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Original Paper

A Randomised Phase III Cross-over Study of Tamoxifen Versus Megestrol Acetate in Advanced and Recurrent Breast Cancer

N.S.A. Stuart,[1] J. Warwick,[1] G.R.P. Blackledge,[1] D. Spooner,[1] C. Keen,[2] A.R. Taylor,[3] C. Tyrell,[4] D.J.T. Webster[5] and H. Earl

[1]CRC Trials Unit, Queen Elizabeth Medical Centre, Birmingham, B15 2TH; [2]Department of Clinical Oncology, Velindre Hospital, Cardiff; [3]Department of Surgery, Stoke Mandeville Hospital, Stoke Mandeville; [4]Department of Clinical Oncology, Freedom Fields Hospital, Plymouth; and [5]Department of Surgery, Velindre Hospital, Cardiff, U.K.

139 peri- and postmenopausal women with advanced or recurrent breast cancer who had not received prior hormonal therapy were randomised in an open, cross-over study comparing the synthetic progestogen megestrol acetate with tamoxifen. The response rate (CR/PR) to megestrol acetate (25%; 95% confidence interval (CI) 15–35%) was not significantly different from that produced by tamoxifen (33%, CI 22–44%). Time-to-treatment failure was also similar in the two groups. Cross-over treatment was given on progression in 76 cases. Cross-over response (CR/PR) was seen in 3 of 35 patients (9%) receiving megestrol acetate as second-line therapy and in 6 of 41 patients (15%) receiving tamoxifen second-line. There was no significant difference in survival between the groups ($P = 0.17$) with median survival times of 24 and 32 months for the megestrol acetate and tamoxifen groups, respectively. The toxicity profile of the two drugs was different, although significant toxicity was rare with either agent. Megestrol acetate is an effective treatment for advanced breast cancer in older women when used either as first- or second-line treatment. Cross-over response is seen following both treatments. Given that most patients now receive tamoxifen as adjuvant treatment, megestrol acetate would appear to be one of the logical choices for patients who find the side-effects of tamoxifen unacceptable and for those who relapse on tamoxifen with further hormone therapy being clinically indicated. Copyright © 1996 Elsevier Science Ltd

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INTRODUCTION

HORMONAL TREATMENT continues to play an important part in the management of locally recurrent or metastatic breast cancer. In adjuvant treatment the anti-oestrogen tamoxifen is the standard hormone therapy, but in advanced disease a range of treatments is used. Tamoxifen, progestogens such as megestrol acetate (Megace) or medroxyprogesterone acetate, and the aromatase inhibitors, aminoglutethimide and formastane (Lentaron), all show activity and are widely used.

Tamoxifen produces an objective response in 25–35% of cases [1]. It is usually well tolerated and is a common first line therapy. Response rates broadly similar to this are produced by the two widely used synthetic progestogens, medroxyprogesterone acetate and megestrol acetate [2–4]. These produce similar side-effects, although medroxyprogesterone acetate may have a more potent progesterone effect and therefore may produce side-effects more often. Megestrol acetate also has a longer half-life and can be given once daily,

Correspondence to N.S.A. Stuart at the Department of Oncology, Ysbyty Gwynedd, Bangor, Gwynedd LL58 8NR, U.K.
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while medroxyprogesterone acetate is usually given up to three or four times per day. Aminoglutethimide produces similar response rates, but tends to have more side-effects. It is, therefore, often reserved for second- or third-line use. Although these agents are in wide use, data comparing them in advanced breast cancer are inadequate. The widespread use of tamoxifen as an adjuvant treatment also makes collection of such data difficult. This paper reports a study comparing tamoxifen with megestrol acetate as first-line hormone therapy for advanced breast cancer.

MATERIALS AND METHODS

Between April 1985 and June 1988, 139 postmenopausal women with advanced or recurrent breast cancer were randomised into an open, multicentre study comparing megestrol acetate (Megace, Bristol-Myers) and tamoxifen (Nolvadex). It was originally planned to randomise 200 patients into this study, but following the widespread acceptance, in the late 1980s, of adjuvant tamoxifen as the best hormonal therapy for postmenopausal patients with this disease, recruitment became increasingly difficult and the study was closed early due to a lack of eligible patients.

No patient had received previous systemic therapy other than adjuvant chemotherapy ending at least 6 weeks previously. All had measurable or evaluable disease. Patients with WHO performance grade 3 or less, with a life expectancy of less than 2 months or with other previous malignancy were excluded. Tumour response and toxicity were assessed by UICC and WHO criteria, respectively. Patients who had undergone hysterectomy or who were within 2 years of menopause were eligible for entry if they were aged over 50 years and had raised serum FSH levels. Patients whose tumours were known to express neither oestrogen receptors (ER) nor progesterone receptors (PR) were not included, but patients in whom the ER and/or PR status were unknown were eligible.

