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Phase II Evaluation of Megestrol Acetate in Previously Treated Patients with Advanced Breast Cancer: Relationship of Response to Previous Treatment

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Abstract—*Thirty-seven patients with advanced breast cancer were treated with megestrol acetate* 160 mg *daily. All patients except two had been heavily pre-treated with hormonal therapy; eight patients also received chemotherapy. Complete and partial responses occurred in* 25% *with a mean duration of* 5 months (*range* 2–24 months). *A further* 38% *of patients had static disease for* 2 months *or greater. Seven patients had previously received medroxyprogesterone acetate, and responses were seen even in patients who had failed to respond to this therapy. This was thought to be due to the higher levels of progestogenic activity which can be routinely achieved with megestrol acetate. Toxicity was minimal, and we would therefore consider that megestrol acetate should be the progestogen of choice in advanced breast cancer.*

INTRODUCTION

MANY patients with advanced breast cancer are suitable for treatment by hormonal manipulation. Several kinds of medical hormone manipulation including oestrogens, anti-oestrogens, aromatase inhibitors and progestogens may be of value in around 30–40% of patients presenting with advanced breast cancer [1]. Megestrol acetate (17α-acetoxy-6-methylpregna-4,6-diene-3,20-dione) is a synthetic, highly potent progestogen. It is well absorbed after oral administration [2]. Megestrol acetate has been used in advanced breast cancer in a number of studies. Ansfield *et al.* [3] showed an overall response rate of 31% at a dose of 160 mg daily. In a larger study of Alexieva-Figusch *et al.* [4] there was an objective response rate of 30% in 160 patients. There was stabilisation of disease in a further 36% of patients. Patients responding to previous hormonal therapy are more likely to respond to subsequent hormone manipulation than non-responders [5]. Sequential response to different agents within the same hormone class, however, has been less frequently studied. We report a study of megestrol acetate in patients with advanced breast cancer who have been treated extensively with previous hormonal manipulation and chemotherapy. The benefit of megestrol acetate with respect to previous treatment and response to that treatment has been studied.

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MATERIALS AND METHODS

Patients were entered into the study with biopsy proven breast cancer. All patients had evidence of recurrent or advanced breast cancer and had evidence of progression prior to starting Megestrol Acetate therapy. All but two of 37 evaluable patients had received previous hormone therapy and/or cytotoxic chemotherapy. Patient characteristics and the previous treatments received are shown in Table 1. All patients were post menopausal with the exception of two perimenopausal patients. Previous therapy had ceased at least 4 weeks prior to entry into the trial.

Megestrol acetate was administered at a dose of 40 mg four times a day for a minimum of 12 weeks, unless a contraindication to treatment developed. Treatment was continued in the responders to relapse. Patients were assessed formally at 6 weeks, 12 weeks and then at 3-month intervals until progression. Patients were assessed for response using UICC criteria for breast cancer, and toxicity was assessed using WHO criteria [6, 7].

Table 1. Patient characteristics

		n	(%)
Total		37	
Age	Mean 63 (Range 34–82)		
Menopausal status	Peri-	2	(5)
	Post-	35	(95)
Previous treatment			
None		2	(5)
Tamoxifen +/− other hormone		27	(73)
Tamoxifen + chemotherapy		8	(22)
Medroxyprogestrone acetate		7	
Sites of disease			
Soft tissue		37	
Bone		13	

RESULTS

Response

There were 37 evaluable patients. All patients had evidence of progressive soft tissue disease. In addition 13 patients had bone disease. One patient achieved a clinical complete remission and there were eight patients who had partial remissions giving a response rate of 25% (see Table 2). The mean time on treatment for all patients was 3.5 months (range .5–25 months). Mean response duration was 5 months with a range of 2–24 months. There were a further 14 patients who had static disease for a period of 2 months or greater. Fourteen patients had evidence of progression. Responses were noted predominantly in soft tissue disease. Seven out of the 13 patients who had evidence of bone disease noticed reduction in bone pain from bone metastases. None of the seven patients, however, had changes on X-ray sufficient to fulfil UICC criteria for response in bone. Three of these patients achieved a soft tissue complete remission. Three had static disease and one had evidence of soft tissue progression.

Table 2. Response rate

	n	(%)			
Complete remission	1	(3)	)	)	
			) 25%	)	
Partial remission	8	(22)	)	) 62%	
				)	
Static	14	(38)		)	
Progression	14	(38)			

Response to megestrol acetate when compared with response to previous treatment is shown in Table 3. Five of 11 patients who had responded to previous hormone therapy of any kind showed tumour regression on megestrol acetate. Only three of the 18 patients who had either static disease or no response to previous hormone therapy responded to megestrol acetate. There was one partial remission to megestrol acetate in a previous responder to chemotherapy.

