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High Dose Versus Low Dose Medroxyprogesterone Acetate: a Randomized Trial in Advanced Breast Cancer

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Abstract—*One hundred and twenty-four patients with advanced breast cancer were randomly allocated to treatment with either low dose* (300 mg/*day*) *or high dose* (1000 mg/*day*) *oral medroxyprogesterone acetate. The objective response rate was* 24% *for both treatment groups. For premenopausal patients, responses were achieved in two out of four on low dose and three out of six on high dose therapy* (*overall* 5 *out of* 10 *responders*). *No significant differences in response were seen in relation to previous endocrine therapy or site of disease. Both treatments were associated with a high incidence of bone pain relief* (43 *and* 52%) *but a low objective response rate* (13%) *in bone. Median response duration* (10 *vs.* 11 *months*) *and survival* (13 *vs.* 11 *months*) *were not significantly different for the two treatments. Both treatments were in general well tolerated, but toxicity was greater with the high dose treatment. Low dose oral medroxyprogesterone acetate is as effective as high dose therapy in the treatment of advanced breast cancer, and is cheaper and less toxic.*

INTRODUCTION

THERE has recently been renewed interest in the synthetic progestin medroxyprogesterone acetate (MPA) as treatment for advanced breast cancer, following reports that high dose intramuscular (i.m.) MPA achieved tumour responses in 30–45% of patients [1–5]. Similarly high response rates have more recently been reported with oral MPA [6–8]. However, claims for the benefit of high dose treatment have been based largely on retrospective comparisons with earlier studies of low dose therapy [9–13]. Two published randomized trials have compared low vs. high dose i.m. induction MPA for 1 month [5, 14]; the first showed no significant response difference [14] and the second showed an improvement in response rate but not duration or survival for high dose treatment [5]. At least three recent studies have reported a relatively low response rate (16–19%) for high dose intramuscular MPA [15–17].

We have therefore carried out a randomized trial of oral high dose (1000 mg daily) vs. low dose (300 mg daily) MPA in patients with advanced breast cancer. This question seemed important because of cost, because of suggestions that high dose therapy might be associated with an increased incidence of side-effects [7, 14, 18] and to see whether claims based largely on non-randomized data could be confirmed. There is currently conflicting information on MPA in the treatment of pre-menopausal patients [4, 14, 19] and they were also included in this trial.

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PATIENTS AND METHODS

One hundred and twenty-four patients with histologically proven and measurable advanced breast cancer referred to the Royal Marsden Hospital, Breast Unit, between February 1983 and July 1985 were randomized to receive medroxyprogesterone acetate orally at a dose of either 300 mg/day (100 mg × 3) (66 patients) or 1000 mg/day (250 mg × 4) (58 patients). Treatment was continued until disease progression. If unacceptable toxicity developed, low dose therapy was stopped and high dose therapy was either reduced or stopped.

Patient details are given in Table 1. Most had received previous endocrine therapy. There were no significant differences between the two groups for prognostic factors including age, menopausal status, disease free interval, sites of disease and response to previous endocrine therapy. Eighteen patients treated with high dose MPA had received

Table 1. Age, menopausal status, previous therapy, disease sites and tumour-free interval in patients on low dose and high dose therapy

	Low dose	High dose
Number	66	58
Median age (years)	59 (28–78)	59 (37–80)
Menopausal status:		
pre	4	6
peri (≤ 2 years)	6	5
post	56	46
male	0	1
Previous endocrine therapy	48	43
Responders to endocrine therapy	20	17
Previous chemotherapy (including adjuvant)	6	18
No previous treatment	18	14
Median number sites of disease	2 (1–6)	3 (1–7)
Visceral disease:		
lung metastases	21	11
liver metastases	8	8
Median tumour-free interval (from diagnosis) (range)	31 months (0–172 months)	28 months (0–297 months)

previous chemotherapy (adjuvant or otherwise) compared with only six treated with low dose MPA and this difference arose on a random basis. Twenty-one patients with visceral lung involvement received low dose treatment compared with only 11 receiving high dose treatment. Cytoplasmic hormone receptor data were not available in the great majority of patients.

