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A Phase II Study of Carboplatin and Cisplatin in Advanced or Recurrent Squamous Carcinoma of the Uterine Cervix

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Between March 1990 and July 1992, 42 women with squamous carcinoma of the uterine cervix were prospectively treated with carboplatin (260 mg/m^2) on Day 1 and cisplatin (50 mg/m^2) on Day 2 every 28 days. Patients had either stage IVb (FIGO) cancer (5 patients) or recurrent cancer (37 patients) and a Zubrod score ≤2. Forty-one patients had received either radiation or surgery as primary therapy; 179 cycles of chemotherapy were delivered. The mean number of cycles administered to each patient was 4 (range, 2–8 cycles). Dose escalation was possible in 32 cycles (23.4%) and dose reduction was required in 10 cycles (7.3%). The dose-limiting toxic effect was myelosuppression, with grade 3–4 thrombocytopenia in 39 cycles (22%) and neutropenia in 19 cycles (11%). Neurotoxic effects were observed in 3 patients. Forty-two patients were evaluable for response: 1 had a complete response and 11 had a partial response (response rate 28.6%, 95% confidence interval, 14.9–42.3%). For all patients and for responders, median progression-free interval was 4.4 and 9.5 months, respectively, and median length of survival was 8.9 and 9.5 months, respectively. This regimen was well tolerated and had significant activity in the treatment of cervical cancer. Comparison to other platinum-based regimens in a Phase III trial should be considered. © 1994 Academic Press, Inc.

INTRODUCTION

Cervical carcinoma is best treated with either radiation therapy or radical surgery. For those patients whose disease fails to respond to these modalities, palliative therapy is employed. Results with chemotherapy have been disappointing and prolonged survival is unusual. Cisplatin is considered the most active drug in this disease site and has been used as a single agent and in a variety of combination regimens [1–5]. Carboplatin is also an active agent in the treatment of squamous carcinoma of the cervix [6–10].

Although the relationship between dose intensity and response to platinum-based regimens remains somewhat controversial, some believe that the ability to administer a greater amount of "platinum" may translate into greater treatment efficacy. Since carboplatin and cisplatin have different dose-limiting toxic effects, the simultaneous use of this combination may improve the efficacy of either drug alone. Regimens using these two agents have been evaluated in other tumor sites, but it is difficult to compare these results to regimens with only one of these compounds [11–13]. There are data to indicate that the use of both agents increases platinum–DNA adduct formation [14].

This study was undertaken to determine the efficacy and safety of carboplatin and cisplatin administered to women for the treatment of squamous carcinoma of the cervix.

PATIENTS AND METHODS

Between March 1990 and July 1992, we conducted a prospective clinical trial in which 42 patients with advanced primary or recurrent squamous cell carcinoma of the cervix were treated at The University of Texas M. D. Anderson Cancer Center with the combination of carboplatin and cisplatin. Prior to each patient's entry into the study, histologic or cytologic confirmation of squamous cell carcinoma was performed. Patients with adenocarcinoma and other histologies were excluded from this study. All patients had recurrent disease that had failed primary therapy or stage IVb (FIGO) cancer. Pa-

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TABLE 1
Dose Modifications

	Dose levels				
Drug	−1	0	+1	+2	+3
Cisplatin (mg/m²)	50	50	50	75	75
Carboplatin (mg/m²)	200	260	300	300	360
	Dose adjustment criteria				
Granulocyte nadir per mm³	or	Platelet nadir per mm³		Dose modification	
>1000	or	>100,000		⇑ 1 level	
500–1000	or	50–100,000		No change	
<500	or	<50,000		⇓ 1 level	
Infection or bleeding				⇓ 1 level	

tients had not received any prior cytotoxic therapy except for radiosensitizers administered during radiotherapy. Patients must have had a Zubrod performance rating of 2 or less and an expected survival of at least 2 months. Other requirements for study entry included an absolute granulocyte count >1500 mm³, platelet count >100,000 mm³, serum creatinine <1.5 mg/dl, and creatinine clearance >50 cc/min (if tested). No patient had received external beam pelvic or extended-field radiotherapy within 4 weeks prior to chemotherapy. Patients who were potentially curable by radiotherapy or radical surgery were not eligible.

Patients underwent a pretreatment evaluation that included history and physical examination, laboratory profile, and radiologic tests deemed appropriate based on the clinical presentation. Stage was assigned according to the clinical criteria established by the International Federation of Gynecology and Obstetrics (FIGO). Lesions were measured in two dimensions by physical examination or by radiologic criteria. The physical examination was repeated at the time of each treatment cycle.

