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Treatment of Advanced Endometrial Adenocarcinoma with Cyclic Sequential Ethinyl Estradiol and Medroxyprogesterone Acetate

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Abstract—*Fifteen patients with recurrent or progressive endometrial adenocarcinoma of moderate to poor histologic differentiation were entered in a phase II trial of sequentially administered oral ethinyl estradiol and medroxyprogesterone acetate. There were no significant clinical responses in 12 patients evaluated for response and four patients experienced thromboembolic complications. This cyclic treatment regimen is considered ineffective for this patient population at the dosages and schedules used.*

INTRODUCTION

THERE IS a need for more effective therapy in patients with endometrial carcinoma. Patients who relapse typically have adverse prognostic features in the primary tumors such as moderate to poor tumor differentiation, deep myometrial invasion or lymphatic invasion [1]. Hormonal preparations including the progestogens medroxyprogesterone acetate (MPA) and megestrol have been relatively less successful when used in the treatment of patients with advanced poorly differentiated carcinomas [2, 3]. Reduced responsiveness to progestogens could be associated with an absolute or relative deficiency of progesterone receptors [3]. It has been proposed that PR may be induced with agents such as Tamoxifen or ethinyl estradiol [4]. In a previous phase II trial, however, we were unable to demonstrate improved clinical activity in patients with recurrent endometrial carcinoma who received sequentially administered Tamoxifen and MPA [5]. The current trial followed earlier published results with the use of sequentially administered ethinyl estradiol (EE) and MPA in carcinomas of the breast [6] and ovary [7] respectively.

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PATIENTS AND METHODS

Eligible patients included: a histologic diagnosis of recurrent or metastatic endometrial carcinoma, performance status ≤Zubrod 2, life expectancy >12 weeks, adequate oral intake and, if data were available, a tumor estrogen receptor value (ERc) ≥than 10 mol/mg cytosol protein in a standardized assay performed in the clinical laboratories at the U.T. M.D.A.C.C. [8]. One treatment cycle consisted of a single daily dose of EE (Feminone) 50 mcg, administered orally from days 1–7 followed by a single 400 mg daily dose of MPA (Provera) administered orally days 8–25. No medication was taken from days 26–30 after which the cycle was repeated. Patients were evaluated for response and toxicity. The EE and MPA were provided by the Upjohn Company, Kalamazoo, Michigan, U.S.A. The statistical design for this study considered a treatment response of ≤20% as being unacceptable. Thus, if no responses were observed in the first 12 patients the trial would be terminated and the treatment rejected.

CLINICAL RESULTS

Patients ages ranged from 54 to 74 (median 65 years). Profiles and outcomes on 15 patients are shown in Table 1. The sixth patient was considered inevaluable for response or toxicity since she developed intestinal obstruction on the second day of EE administration. Two other patients who received less than a single course were considered inevaluable for response. All patients initially under-

Table 1. Patient profiles and clinical outcome

Previous history												
Age	Path/ grade	Init/stage	Surgery	Radiotherapy	Chemo.	Tumor site	Zubrod	EE/MPA courses	Response (duration in weeks)	Survival (weeks)	ER/PR(fm/ mg protein)	Comments
54	PS/3	IA	H&O	—	PAC	pelv†	0	3	NC (8) PD	18	—	
62	AC/3	III	—	—	PAC A, DTIC	vag†	1	2	PD	9	28.6/neg	
74	AC/2	IB	H&O	—	PAC*	vag + pln†	0	3.5	NC (8)	34	23.9/nd	TIA, DVT
70	AC/3	III	—	WP + ICR	F, AC	abd, pelv‡	1	2	PD	10	—	
61	PS/3	II	H&O	ICR	—	paln	0	2	PD	46	43.1/21.1	
54	AC/2	IA	H&O	WP + ICR	—	abd, pulm	1	<1	NE	64	48.4/neg	
73	AC/3	IB	H&O	—	PAC*	adb, pelv, hep†	1	3	NC (8) PD	15	—	
65	PS/3	II	H&O	WP + ICR	PAC*	abd, hep†	0	1.5	PD	12	19.6/43.7	Subdural, TIA
63	AC/2	IB	H&O	ICR	PAC*	abd, hep†	2	1	PD	22	—	DVT
66	AS/3	IB	H&O	WP + ICR	PAC*	abd†	1	2	PD	18	—	
60	AC/2	IA	H&O	ICR	—	abd, hep†, sacrum	2	<1	NE	4	—	DVT
66	AS/3	II	H&O	WP + ICR	PAC*	abd, hep†	0	7	MR (28)	60+	30.1/109.7	
72	PS/3	IV	H&O	—	PAC	abd, pelv‡ hep†	1	<1	NE	7	—	Noncompliance
65	AS/2	II	—	WP + ICR	—	pulm, pelv‡	0	3	PD	24	—	
55	PS/3	IV	H&O	—	PAC*	abd, pelv†‡	1	3	NC (8)	38	33.5/neg	—

