A Phase II Trial of Methotrexate, Vinblastine, Doxorubicin, and Cisplatin in the Treatment of Metastatic Carcinoma of the Uterine Cervix

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BACKGROUND. Patients with metastatic carcinoma of the uterine cervix have limited survival. Thus, new chemotherapeutic agents and combinations are needed to improve patient outcome.

METHODS. Twenty-seven patients with Stage IV primary or recurrent carcinoma of the uterine cervix were assigned to chemotherapy treatment at 4-week intervals with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). The treatment was comprised of methotrexate, 30 mg/m^2 administered intravenously (i.v.) on Days 1, 15, and 22; vinblastine, 3 mg/m^2 i.v. on Days 2, 15, and 22; doxorubicin, 30 mg/m^2 i.v. on Day 2; and cisplatin, 70 mg/m^2 i.v. on Day 2. Granulocyte-colony stimulating factor (G-CSF) was given subcutaneously on Days 6–10 at a dose of 5 μg/kg.

RESULTS. After a median of 4 cycles (a maximum of 6 in responders), the authors observed objective responses in 14 patients (52%), including 3 complete responses (11%) and 11 partial responses (41%). Median overall survival was 11 months (range, 4–15+ months), and median progression free survival of the responders was 8 months (range, 6–15+ months). Toxicity was acceptable and included neutropenia, alopecia, vomiting, and stomatitis.

CONCLUSIONS. MVAC is an active regimen in the treatment of patients with advanced or recurrent carcinoma of the uterine cervix. It produced responses in one-half of the patients in this study, and it can be administered on an outpatient basis. The addition of G-CSF appears to reduce hematologic toxicity. ***Cancer* 1997;79:2391–5.** © *1997 American Cancer Society.*

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Carcinoma of the uterine cervix is usually radioresponsive and highly curable in the early stages. Either surgery or radiotherapy alone for Stage IB and IIA tumors has resulted in 5-year survival rates of 75–90%. Nevertheless, for patients presenting with Stage IV disease or for those with recurrent disease after radiotherapy, no consistent improvement in survival has been observed over the last 30 years.[1] For those patients who have advanced or recurrent disease that is not curable by surgery or irradiation, treatment with cytotoxic agents alone or in combination can be considered. Response rates of the most active single agents vary between 20–35%, with a median response duration of 3–6 months and a 5- to 9-month survival rate. Also, several combination chemotherapy regimens have been explored with response rates of approximately 40%.[2,3]

Long et al.[4] administered a four-drug combination comprised of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and observed objective responses in 66% of patients with a median overall

survival of 11.5 months and a median time to progression of 6.9 months. The main toxicity observed was severe neutropenia (World Health Organization [WHO] Grade 3 and 4), which was observed in >50% of the patients. In an attempt to reproduce these promising results and to reduce hematologic toxicity, the authors treated 27 patients with primary Stage IV or recurrent carcinoma of the uterine cervix using the MVAC regimen with the addition of granulocyte-colony stimulating factor (G-CSF).

PATIENTS AND METHODS

Eligibility Criteria

Patients were eligible for the study it they had primary Stage IV (International Federation of Gynecology and Obstetrics [FIGO]) or recurrent cervical carcinoma; no previous treatment with cytotoxic chemotherapy; tumor measurable by physical examination or imaging techniques; a leukocyte count $> 3.5 \times 10^9$/L; a platelet count $> 150 \times 10^9$/L; a serum creatinine level < 0.15 mmol/L; no brain metastases; and no active infections. Patients with a serious concurrent medical illness were excluded. The study was approved by the Hospital Ethics Committee and informed consent obtained from all patients.

Chemotherapy Regimen and Dose Modification

Each cycle was comprised of 30 mg/m^2 of methotrexate by intravenous infusion on Days 1, 15, and 22; 3 mg/m^2 of vinblastine as an intravenous bolus on Days 2, 15, and 22; 30 mg/m^2 of doxorubicin as an intravenous bolus on Day 2; and 70 mg/m^2 of cisplatin in a 2-hour intravenous infusion on Day 2. Appropriate hydration and antiemetics were used.

The cycles were repeated every 28 days on an outpatient basis. G-CSF was given daily on Days 6–10 at a dose of 5 μg/kg of body weight by subcutaneous injection. Dose modification on Days 15 and 22 included a 50% dose reduction of vinblastine and methotrexate for a leukocyte count between 2×10^9–3×10^9/L or a platelet count between 75×10^9–100×10^9/L and suspension of treatment for a leukocyte count $< 2 \times 10^9$/L or a platelet count $< 75 \times 10^9$/L. At scheduled retreatment on Day 29, a new chemotherapy cycle was administered if the leukocyte count was $>3.5 \times 10^9$/L and the platelet count was $>100 \times 10^9$/L. If these values were not reached at scheduled retreatment, therapy was delayed by weekly intervals. Methotrexate and cisplatin were reduced 50% for a creatinine level > 2 times baseline and withheld for a creatinine level > 3 times baseline. If a patient developed $\geq$ Grade 2 mucositis, Day 15 or Day 22 administration of chemotherapy was deleted. If treatment was delayed by 3 weeks for any reason the patient was taken off study.