TABLE 2
Patient Characteristics

Stage (FIGO)	*N* = 42
I b, II a	20 (48%)
II b	6 (14%)
III a	2 (5%)
III b	4 (10%)
IV b	5 (12%)
Unstaged	5 (12%)
Grade	
0	3 (7%)
1	2 (5%)
2	15 (36%)
3	22 (52%)
Zubrod score	
0	14 (33%)
1	25 (60%)
2	3 (7%)

TABLE 3
Therapy Administered Prior to Study Entry

Prior therapy	1st line	2nd line	3rd line
None	1	26	40
Primary radiotherapy	32	4	0
Radical hysterectomy	3	2	0
Palliative radiotherapy	1	4	0
Chemoradiation	3	0	0
Paraortic radiotherapy	1	3	1
Pelvic exenteration	0	2	0
Other surgery	2	1	1

Chemotherapy was administered over a 2-day period and repeated every 28 days. On Day 1, patients were treated with carboplatin (260 mg/m²) given intravenously (iv) over 1 hr. On Day 2, cisplatin (50 mg/m²) was given iv as a 4-hr infusion with vigorous hydration. Dose modifications are outlined in Table 1.

Outcome measures of interest included tumor response, progression-free survival, length of survival, and toxic effects. Complete clinical response to chemotherapy was defined as the disappearance of all clinical evidence of tumor for a minimum of 4 weeks. A partial response was defined as a 50% or greater decrease in the sum of the product of the diameters of the measured lesions. In addition, no simultaneous increase in the size of any existing lesion or appearance of new metastatic lesions could occur. Stable disease was defined as no change in the tumor size (less than a 50% decrease or a 25% increase in tumor volume). Progressive disease was defined as an increase of 25% or more in the size of any existing lesion or as the appearance of any new metastatic lesions. Patients were removed from the study if their disease progressed, if the toxic effects of treatment were unacceptable, or if they requested it.

Survival was calculated using the life-table analysis of Berkson–Gage [15].

RESULTS

The median age of the patients at study entry was 46 years (range, 29–82 years). The initial stage and grade of the tumors are presented in Table 2. In one patient, chemotherapy was administered as primary therapy. Recurrent or persistent disease following primary treatment was the indication for therapy in 41 patients. All patients were evaluable for response. The mean Zubrod score was 0.7. Forty patients had been previously treated with ra-

TABLE 4
Response to Therapy

Response	*N*	%
Complete response	1	2.4
Partial response	11	26.2
No response (stable)	9	21.4
No response (progression)	21	50.0
Inevaluable	0	

diation therapy. The details of prior therapy are described in Table 3.

Disease was confined to the pelvis in 16 patients (38%), 9 patients had para-aortic metastases (21%), 12 patients (29%) had other distant disease, and 5 (12%) had pelvic and distant lesions.

Patients received a total of 179 cycles of therapy. The mean number of cycles administered to each patient was 4 (range, 2–8 cycles). Dose was escalated in 23.4% of cycles, and dose decrease was necessary in 7.3%. As expected, the dose-limiting toxic effect was thrombocytopenia, with grade 3 or 4 toxic effects seen in 22% of cycles. Grade 3 or 4 neutropenia was observed in 11% of cycles, with maximal platelet toxic effects typically observed 3 weeks into each cycle. Sepsis associated with neutropenia was observed 11 times. Grade 2 peripheral neuropathy developed in 3 patients, and grade 2 ototoxic effects were seen in 1 patient. Grade 3 or 4 nausea and vomiting was seen in 17.3% (31/179) of treatment cycles. There were no treatment-related deaths.

Response data are shown in Table 4. One patient had a complete response, and 11 patients had a partial response. The overall response rate was 28.6% (95% confidence interval, 14.9–42.3%). The median progression-free interval for all patients was 4.4 months and was 9.5 months for responders. Median survival for all patients was 8.9 months and was 16.9 months for responders. The response rate for the 16 patients who were being treated for pelvic disease was 31%, while 27% of the 26 patients who had some disease outside of the pelvis responded to therapy. At the time of last analysis, 6 patients are alive with disease and 36 are dead of disease.