Abbreviations: PS—papillary serous; AC— adenocarcinoma; AS—adenosquamous; WP—whole pelvis; ICR—intracavitary radiation; NC—no change; PAC—*cis*-platinum, doxorubicin, cyclophosphamide; F—5-fluorouracil; pln—pelvic lymph node metastases; paln—paraaortic lymph node metastases; PD—progessive disease; MR—minor response; NE—not evaluable; TIA—transient ischemic attack; DVT—deep venous thrombosis; H&O—hysterectomy and salpingoophorectomy; pelv—pelvis; vag—vagina; abd—abdomen; pulm—pulmonary; hep—hepatic; *adjuvant; †CT documented; ‡advanced primary disease.

went surgery or radiation as primary or adjuvant treatment. Eleven patients had recurrent disease and four had advanced primary tumors. Prior chemotherapy had been given to 11 patients but six were treated in an adjuvant setting. All patients had pathologically confirmed measurable disease which was documented by computerized tomography or other radiologic methods in 12 patients and clinically in the remaining patients. Eleven patients received more than one course of EE/MPA.

There was one minor objective response which occurred in the liver with a best response duration of 3 months and 7 months duration of treatment with EE/MPA. This patient had an adenosquamous carcinoma which relapsed in the liver within 2 months of completing a 6 month course of adjuvant chemotherapy consisting of cisplatin, doxorubicin and cyclophosphamide. With progression this patient was begun on Tamoxifen 10 mg b.i.d. and remains alive and asymptomatic with sustained stable disease at 13+ months. Three other patients had stable disease for 8, 8 and 12 weeks. Seven patients subsequently received Tamoxifen as a single agent or combination chemotherapy. One partial response occurred in a chemotherapy treated patient. Of 15 patients evaluated for toxicity, four experienced five complications including deep venous thrombosis (DVT) in three patients, a transient ischemic attack (TIA) in two, one of whom incurred a subdural hemorrhage possibly related to concurrent warfarin therapy for a prior DVT. DVT developed during the first therapy cycle in one patient and within 1 month of discontinuing therapy in two patients. DVT resolved in the three patients following anticoagulation therapy and the patient with TIA was taken off protocol without further neurologic sequelae although she subsequently developed a DVT. All of three patients who developed DVT had extensive ipsilateral pelvic side wall disease. Despite the significant occurrence of vascular episodes, there were no deaths attributable to EE/MPA. Hormone receptor values were measured in seven patients, and in five, tissues were obtained close to the time of protocol entry.

DISCUSSION

Cyclic administration of EE and MPA produced only one, albeit minor response, out of 12 patients with recurrent endometrial cancer who were evaluable for response. Included were seven patients with ERc positive tumors one of whom had a minor response although this patient's PR value was also high. The number of thromboembolic episodes was disturbingly high in contrast to previous experience

with similar regimens ultilizing EE and MPA in carcinoma of the breast [6] and ovary [7]. The frequency of venous thrombosis could be related to the ipsilateral pelvic tumor locations in these patients or to other factors such as advanced age and increased susceptibility to thrombosis perhaps from the estradiol component. Based on this study and our past experience with Tamoxifen and MPA [5], we are unable to recommend either of these sequential approaches over any available single agent hormonal therapy in the treatment of similar patients with advanced endometrial carcinoma.

REFERENCES

1. DiSaia PF, Creasman WT, Boronow RC, Blessing JA. Risk factors and recurrent patterns in Stage I endometrial cancer. *Am J Obstet Gynecol* 1985, **151**, 1009–1015.
2. Podratz KC, O'Brien PC, Malkasian GD *et al.* Effects of progestational agents in treatment of endometrial carcinoma. *Obstet Gynecol* 1985, **66**, 106–110.
3. Ehrlich CE, Young PCM, Stehman FB *et al.* Steroid receptors and clinical outcome in patients with adenocarcinoma of the endometrium. *Am J Obstet Gynecol* 1988, **158**, 797–807.
4. Namer M, Lalanne C, Baulieu EE. Increase of progesterone receptor by Tamoxifen as a hormonal challenge test in breast cancer. *Cancer Res* 1980, **40**, 1750–1752.
5. Kline RC, Freedman RS, Jones LA *et al.* Treatment of recurrent or metastatic poorly differentiated adenocarcinoma of the endometrium with tamoxifen and medroxyprogesterone acetate. *Cancer Treat Rep* 1987, **71**, 327–328.
6. Hortobagyi GN, Kau SW, Hug V *et al.* Cyclic combined hormonal therapy for metastatic breast cancer (Abstract). *Pro Am Ass Cancer Res* 1986, **27**, 219.
7. Freedman RS, Saul PB, Edwards CL. Ethinyl estradiol and medroxyprogesterone acetate in patients with epithelial ovarian carcinoma: a Phase II Study. *Cancer Treat Rep* 1986, **70**, 369–373.
8. Raynaud JP, Ojasoo T, Delarue JC *et al.* Estrogen and progestin receptors in human breast cancer. *Progesterone Receptors in Normal and Neoplastic Tissues*. New York, Raven Press, 1977, 171–91.