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A Phase II Study of Tamoxifen in Ovarian Cancer

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Abstract—*A phase* II *study of tamoxifen was conducted in* 22 *patients with stage* III *and* IV *ovarian cancer who had failed chemotherapy and who had evaluable disease. Tamoxifen was administered at a dose of* 20 mg *twice daily continuously until evidence of progression. Twenty-one patients had progression of disease within* 3 months *and one patient had stable disease for* 6 months. *There were no objective responses to this treatment.*

INTRODUCTION

HORMONAL manipulations are of proven value in breast cancer [1], endometrial cancer [2] and prostatic cancer [3] and have been extensively investigated in these tumours. In contrast to the large amount of information available about the hormone sensitivity of these malignancies, little data is available on the response of ovarian cancer to hormonal manipulation. The recent demonstration of oestrogen and progesterone receptors in up to 50% of these tumours [4–7] has suggested a rationale for hormonal manipulation. In addition androgen receptors [8] are common and receptors for follicle stimulation hormone and human chorionic gonadotrophin [9] have been found in some tumours. The earliest suggestion that ovarian cancer might be hormone sensitive resulted from a study using oestrogen (diethylstilboestrol) in patients with advanced disease with 4 out of 14 (28%) patients with advanced disease achieving a partial response [10]. Subsequently progestogens have been used to treat patients who have failed chemotherapy and the published response rates vary from 0 to 65% [11]. If the responses in the published literature are reviewed according to World Health Organisation criteria, the mean response is approx. 16% with a range of 0–38% [11]. Recently it has been suggested that the anti-oestrogen tamoxifen might have therapeutic activity in ovarian cancer [12–14]. This phase II study was conducted to further evaluate the role of tamoxifen in ovarian malignancy.

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MATERIALS AND METHODS

Patients

Twenty-two patients with stage III or IV epithelial ovarian cancer who had failed to respond to or who had relapsed following cytotoxic chemotherapy were studied. All patients had an histologically proven diagnosis of ovarian carcinoma and all had measurable disease. Patients had an estimated life expectancy of at least 3 months. Patients with any evidence of intestinal obstruction were excluded.

Patient characteristics are shown in Table 1.

Tamoxifen therapy

Tamoxifen was administered at a dose of 20 mg twice daily and continued until there was unequivocal evidence of progressive disease.

RESPONSE

Response was assessed by standard World Health Organisation criteria [15].

RESULTS

Twenty-one patients experienced progression of disease within 3 months. In one patient the disease was stable for 6.5 months. No patient had an objective response to treatment. The median survival was 3.5 months with a range of 0.75–12 months.

DISCUSSION

A number of studies have suggested that tamoxifen may have activity in ovarian cancer. Myers *et al.* [12] described three patients with advanced recurrent disease who were treated with tamoxifen. One patient achieved a complete response and two