Definition of Response and Patient Follow-Up

WHO criteria for response and toxicity were used.[5] A complete response (CR) required disappearance of all clinically detectable disease for at least 4 weeks. A partial response (PR) required a >50% reduction in the sum of the products of the 2 largest perpendicular dimensions of bidimensionally measurable lesions. MVAC was administered at 4-week intervals, and response to treatment was assessed every other cycle. Patients demonstrating progressive disease were removed from the study at the time of progression. Patients with stable disease received a total of four courses of chemotherapy and those with objective response six courses. After completion of treatment, all patients were examined every 2 months and restaging procedures were repeated every 4 months. Patients with recurrent disease causing symptoms were treated with interferon-α and 13 *cis*-retinoic acid.

Dose Delivery Analysis

Dose intensity is a measurement of the dose received as a function of time. The authors used the method described by Hryniuk and Goodyear.[6] A value for received dose intensity was calculated by dividing the cumulative dose treatment given to each patient. One dose interval was added to the treatment period of each patient to adjust for methodologic problems in dealing with those patients who received < six cycles.[7] The received dose intensity was calculated from the beginning of chemotherapy.

Statistical Analysis

Overall survival and progression free survival of responding patients were measured from the beginning of treatment using the method of Kaplan and Meier.[8] Differences in survival were compared with the log rank nonparametric statistical test using a microcomputer-assisted program.[9]

RESULTS

From June 1995 through January 1996, 27 patients with cervical carcinoma were accrued onto this study. All were considered eligible for evaluation of response and toxicity. The main characteristics of the patients are summarized in Table 1. The majority of patients had previously received pelvic irradiation, had disease confined to the pelvis, and had squamous cell histology.

A total of 129 MVAC cycles were administered to 27 patients with recurrent or advanced cervical carcinoma. Fourteen patients achieved objective clinical

TABLE 1
Patient Characteristics

Characteristic	No. of patients (%)
Age (yrs)	
Median	49
Range	37–73
ECOG performance status	
0	12 (44)
1	10 (37)
≥2	5 (19)
Initial stage (FIGO)	
I	7 (26)
II	5 (19)
III	11 (41)
IV	4 (15)
Histologic type	
Squamous cell carcinoma	25 (93)
Adenocarcinoma	2 (7)
Previous treatment	
Irradiation	13 (48)
Radical hysterectomy	2 (7)
Combined surgery and irradiation	10 (37)
No treatment	2 (7)
Sites of metastatic tumor involvement	
Pelvic only	13 (48)
Extrapelvic only	7 (26)
Extrapelvic + pelvic	7 (26)
Number of sites of tumor involvement	
1	17 (63)
2	8 (30)
≥3	2 (7)

ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics.

TABLE 2
Response to MVAC

Response	No. of patients	%	95% confidence interval
Objective response	14	52	32–71%
Partial response	11	41	22–61%
Complete response	3	11	2–29%

MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin.

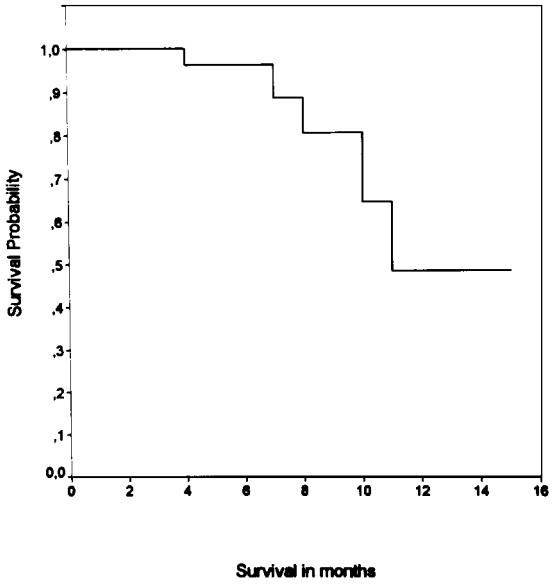

FIGURE 1. Survival of patients treated with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy.

TABLE 3
Toxicity of the MVAC Regimen

	% of Patients affected (WHO grade)				
Toxicity	0	1	2	3	4
Leukocyte count	33	4	18	15	30
Hemoglobin	22	33	30	7	8
Platelets	74	0	7	12	7
Alopecia	0	0	11	89	0
Nausea and emesis	4	22	56	18	0
Renal	85	11	0	4	0
Diarrhea	70	22	4	4	0
Stomatitis	48	15	15	22	0
Infection	78	15	7	0	0
Neurotoxicity	93	7	0	0	0

MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin; WHO: World Health Organization.

response (52%), including 11 PRs (41%) and 3 CRs (11%). Response rates and 95% confidence intervals are shown in Table 2.

