcinoma (grade 2/3 = 6/21), 1 case of adenocarcinoma, and 1 case of undifferentiated cancer. According to the Japanese staging system for urothelial cancer [5], 6 patients were in stage II, 9 were in stage III, and 14 were in stage IV (Table 1).

Of the 29 patients, 18 had lesions evaluable for response and survival; however, the other 11 were given M-VAC therapy as postsurgical adjuvant therapy. Therefore, these 11 patients were excluded from evaluation for response and survival. All 29 patients treated with M-VAC therapy were evaluated regarding the RDI in relation to G-CSF.

Pretreatment evaluation included an interview regarding the personal and medical history, a physical examination, a performance-status check, a hemogram, an ECG, chest X-rays, abdominal computerized tomograms (CT), an intravenous pyelogram, abdominal ultrasound, determination of serum creatinine levels and creatinine clearance, and pulmonary function tests. During the study, hematologic and roentgenographic evaluations of each patient were conducted at least once a week.

Therapy

The M-VAC regimen was given according to the original design of Sternberg et al. [16]. However, the dose of each drug was reduced depending on the performance status or the side effects encountered in each patient, and symptomatic treatment of side effects was allowed.

The clinical response to the M-VAC therapy was evaluated according to the following criteria [8]: complete response (CR), the complete disappearance of the tumor according to all clinical criteria for at least 4 weeks; partial response (PR), a reduction of $\geq$50% in tumor size for at least 4 weeks; no change (NC), a decrease of $<$50% in tumor size or stable disease; and progressive disease (PD), an increase of $>$25% in tumor size or the appearance of a new lesion.

G-CSF (rhG-CSF, Kirin Brewery Co., Ltd., and Sankyo Co., Ltd.; or rG-CSF, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) [2, 6] was injected subcutaneously at a dose of 75–125 μg/body. The G-CSF was given prophylactically immediately after the starting of the chemotherapy. However, in some patients it was given therapeutically after a decrease in the number of leukocytes. When the peripheral leukocyte count exceeded 20,000/mm^3, the administration of G-CSF was stopped.

Calculation of the RDI for M-VAC

The ideal schedule for M-VAC is 30 mg/m^2 MTX given on days 1, 15, and 22; 3 mg/m^2 VLB given on days 2, 15, and 22; and 30 mg/m^2 ADM and 70 mg/m^2 CDDP given on day 2. A second cycle would be begun on day 29. The ideal DIs were 22.5 for MTX, 2.25 for VLB, 7.5 for ADM, and 17.5 for CDDP. These calculations were taken as the standard for each drug in the M-VAC combination. The received DI was evaluated over time by summing the doses in all cycles for each patient. Owing to the retrospective nature of this analysis, no attempt was made to determine individual prognostic factors that may have affected the outcome.

The administration period can be determined only when the next cycle of M-VAC begins. Therefore, our assumed cycle length was 1 week after the last day of therapy. For patients who ended the therapy without completing a cycle, the cycle length was calculated as 4 weeks.

Statistical methods

Analysis was conducted using the Mann-Whitney *U*-test. Survival curves were plotted according to Kaplan and Meier's method. Curves were compared using the generalized Wilcoxon test.

Results

The mean number of chemotherapeutic courses given to the 18 evaluable patients were 2.4 (range, 1–7). Among the evaluable patients, 2 (11.1%) achieved a complete response (CR), 7 (38.9%) showed a partial response (PR), 6 (33.3%) showed no change, and 3 (16.7%) had progressive disease. The overall response rate was 50.0% (9/18) as shown in Table 2.

With a median follow-up period of 14.6 months (range, 3.9–59.2 months), 4 of the 9 responders have relapsed. All of them were PR cases, and the duration between evaluation of the PR and the relapse ranged from 1.5 to 25.0 months.

Of the 18 patients, 6 have died due to progressive disease. The mean 1- and 3-year survival rates of the 18 evaluable cases were 59.4% and 44.6%, respectively. The mean 1-year survival rates of the responders (CR + PR) and nonresponders (NC + PD) were 60.0% and 55.6%, respectively. The difference between these rates was not statistically significant.

The RDI for the M-VAC therapy was 0.87 as compared with 0.81 for MTX, 0.80 for VLB, 0.92 for ADM, and 0.91 for CDDP. The RDI for the M-VAC therapy in the 18 evaluable cases ranged from 0.61 to 1.00. Within this range, chemotherapeutic effects were unlikely to correlate with the RDI. The RDIs of each drug and the combination in the responders and nonresponders are shown in Table 3. No

Table 1 Clinical stages and site of the primary lesion[a]

Stage	Upper tract (U)	Bladder (B)	U + B	Urethra	Total
II	2 (1)	2 (1)	1 (0)	1 (1)	6 (3)
III	5 (1)	3 (2)	1 (0)	0 (0)	9 (3)
IV	6 (5)	7 (6)	1 (1)	0 (0)	14 (12)
	13 (7)	12 (9)	3 (1)	1 (1)	29 (18)

[a] Numbers of patients evaluable for response and survival are given in parentheses

Table 2 Response rate to M-VAC therapy

Number of patients	Response				Objective response (CR + PR)
	CR	PR	NC	PD	
18 (100%)	2 (11.1%)	7 (38.9%)	6 (33.3%)	3 (16.7%)	9 (50%)

Table 3 RDI (± SD) versus response

	MTX	VLB	ADM	CDDP	Combination
Responders	0.77 ± 0.21	0.79 ± 0.2	0.94 ± 0.20	0.89 ± 0.12	0.85 ± 0.16
Nonresponders	0.81 ± 0.23	0.77 ± 0.28	0.93 ± 0.1	0.91 ± 0.15	0.86 ± 0.15
P value[a]	0.74	0.87	0.95	0.74	0.91