Table 3. Response rate by previous treatment

Previous treatment (and response)	Number	Responders CR	PR	Static	Progression
Hormone(CR/PR)	11	1	4	4	2
Hormone (Static/Prog.)	18	0	3	10	5
(Included in above responses)					
Medroxyprogesterone Ac.					
(2 PR, 5 Prog.)	*7*	*0*	*2*	*2*	*3*
Chemotherapy (CR/PR)	4	0	1	0	3
Chemotherapy (Prog.)	4	0	0	0	4

Seven patients had received previous therapy with high dose intramuscular medroxyprogesterone acetate. All these cases had progressed after an initial response or failed to respond at all to this treatment. Two of these patients demonstrated a partial response to megestrol acetate, two had static disease and three showed evidence of progression.

Toxicity

There were seven cases in which side effects other than weight gain occurred. Treatment was stopped in two instances. One patient complained of neck pain and tightening of the throat. An ECG performed at that time was normal, and there was no evidence of an anaphylactic reaction, but she was unwilling to continue treatment. Another patient who had a previous myocardial infarction, developed evidence of congestive cardiac failure and fluid retention. In a further case, the treatment was modified because acute left ventricular failure developed within 48 hr of starting megestrol acetate. The dose was reduced to 40 mg bd and the heart failure resolved.

There were four cases who reported toxicity where treatment modification was unnecessary. One patient had an aching arm; two mild nausea; one patient felt tired with nocturia and fluid retention. There was no haematological toxicity. When weight gain was studied most patients reported an increased appetite and sense of well-being and many patients said that they had put on weight. In 13 patients there were accurate sequential weight measurements. Weights increased, less than 10% in five, and between 10 and 15% of the initial weight in one patient. In four patients with evidence of progressive disease the weight decreased. In the other three patients in whom sequential measurements were available, the weight was stable during treatment.

DISCUSSION

This study confirms the activity of megestrol acetate in advanced breast cancer, and further defines the role of the agent in patients previously treated with other forms of hormonal manipulation. The group of patients studied had been extensively pre-treated with hormonal therapy and, in eight cases, with chemotherapy as well. Extensive pre-treatment of any kind results in a lower response rate for subsequent agents. This is reflected in this study, with a CR and PR rate of 25%, and a further 38% of patients having static disease. With less previous treatment results similar to those achieved by Alexieva-Figusch *et al.* [4] would have been expected.

Ross *et al.* [5] noted that response rates to megestrol acetate were not altered in patients who had previously responded to tamoxifen. This was also seen in this study, presumably reflecting continued sensitivity of those malignant cells to alterations in the hormonal environment. Receptor status was not routinely performed in this group of patients, but other studies would suggest that such responses occur in association with both oestrogen and progestogen receptor positivity [8].

It is of note that in this study responses and significant periods of static disease were seen with megestrol acetate following failure of medroxyprogesterone acetate therapy. Ganzina [9] demonstrated that high doses of MPA were needed to achieve therapeutic levels and that even with oral doses of 1g daily or more these could not be invariably achieved. In contrast Lenaz *et al.* [2] demonstrated that therapeutic levels of megestrol acetate were routinely achieved, or exceeded, by the administration of 160 mg daily. In the five cases who had progressing disease on MPA, it is possible that inadequate doses of progestogen were being given, and that the higher progestogenic activity of megestrol acetate was then of benefit. Johnson *et al.* [10] demonstrated a correlation between response and MPA blood levels. This does not, however, explain the two patients who had responses to MPA, progressed, and who then subsequently benefitted from megestrol acetate. This might be evidence of a dose response for progestogens, but could only be assessed using megestrol acetate because of the sharp increase in toxicity seen with MPA at doses above 1g daily.

Megestrol acetate was well tolerated. Only two patients required cessation of treatment, and only one required dose modification. Several patients noted significant weight gain, but this was not a troubling phenomenon, and was not regarded as a problem by the patients. A feeling of well-being was experienced by most patients, even those without objective evidence of response, and was regarded by the patients as being of benefit.

This study of megestrol acetate has encouraged us to evaluate the drug further. Morgan *et al.* [11] have suggested in a small randomised study that it is equivalent to tamoxifen as treatment at first relapse in patients with breast cancer. The small numbers in the study meant that response rates by site, etc, could not be reliably evaluated for the two agents. A multi-centre prospective randomised study is now in progress to evaluate the relative benefits of tamoxifen and megestrol acetate as first line hormone treatment in patients with advanced breast cancer.

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