Pre-treatment assessment included full clinical examination, peripheral blood count, biochemical liver function tests and chest X-ray. Other investigations including skeletal X-rays, isotopic bone scan, liver scan or ultrasound and bone marrow aspiration were performed when clinically indicated. Patients were reassessed at 1 month and 2 months after starting treatment, and thereafter at 3 month intervals or earlier if clinically indicated.

Tumour response at each site of metastatic disease was assessed objectively according to standard UICC criteria [20]. Patients were defined as having stable disease if there was no evidence of disease progression for at least 3 months from the start of treatment and if tumour-related symptoms (e.g. bone pain) improved during this period. To assess toxicity patients were weighed, had their blood pressure measured, were examined clinically for facial and peripheral oedema and were asked about possible side-effects at each clinic visit.

Response duration and survival were measured from start of treatment, and compared by standard life table analysis [21], using the modified Wilcoxon test [22].

RESULTS

Complete or partial remissions were obtained in 16 out of 66 low dose patients (24%) and 14 out of 58 high dose patients (24%) (95% confidence interval 14–37% for both arms) (Table 2). A further 12 low dose patients (18%) and 17 high dose patients (29%) had stable disease for at least 3 months (not significantly different: $\chi^2 = 2.08$, $P > 0.05$). Two out of four pre-menopausal patients treated with low dose MPA and three out of six treated with high dose MPA responded, giving an overall response rate of five out of 10 (50%) in this sub-group (Table 3). The one male patient in the study achieved a partial response of 9 months duration to high dose therapy.

Table 2. Response

	Low dose	High dose
Patients	66	58
Complete remission	0	3 (5%)
Partial remission	16 (24%)	11 (19%)
Stable disease	12 (18%)	17 (29%)
Progressive disease	37 (57%)	22 (38%)
Not assessable*	1 (1%)	5 (9%)

*Because of toxicity.

For both low and high dose therapies, responses were seen both in patients who had responded to previous endocrine therapy (20% and 41%, respectively no significant difference) and in non-responders to previous endocrine therapy (2% and 15%, respectively) (Table 3).

Details of response by site of disease are given in Table 4. No differences in response emerged for any site for the two treatments. Both treatments were effective in achieving bone pain relief (43% and 52%), although objective radiological evidence of response at this stage occurred in only 13% of

Table 3. Response by menopausal status and related to previous endocrine therapy

	Low dose			High dose		
	Patients	Responders		Patients	Responders	
Premenopausal	4	2		6	3	
Previous endocrine therapy						
None	19	6	(32%)	14	4	(29%)
Response	20	4	(20%)	17	6	( )
No response	27	6	(22%)	27	4	(15%)

Table 4. Response by site

	Low dose		High dose	
	Patients	Responders	Patients	Responders
Soft tissues	41	7 (17%)	35	5 (14%)
Bone	32	4 (13%)	31	4 (13%)
Bone pain	21	9 (43%)	23	12 (52%)
Pleura	6	2 (33%)	20	6 (30%)
Lung	21	1 (5%)	11	2 (18%)
Liver	8	1 (13%)	8	1 (13%)