[a] Mann-Whitney *U*-test

Table 4. G-CSF administration versus RDI (± SD)

G-CSF	MTX	VLB	ADM	CDDP	Combination
+ (n = 31)	0.85 ± 0.23	0.86 ± 0.23	0.98 ± 0.08	0.93 ± 0.13	0.92 ± 0.15
− (n = 37)	0.85 ± 0.18	0.84 ± 0.19	0.87 ± 0.18	0.92 ± 0.14	0.87 ± 0.15
P value	0.89	0.80	0.003*	0.58	0.19

* Difference statistically significant (Mann-Whitney *U*-test)

statistically significant difference was found between the responders (0.85) and the nonresponders (0.86).

Concerning the relationship between the RDI and survival, the standard-dose group, in which the RDI was 0.7 or more, showed a 3-year survival rate of 56.4%. On the other hand, in the modified-dose group with an RDI of less than 0.7, all patients died within 10 months. However, the modified-dose group included only four patients, and three of them were in stage IV.

The effect of G-CSF administration on the RDI of each drug and the combination was analyzed for the 68 courses given to the 29 patients (Table 4). G-CSF was given in 31 of the 68 courses. G-CSF administration did not produce a significant increase in the RDI of M-VAC therapy (as the mean of the four drugs' RDIs). However, the RDI of ADM was significantly increased in the courses during which G-CSF was given. The same result was obtained when the relationship between G-CSF administration and the RDI was analyzed in the eight patients who received courses both excluding and including G-CSF.

Discussion

Dose reduction, drug withdrawal, and other changes have been performed in many studies of cancer chemotherapy. As expected, these changes have decreased the actual dose intensity and have been reflected in a poorer clinical response.

Studies on ovarian cancer reported that when differences in case selection and prognostic factors (extent of disease, performance status) were ignored, there was a correlation between the DI of CDDP and the survival. At a dose rate of 12.5 mg/m^2 per week, the median survival duration was only 21–22 months. At a dose rate of 17 mg/m^2 per week, a median survival duration of 28 months was reported, whereas at 25–33 and 40–50 mg/m^2 per week, the median survival duration was greater than 26 and 37 months, respectively [3, 9, 11].

Similar results have been reported for testicular cancer [10, 12]. In a study reported by the Southwest Oncology Group, patients with disseminated testicular cancer were randomized to receive VLB and bleomycin (BLM) in standard doses and either standard-dose CDDP at 120 mg/m^2 (DI, 30 mg/m^2 per week) or low-dose CDDP at 75 mg/m^2 (DI, 19 mg/m^2 per week). A significantly greater proportion of patients achieved a CR on the standard-dose arm (63%) as compared with the low-dose arm (43%, P = 0.03). That study also showed that a reduced DI was associated with an increased chance of relapse after a CR [12].

Another randomized trial that addressed the issue of the DI of CDDP in testicular cancer was a trial conducted at the National Cancer Institute. In this trial, patients were randomized to receive high-dose therapy with high-dose CDDP (40 mg/m^2 per day for 5 days), etoposide (100 mg/m^2 per day for 5 days), VLB (0.2 mg/kg on day 1), and BLM (30 u on days 1, 8, and 15) or standard therapy with CDDP (20 mg/m^2 per day for 5 days), VLB (0.3 mg/kg on day 1), and BLM (30 u on days 1, 8, and 15). As many as 88% of the patients achieved a disease-free status as compared with 67% given the standard-dose therapy (P = 0.14). In all, 68% of the patients randomized to the high-dose therapy arm remained alive and continuously free of disease as compared with 33% of those randomized to the standard-dose therapy (P = 0.02) [10].

Concerning urothelial cancer, Kotake et al. [7] evaluated the effect of the DI on the treatment results of M-VAC therapy in 86 patients. They compared the response between a standard-dose group (RDI, ≥ 0.7) and a modified-dose group (RDI, < 0.7), but the CR rate was not improved significantly [7]. Scher et al. [14] evaluated the DI of CDDP and ADM in M-VAC therapy and reported that the DI was not a significant prognostic factor.

Our findings demonstrated a similar tendency; that is, the RDI did not affect the response to M-VAC therapy in the RDI range between 0.61 and 1.0. No correlation between the RDI and survival was demonstrated in this study. The reason is that only four patients were included in the modified-dose group, and three of them were in stage IV; therefore, the outcome was affected by a poor performance status. It was reported that a steep dose-response relationship with CDDP appeared to exist in urothelial tumors, and the delivered dose was at the lower end of the dose rate versus the dose-response line generated for CDDP in urothelial, ovarian, and testicular tumors [1, 9].

These considerations have implications for future trial design, particularly with the recent availability of G-CSF. G-CSF administration did not cause a significant increase in the RDI of M-VAC expressed as the average for each drug in our study, but the RDI of ADM was significantly increased by G-CSF. This result might have been due to the low rate of severe bone marrow suppression in M-VAC therapy and to the therapeutic administration of G-CSF in some patients.

However, a recently completed phase I trial of M-VAC plus G-CSF at the Memorial Sloan-Kettering Cancer Center did not reveal sufficient escalation in the dose intensity to bring about an increase in the proportion of complete responders, which is a prerequisite for improving the survival in advanced urothelial cancer [15]. Therefore, alternate scheduling strategies might be required to increase the CR rate [13].

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