Table 1. Patient characteristics and response to treatment

Patient (SBH)	Age at diagnosis	Residual bulk of disease (cm^2)	Prior C/T (duration in months)	Response to C/T	Prior R/T	Progression free interval after stopping C/T (months)	Karnofsky performance status before Tamoxifen	Response to Tamoxifen	Time to progression on Tamoxifen	Survival from start of Tamoxifen (duration in months)
HP	56	0	MeCCNU, MMC, 5FU (24) PACE (1) Cis-Plat (2)	CR PR PD	2500 cGy post op	0	50	PD	1	1.5
GC	68	>2cm	CB (4) PACE (12)	PD PR	No	0	90	PD	2	5
MO	37	<2cm	Melph (23) PACE (2) CB (4) Ifos (2) Melph (20)	PR NC PD NC PD	No	0	70	NC	3	6.5
KS	62	>2cm	CB (4)	PR	No	0	70	PD	1. 5	2
JG	54	>2cm	PACE (8) CB (5)	PR PR	No	4	70	PD	2	3
IH	54	>2cm	PACE (8) 5FU, MTX, DBD (2)	PR PD	No	0	70	PD	1	4
EM	42	>2cm	PACE (8) CB (19)	PR PR U/A	No	2.5	60	PD	1	1
SH	55	>2cm	PACE (5) CB (9) Vinb+Bleo (1)	PR NC PD	No	0	80	PD	1. 5	5
PR	44	>2cm	PACE (5)	PR	No	1	50	PD	2	3.5
DR	72	>2cm	CB (2)	PD	No	0	80	PD	1.5	4.5
EB	68	<2cm	CB (24) Melph (16) Melph (3)	PD PR PD	No	0	80	PD	1.5	12
(Southampton)										
MS	63	>2cm	CB (5)	PD	No	0	80	PD	1.5	2.5
HG	54	>2cm	CB (3)	PD	No	0	70	PD	2.0	3.5
PD	50	>2cm	CB (3) PACE (5)	PR PR	No No	0 0	60	PD	0.75	1.0
JA	53	>2cm	CB (24) PACE (6)	CR CR	No	5 mth	80	PD	2.0	3.0
JS	49	>2cm	PACE (4) CB (5)	CR PD	No	0	70	PD	2.5	4.0
BH	50	>2cm	CB (5) PACE (6)	PD NC	No	0	80	PD	1.75	3.0
MW	75	>2cm	PACE (6) CB (12)	PR NC	No	0	80	PD	2.0	2.5
MB	64	>2cm	CB (3) PACE (7)	PD PR	No	5 mth	90	PD	3.0	7.0
VP	56	>2cm	CB (11) PACE (1)	PD PD	No	0	70	PD	1.0	1.5
EL	79	>2cm	CB (12)	NC	No	0	90	PD	2.5	4.0
DW	57	>2cm	CB (6)	PD	No	0	80	PD	3.0	Alive at 8 mth when lost to FU

Key: Bleo = Bleomycin; CB = Chlorambucil; Cis Plat = *Cis*-Platinum; DBD = Dibromodulcitol; Ifos = Ifosfamide; MeCCNU = Methyl CCNU; Melph = Melphalan; MMC = Mitomycin; PACE = Platinum, Adriamycin, Cyclophosphamide; Vinb = Vinblastine; 5FU = 5 Fluorouracil.

had good partial responses. Subsequently a study of 13 patients with rapidly advancing tumours that had failed conventional therapy was reported with one patient achieving a partial response and four patients had stabilisation of disease [13]. In this study tamoxifen was started at a dose of 10 mg twice daily and was increased in some patients. The one partial response occurred at a dose of 20 mg twice daily after the patient had progressed on the initial dose. Recently Pagel *et al.* [14] treated 36 patients with ovarian cancer who had been heavily pre-treated with chemotherapy. Thirteen patients (36%) achieved a response, three of these being complete responses and 10 partial responses. The median duration of response was just over 6 months. One third of the patients had tissue analysed for oestrogen receptor status and the initial data suggested a correlation between receptor positivity and response.

In contrast to this data, Shirley *et al.* [16] treated 18 patients with advanced ovarian cancer with tamoxifen at doses of 20–40 mg daily. No objective responses occurred but stable disease was observed in 10 patients for a median of 10 weeks. The pilot study presented here showed no responses in 22 patients, with 21 patients showing evidence of progressive disease in less than 12 weeks. The mean Karnofsky performance status was 70 suggesting that these patients were not moribund and the patients were not more heavily pre-treated than those previously reported. Receptor status was not measured in these patients because of the difficulty in obtaining tumour tissue from patients in whom a laparotomy would be inappropriate and of no therapeutic benefit.

Response to tamoxifen in carcinoma of the breast often takes 12 or more weeks, and 21 of the 22 patients presented here had progressed within that time. Tamoxifen has a long terminal half-life and with a standard dosage schedule of 10–20 mg twice daily it can take several weeks for plateau concentrations to be achieved [17]. Although the concentrations of tamoxifen required for a therapeutic response are unknown, it is possible that the response rate might have been better if a loading dose had been given and plateau levels rapidly reached. This does not explain the difference between our results and previous studies as a loading schedule was not given to these patients.

Despite the negative results reported here, further studies of tamoxifen in carcinoma of the ovary are indicated because of the low toxicity of tamoxifen, the poor response to chemotherapy at this stage of disease and the positive results reported by others [12–14]. Routine estimation of oestrogen and progesterone receptor status at the time of initial operation would enable this information to be available should the patients relapse and be treated with tamoxifen at a later date. Consideration should be given to using a loading dose of tamoxifen so that rapid plateau concentrations can be achieved.

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