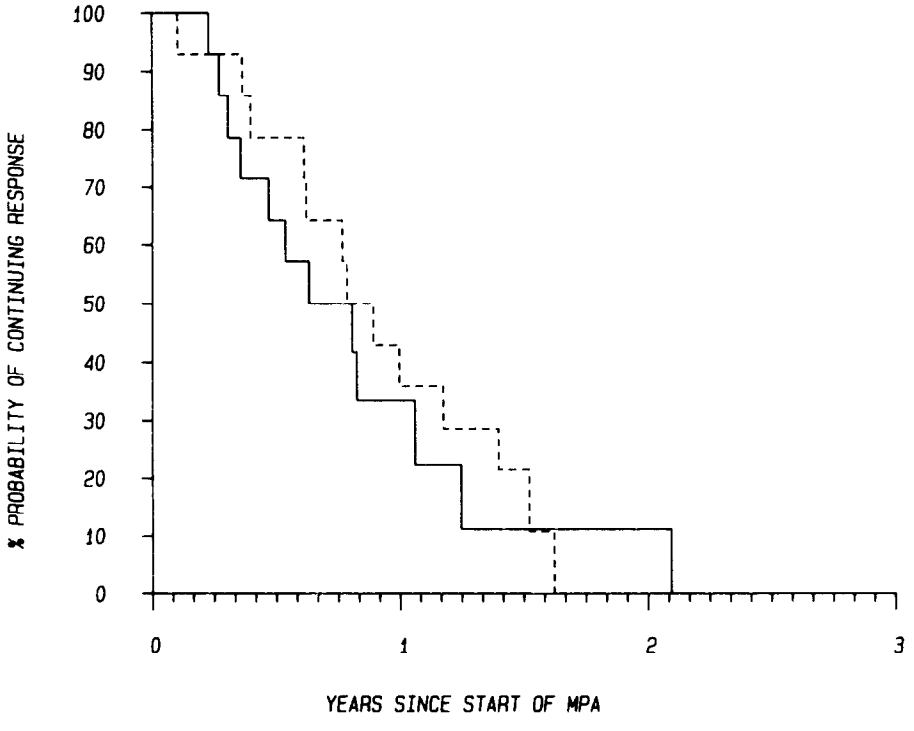

Fig. 1. Response duration for low dose (-----) and high dose (———) MPA.

patients for each treatment.

Median response duration was 11 months for responders to low dose therapy (range 2–19 months) and 10 months for responders to high dose therapy (range 3.5–25 months) (Fig. 1). Median survival was 13 months and 11 months for all patients treated with low and high dose therapy, respectively (Fig. 2). None of these differences were statistically significant.

In general, treatment was well tolerated for both treatment arms, but toxicity was greater for patients on high dose than on low dose therapy. Details are given in Table 5. The main problems were fluid retention (as assessed clinically by facial or peripheral oedema) (26% vs. 6%), greater than 10% weight gain (10% vs. 2%), and vaginal bleeding (9% vs. 5%). Only one patient (2%) on low dose therapy had to discontinue treatment (because of

Table 5. Toxicity in 66 patients on low dose treatment and 58 on high dose treatment

	Low dose	High dose
Fluid retention	4 (6%)	15 (26%)
>10% weight gain	1 (2%)	6 (10%)
Rise in blood pressure*	0	2 (3%)
Vaginal bleeding	3 (5%)	5 (9%)
Nausea	1 (2%)	0
Hypercalcaemia	1 (2%)	0
Dizziness	0	1 (2%)
Exacerbation diabetes	0	1 (2%)
Exacerbation psoriasis	0	1 (2%)
Dose reduction†	0	5 (9%)
Treatment stopped†	1 (2%)	5 (9%)

*A sustained >10% rise—pretreatment resting systolic or diastolic pressure.
†See text for details.

for progestagen therapy in advanced breast cancer have been non-randomized [3, 4, 6, 7, 15, 17]. The argument favouring this approach has therefore been based largely on retrospective comparisons with earlier studies of low dose therapy [9–13], which may be influenced by important differences in other prognostic criteria. Even in one well constructed randomized trial comparing high dose with low dose intramuscular induction therapy (1000 mg i.m. daily vs. 500 mg × 2 weekly for 1 month, with subsequent maintenance treatment of 500 mg i.m. weekly in both arms) the only significant difference to emerge in favour of high dose treatment was in response rate (33% vs. 15%); no difference was found for remission duration, time to progressive disease or survival [5]. Moreover the response rate difference depended largely on a surprisingly low response for low dose therapy, compared with other studies [14, 18] rather than a high