DISCUSSION

Recurrent cervical cancer not responsive to either surgery or radiation therapy is usually considered incurable. Efforts to provide palliation with chemotherapy have, in general, produced poor results. Even when regimens produce 30–40% response rates, median survival is an abysmal 7 months [16]. The highest response rates are achieved with platinum-based multidrug therapy. When analysis is confined to squamous cell histology in patients who have received previous irradiation, long-term response to either cisplatin-based regimens [4,5,17–22] or carboplatin-based regimens [9,10] is uncommon. A recent M. D. Anderson report analyzed mitomycin-C, bleomycin, and cisplatin combination therapy for patients with advanced or recurrent squamous carcinoma of the cervix. Only 7 of 44 previously treated patients (16%) responded. The progression-free interval for responders was 14.5 months, a significantly greater time period when compared with only 2.6-month progression-free interval for nonresponders. The identification of a regimen that provides a more durable response and a higher response rate is a high priority.

In an analysis of patients treated with platinum-based regimens for ovarian carcinoma, Levin and Hryniuk found a correlation between dose intensity and therapeutic outcome [23]. In the case of squamous carcinoma of the cervix, a randomized trial conducted by the Gynecologic Oncology Group suggested that greater platinum dose intensity translated into a higher response rate [24]. This study randomized 497 evaluable patients into 3 groups given cisplatin at doses of 100 mg/m^2 (single bolus), 50 mg/m^2 (single bolus), or 20 mg/m^2 (given daily for 5 days). Patients who received the bolus dose of 100 mg/m^2 had a response rate of 31.4% compared with 20.7% for patients treated at 50 mg/m^2 (P) = 0.015). However, there was no difference in progression-free interval or survival between the two groups.

Although the issue of platinum dose intensity remains controversial, several strategies have been employed to increase platinum dose intensity, including trials of new platinum analogues, uroprotective methods, and bone marrow transplant. The strategy of combining cisplatin and carboplatin into one regimen has also been evaluated.

In the case of cisplatin, the administered dose is limited by neurotoxic, ototoxic, and nephrotoxic effects. Therapy with carboplatin is limited by myelosuppression, predominantly thrombocytopenia. Since the toxic effects of these two drugs are mostly nonoverlapping, the combination is an attractive method of increasing total platinum exposure.

In a study reported by Gill and co-workers [14], platinum–DNA adduct formation was measured in buccal cells and lymphocytes from women with ovarian cancer who were treated with carboplatin (Day 1) and cisplatin (Day 3). In nearly all cases, adduct levels increased after exposure to carboplatin and then increased further after the cisplatin dose was administered. The levels of adducts were also related to the total dose of platinum drug received.

In clinical trials the combination of carboplatin and cisplatin has been assessed in head and neck cancer [25], lung cancer [12,26], and most extensively in ovarian cancer [13,14,27,28]. In the absence of data from a ran-

domized study, it is difficult to evaluate these trials other than to note that the regimen is reasonably well tolerated, shows significant activity, but is not clearly superior to either agent alone. In fact, Calvert provides a cogent argument that we should direct our efforts toward increasing dose intensity with both carboplatin and cisplatin, but not as part of the same regimen since using both together may actually limit dose intensity [29].

Nevertheless, the use of carboplatin and cisplatin in combination for the treatment of cervical cancer does address some unique problems found in this patient population and adds flexibility to the treatment approach. Since women with poor-prognosis cervical cancer are usually treated with radiation therapy, often to an extended field encompassing the para-aortic area, achieving dose intensity with a drug limited by myelosuppression is challenging. Other strategies to increase dose beyond the tolerance of the marrow, such as peripheral stem cell support, are usually not considered for this patient population because of their short survival potential. Consequently, the tolerable dose of carboplatin is often more limited in this group of patients when compared with treatments for other solid tumors. Similarly, some degree of renal dysfunction due to obstructive uropathy is common in women with recurrent cervical cancer, which limits the potential dose intensity of cisplatin. Using both drugs together, each agent taken to the maximum tolerated dose for that particular patient, one can achieve greater platinum intensity than that achieved using either one alone because of the limitations mentioned above.

In this study, the combination of cisplatin and carboplatin was well tolerated by most patients. The response rate of 28.6% compares favorably with the response rate of 16% seen in the study of mitomycin-C, bleomycin, and cisplatin in a similar patient group from our institution. We conclude that the combination of cisplatin and carboplatin should undergo further evaluation in a Phase III trial of comparative efficacy and toxic effects along with assessment of quality of life.

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