The median overall survival for all eligible patients was 11 months (range, 4–15+ months). The survival curve is shown in Figure 1. At last follow-up, the median overall survival for patients who achieved an objective response had not been reached. The median overall survival duration of the patients with only extrapelvic disease was 10 months (range, 8–15+ month), whereas the median overall survival of the patients with pelvic with or without extrapelvic disease was 11 months (range, 4–15+ months) ($P = 0.5660$). The median progression free survival for patients who achieved an objective response was 8 months (range, 6–15+ months).

Toxicities were comprised primarily of neutropenia, alopecia, nausea and emesis, and stomatitis (Table 3). Only 4% of courses were complicated by an increase of serum creatinine necessitating dose reductions of cisplatin and methotrexate. The relative dose

TABLE 4
Relative Dose Intensity of MVAC

	Relative dose intensity (% of patients)			
Drug delivery	**>90%**	**81–90%**	**71–80%**	**<70%**
Methotrexate	15	22	19	44
Vinblastine	15	22	19	44
Doxorubicin	30	41	26	3
Cisplatin	33	15	33	19

MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin.

intensities are shown in Table 4. For methotrexate and vinblastine, only 37% of patients had a dose intensity > 80% of the intended dose. The reason for this dose reduction was primarily stomatitis. For doxorubicin, this figure was 71% and it was 48% for cisplatin. The percentage of optimal dose delivered was 75% for methotrexate, 75% for vinblastine, 85% for doxorubicin, and 82% for cisplatin.

DISCUSSION

Patients with Stage IV cervical carcinoma as well as those with persistent or recurrent disease after radiotherapy have a low chance of cure with standard treatment modalities. Thus, these patients are candidates for chemotherapy. Several agents have been used and cisplatin appears to be the most active.[10] Ifosfamide, vincristine, methotrexate, and doxorubicin also have a modest single agent activity.[10–12] Combination chemotherapy studies have demonstrated only slightly better results.[13] More recently, combinations of bleomycin and ifosfamide with cisplatin (BIP) or carboplatin (BIC) have been associated with objective responses in approximately 60% of patients, with a median overall survival of 10–12 months.[14,15] However, these studies indicated severe hematologic toxicity with mortality related to myelosuppression and sepsis in 2.5–4% of patients.

The purpose of the current study was to treat patients with advanced or recurrent cervical carcinoma with an effective regimen on an outpatient basis. Therefore, the MVAC regimen was chosen, which has been reported to be active against squamous cell carcinoma of the uterine cervix.[4] In this Phase II study, the median overall survival was 11.5 months and the objective response rate was 66%. Toxicity was moderate with no treatment-related deaths; however, Grade 3 and 4 neutropenia was observed in >50% of the patients.[4] The authors used the MVAC regimen at the same doses with G-CSF support to reduce the incidence and degree of myelosuppression in these patients who had usually received whole pelvis irradiation. Using a bone marrow stimulant, they decreased the incidence of neutropenia but in 12 of 27 patients (44%) the relative dose intensity of vinblastine and methotrexate was <70%. These data indicate that further escalation of MVAC doses is unlikely, because stomatitis may become the dose-limiting complication.

The combination of methotrexate, vinblastine, doxorubicin, and cisplatin, as administered in the current study, produced objective responses in 52% of patients, a figure similar to that reported by Long et al.[4] The median overall survival of the patients in the current study was 11 months, which is similar to those obtained with BIP and BIC as well with MVAC in the study by Long et al.[4] When the patients in the current study were separated into two groups of those with only extrapelvic disease (tumor sites outside previously irradiated areas) and those with pelvic (tumor sites inside previously irradiated areas) with or without extrapelvic disease, no differences in response or overall survival were observed ($P = 0.5660$, log rank test). This observation is in contrast with the findings of Murad et al.,[15] who reported significantly higher response rates and overall survival in nonirradiated patients.

The toxicity of MVAC with G-CSF support was acceptable. The main toxic effects were alopecia, nausea and emesis, and myelosuppression. Twelve patients (44%) experienced severe neutropenia (WHO Grade 3 and 4) and this rate appeared to be lower than the incidence of Grade 3 and 4 leukopenia observed in the study of Long et al.[4] Furthermore, only three episodes of neutropenic fever were encountered that were successfully treated with intravenous antibiotics.

The results of the current study indicate that MVAC is an active regimen against metastatic cervical carcinoma that can be given on an outpatient basis. It produces responses in 52% of patients, including some CRs. The addition of G-CSF reduces MVAC myelotoxicity and permits the administration of six cycles to responders. However, the activity of the MVAC regimen needs to be confirmed by Phase III trials in patients with metastatic disease.

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