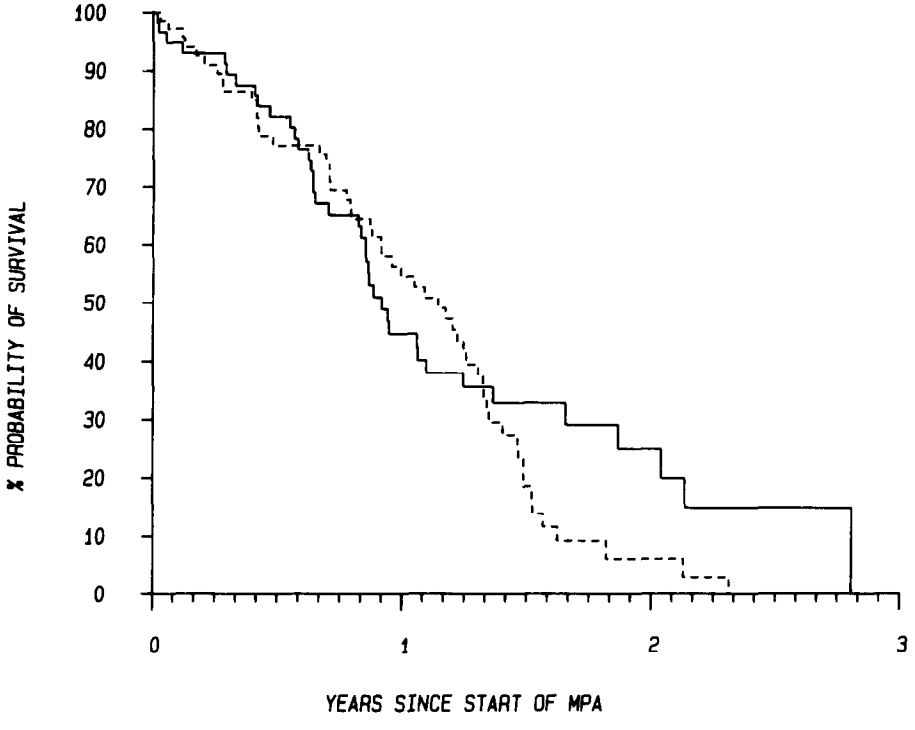

Fig. 2. Survival for low dose (-----) and high dose (———) MPA.

hypercalcaemia), compared with five patients (9%) on high dose treatment (2 fluid retention, 1 hypertension, 1 dizziness and 1 exacerbation of diabetes mellitus). A further five patients (9%) on high dose therapy required a dose reduction from 1000 to 300 mg daily because of toxicity (2 fluid retention, 2 vaginal bleeding and 1 exacerbation of psoriasis). In total therefore, 10 high dose patients required dose reduction or cessation compared with one low dose patient ($P = 0.002$).

DISCUSSION

Most of the studies reporting high response rates response for high dose treatment. And in a second similarly designed trial, no response difference was found [14].

Our trial of oral high vs. low dose MPA has failed to demonstrate any difference in response rates, in agreement with the results of Pannuti *et al.* [14] in which treatment was given intramuscularly. In addition, like Cavalli *et al.* [5] we found no significant difference in response duration or survival. High dose MPA was associated with a greater incidence of side-effects including in particular fluid retention and weight gain, such that 18% of patients in this group had to stop treatment or reduce dosage

compared with only 2% on low dose treatment. Cavalli *et al.* [5] found no significant difference in toxicity between the two treatment arms, but this could have been because high dose therapy was only continued for a month. Other studies have shown a significant incidence of side-effects on high dose treatment including fluid retention, weight gain, hypertension, vaginal bleeding and muscle cramps [7, 8, 14, 17].

Our response rate of 24% is lower than that reported in some non-randomized studies of high dose oral or i.m. treatment [1, 2, 8, 6], but the most likely explanation for this is the large proportion of previously treated patients in our study and the number with liver metastases or oestrogen receptor unknown tumours; these factors have been reported by others to have poor response rates [3–5, 17, 19, 23].

It could be argued that because the oral absorption of MPA is highly variable [24] this might explain an inability to show a therapeutic benefit for high dose MPA. However, this is unlikely. First, recent pharmacokinetic studies have confirmed a 5-fold difference in plasma levels for doses of 900 mg compared with 300 mg orally daily [25]. Second, no direct relationship between plasma concentrations of MPA and response has been demonstrated [19].

Two other clinical points to note emerged from this trial. First, our results confirmed other studies reporting that high dose MPA achieves a high incidence of bone pain relief [4, 5, 8, 14], but the effect was also seen for low dose treatment. Second, responses were seen in five out of 10 pre-menopausal patients, and again independently of dose. There is conflicting information on MPA in the treatment of pre-menopausal patients with some reports suggesting a decreased response rate [4, 19] and others an increased activity in pre-menopausal women [14], and further study is indicated in this sub-group of patients.

In conclusion, we have found no therapeutic benefit for high dose over low dose progesterone therapy in the treatment of advanced breast cancer, and high dose treatment is therefore contraindicated on grounds of increased toxicity and cost.

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