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Malignant Uterine Smooth Muscle Tumors: Role of Etoposide, Cisplatin, and Doxorubicin (EPA) Chemotherapy

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Background: Nearly 80% of patients with malignant uterine smooth muscle tumor will suffer local relapse and/or distant metastases after initial surgical resection. There is no convincing evidence that the addition of pelvic radiation improves the outcome. However, adjuvant chemotherapy might be an appropriate therapeutic modality.
Methods: Between 1986 and 1991, 13 consecutive patients with malignant uterine smooth muscle tumors were treated at Yale-New Haven Hospital with a combination chemotherapy containing etoposide 100 mg/M^2 on days 1 and 2, cisplatin 50 mg/M^2 on day 1, and doxorubicin 50 mg/M^2 on day 1, repeated every 28 days. Six patients had Stage I disease, one patient had Stage III disease, and six patients had Stage IV disease. The number of cycles ranged from 2 to 9.
Results: The median follow-up was 30 months (range 4–81). The mean overall survival for the group was 43.1 ± 6.7 months, with the progression-free interval of 25.5 ± 8.0 months. Of the seven patients with evaluable disease, one patient had complete response and one had partial response (total response rate of 28.6%). Of the six patients treated adjuvantly, three recurred at 9, 33, and 59 months (recurrence rate of 50%).
Conclusions: We conclude that this combination has only modest activity against malignant uterine smooth muscle tumors at the schedule and doses tested.

INTRODUCTION

The natural history of the malignant uterine smooth muscle tumors (USMT) exhibits propensity for local recurrence and distant metastases. Many chemotherapeutic protocols have been tried in an attempt to decrease the relapse rate and prolong survival after the initial surgical resection. The Gynecologic Oncology Group (GOG) recently reported on an etoposide-containing regimen showing moderate activity in uterine Mixed Mullerian Tumors (MMT) [1], and printed results of the same protocol in USMT are in preparation. GOG protocol #131 is currently evaluating the efficacy of prolonged oral etoposide in recurrent and advanced USMT. Cisplatin has wide-ranging activity against gynecologic malignancies. Although its activity as a single agent has not been encouraging [2,3], its use in combination protocols against malignant USMT has not been reported. Doxorubicin, in contrast, has been well documented to have efficacy against many soft tissue sarcomas, including malignant USMT [4–7]. We report our experience with 13 consecutive patients with advanced (Stage III and IV) and/or high-grade USMT treated with a combination chemotherapy of etoposide, cisplatin, and doxorubicin (EPA). This combination showed some efficacy in uterine [8] and adnexal

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sarcomas [9] and in metastatic endometrial carcinoma [10].

MATERIALS AND METHODS

Thirteen consecutive patients with the diagnosis of malignant USMT were treated at Yale-New Haven Hospital (YNHH) between 1986–1991. The chemotherapy protocol (HIC 4235) was approved by the Human Investigation Committee of the Yale University School of Medicine.

For the purpose of inclusion into the protocol, the diagnosis of malignant USMT was defined as smooth-muscle tumor with 10 or more mitoses per 10 high-power fields (HPF) or presence of anaplasia, pleomorphism, giant cells, epithelial features, infiltrative pattern of growth with deep myometrial invasion, lymphovascular space invasion, or tumor necrosis. Tissue for diagnosis was obtained from hysterectomy specimens. All specimens were reviewed by one senior gynecologic pathologist (MLC) who had no knowledge of the clinical outcome.

The four patients undergoing surgery at YNHH had total abdominal hysterectomy and bilateral salpingo-oophorectomy, partial omentectomy, pelvic and/or para-aortic lymph node sampling. The nine patients who had their operations elsewhere prior to referral had more limited surgical exploration. The International Federation of Gynecology and Obstetrics (FIGO) staging criteria for endometrial cancer were modified for use in this study: Stage I, sarcoma confined to the uterine corpus, Stage II, sarcoma extending to the cervix, Stage III, sarcoma confined to the pelvis and/or retroperitoneal lymph nodes, and Stage IV, extrapelvic metastases.

Etoposide was given intravenously (IV) on a schedule of 100 mg/M^2 in 500 ml of normal saline over 1 hour on days 1 and 2, 24 hours apart. Cisplatin was given IV on a schedule of 50 mg/M^2 on day 1. Doxorubicin was given by intravenous (IV) push on a schedule of 50 mg/M^2 on day 1. The cycle was repeated every 28 days. The antiemetic protocol included intravenous dexamethasone, metoclopromide, and prochloperazine during the initial 4 years of the study. In the last year of the study, ondansetron was added to the regimen.

If the white blood cell count at the end of 4 weeks did not recover to 3,000/mm^3, the next cycle was delayed by 1 week. At that time, a 20% dose reduction was effected in doxorubicin and etoposide. If the serum creatinine concentration rose to 1.5 mg%, there was a 20% dose reduction of cisplatin and etoposide. Multigated angiography (MUGA) scans were performed at the beginning of the course and at the end of six cycles.

A total of six cycles was administered adjuvantly to each of the six patients with no gross evidence of disease at the end of surgery. The seven patients with measurable disease received the protocol until progression, maximal response, or toxicity precluding further treatment. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria [11]. The product limit estimates of survival time was plotted using the Kaplan-Meier method.

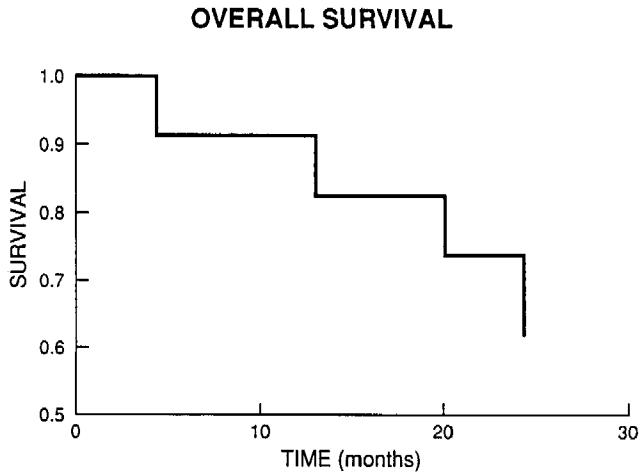

Fig. 1. Overall survival for 13 patients treated with etoposide, cisplatin, and doxorubicin, 1986–1991.

RESULTS

Clinical and pathologic characteristics are summarized in Table I. The median follow up was 30 months (range 4–81). The overall mean survival for the group was 43.1 ± 6.7 months (Fig. 1), and the progression-free interval was 25.5 ± 8.0 months.

Six patients with FIGO Stage I disease had high-grade lesions as defined by either the number of mitoses per 10 high-power fields, or degree of cytologic atypia, lymphovascular space involvement, and necrosis. Six patients with Stage IV disease had lung metastases. One of the patients exhibited an increasing rate of mitoses with two subsequent recurrences. The initial specimen had 3–4 mitoses per 10 HPF, whereas the last recurrence had 15 mitoses per 10 HPF.

The six patients who had no gross residual tumor at the end of surgery received chemotherapy adjuvantly. They have been followed for a median of 63 months (range 24–81). Three patients had lung recurrences at 9, 33, and 59 months, for a recurrence rate of 50%. One of them also had intra-abdominal recurrence.

The seven patients with measurable disease prior to start of chemotherapy were evaluated for response. The median follow-up was 30 months (range 4–60). One complete and one partial response were observed for the response rate of 28.6%. The complete responder had a biopsy-proven solitary lung metastasis, which resolved following hysterectomy and six cycles of the chemotherapy. She was without the evidence of disease at 41 months of follow-up. The partial responder had a fixed pelvic

TABLE I. Characteristics of Patients with Malignant Uterine Smooth Muscle Tumors treated with Exoposide, Cisplatin, and Doxorubicin*

Age		
	median (range)	49 (39–77)
Race		
	white	11
	black	1
	Hispanic	1
Surgery		
	TAH/BSO	12/13 (92%)
	TAH/BSO/LNS	6/13 (46%)
Stage		
	I	6
	III	1
	IV	6
Pathology		
	MF/10 HPF median (range)	10 (6–36)
	LVS	4/13 (31%)
	necrosis	9/13 (69%)
	atypia	10/13 (77%)
Performance status score		
	≤1	10
	2	2
	3	1
Cycles		
	median (range)	6 (2–10)
Toxicity		
	alopecia	13/13 (100%)
	WBC	6/13 (46%)
	nausea and vomiting	5/13 (38%)
	cardiac	2/13 (16%)
	renal	1/13 (8%)

*TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; LNS, lymph node sampling; MF, mitotic figures; HPF, high power fields; LVS, lymph-vascular space invasion; WBC, neutropenia.

mass and lung metastases. At both of these sites, there was >50% decrease in tumor size with neoadjuvant chemotherapy. The patient eventually progressed and died of disease at 36 months of follow-up. Other patients did not respond and died of their disease at 4, 13, 20, 30, and 63 months of follow-up.

Most patients had performance status scores less or equal to 1. There were no deaths attributable to toxicity. All patients had alopecia universalis. Other grade 2 and 3 toxicities are listed in Table I.

DISCUSSION

Malignant smooth muscle tumors are the second most frequent type of uterine sarcomas [12]. The classic initial approach to the patients with malignant USMT has been total abdominal hysterectomy and bilateral salpingo-oophorectomy; however, the effectiveness of surgery alone has been disappointing. Nearly 80% of these tumors recur within 2 years. This poor outcome is due largely to the high likelihood of distant metastases, primarily in the lungs, even in surgical Stage I disease [13]. Our data confirm this finding as six of 13 patients had disease in the lungs at initiation of therapy.

There is as yet no convincing evidence that the addition of pelvic radiation therapy improves survival in women with malignant USMT. However, adjuvant chemotherapy might be an appropriate therapeutic modality, because (1) microscopic metastatic disease may be present at the time of surgery, and (2) widespread recurrent disease with rapid demise frequently ensues.

In the present study the combination of etoposide, cisplatin, and doxorubicin was used in a small group of patients with poor prognostic features. In the advanced stage group, the total response rate was 28.6%. In the adjuvant group, the recurrence rate of 50% was observed with long median follow-up of 66.5 months. Toxicity was well tolerated.

In summary, this combination has modest activity against malignant USMT; however, the response rate was not different from that with doxorubicin alone [14]. Since the optimal chemotherapy has not been identified, further trials of potentially active drugs need to be conducted.

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