Patients gave informed consent according to the rules of local ethical committees. Following consent, randomisation was by telephone call to the CRC Trials Unit, Birmingham with stratification by treatment centre. Patients received megestrol acetate 160 mg once a day or tamoxifen 20 mg once a day as an open treatment. On progression, patients thought suitable for further hormone therapy were crossed over to the alternative treatment after a treatment free period of 4 weeks. Data monitoring was carried out at regular intervals by the sponsors, Bristol-Myers (U.K.) Ltd.

Statistical methods

Data were collected prospectively and originally stored in the SYSTEL database on a Systime 8730 minicomputer at the CRC Trials Unit. Analysis was carried out on a DEC ALPHA 2100 Model A500 MP minicomputer using SAS statistical software (SAS Circle, Cary, North Carolina, U.S.A.). Survival curves were calculated by the product-limit method [5], and the log-rank test was used to test for differences between the curves [5]. Survival was calculated from the date of randomisation to death for patients who have died and from randomisation to the censor date, 31 December 1994, for those who are still alive. Time to progression was calculated from the date of randomisation to the date disease first progressed (or date of death if date of relapse was not known) for patients who relapsed, and from randomisation to the censor date for those who are still alive and relapse free. A chi-squared statistic to test for an association between response and treatment was calculated using Cochran's method for related 2×2 tables to combine the results from several similar studies [6].

RESULTS

Patients

139 eligible patients were randomised, 72 to receive megestrol acetate first and 67 to take tamoxifen first. 2 patients were excluded from this analysis, 1 from the megestrol acetate group (premenopausal status) and 1 from the tamoxifen group (no evaluable disease). By 31 December 1994, 131 patients had died, 1 patient in the tamoxifen group was lost to follow-up soon after randomisation and another in the megestrol acetate group was lost after 5.5 years on study. The remaining 4 patients were followed-up for at least 6 years.

The characteristics of eligible patients are shown in Table 1. The age, performance status, time since diagnosis, and distribution of disease sites were similar in the two treatment arms. ER status of the primary tumour was known in only 10 cases.

Response to first-line treatment

Response status was unknown for 6 patients, while 3 did not receive the allocated treatment (2 died before treatment, 1 refused treatment). Response was therefore measured on 128 patients (63 in the megestrol acetate group, 65 in the tamoxifen group; Table 2). Complete or partial response occurred in 18 of 71 patients randomised to receive megestrol acetate (25%) and in 22 of 66 receiving tamoxifen (33%) and showed no significant difference between the treatments ($P = 0.30$). The 95% confidence interval (CI) for this difference is wide, indicating that the response rate on megestrol acetate could be between 23% lower and 7%

Table 1. Patients' characteristics (n = 137)

	Megestrol acetate ($n = 71$)	Tamoxifen ($n = 66$)
Age (years)		
<55	14	9
55–65	22	24
66–75	18	20
>75	15	12
Unknown	2	1
Median age (years)	65	65
Sites of dominant disease		
Primary tumour	24	31
Local recurrence	5	3
Nodal disease	9	9
Lung metastases	13	8
Bone metastases	12	11
Other	8	4
WHO performance status		
Grade 0	26	24
Grade 1	26	22
Grade 2	12	13
Unknown	7	7
Prior treatment		
Surgery	49	37
Radiotherapy	27	18
Adjuvant chemotherapy	3	2

Table 2. Response to first-line hormonal therapy in all randomised patients (n = 137)

	Megestrol acetate (%) ($n = 71$)	Tamoxifen (%) ($n = 66$)	Total (%) ($n = 137$)
CR and PR	18 (25%)	22 (33%)	40 (29%)
(95% confidence interval)	(15%, 35%)	(22%, 44%)	
Stable (for >3 months)	28 (39%)	24 (36%)	52 (38%)
Progression	17 (24%)	19 (29%)	36 (26%)
Unknown	5 (7%)	1 (2%)	6 (4%)
Treatment not given (2 early deaths, 1 refusal)	3 (4%)	–	3 (2%)

higher than the response rate on tamoxifen. Including patients showing stable disease for more than 3 months, response was seen in 46 patients (65%) randomised to megestrol acetate and in 46 (70%) randomised to tamoxifen. Again, the difference between the response rates was not significant ($P = 0.54$, 95% CI [−21, 11]%). In patients achieving a complete or partial response, the median duration of response was 9 months (range 3–60) in the megestrol acetate group and 14 months (range 2–46) in the tamoxifen group.

Response to cross-over treatment

76 patients progressing on first-line treatment were crossed over to the alternative treatment. Response status is known for 71 of these (Table 3). 6 of 41 patients (15%) progressing on megestrol acetate showed a complete or partial response to second-line tamoxifen. Including patients showing stable disease for more than 3 months, 21 (51%) showed a response. Similarly, 3 of 35 patients (9%) progressing on tamoxifen showed a complete or partial response to second-line megestrol acetate with 13 (37%) showing no progression for at least 3 months. Overall, the median duration of response on cross-over therapy was 12 months (range 6–29) for the 9 patients achieving a complete or partial response. 1 patient who first received tamoxifen achieved a complete response on both therapies and 2 patients, 1 from each treatment group, had disease which was progressing on their first treatment and showed no further progression for 6 and 9 months, respectively, after crossing to second-line treatment. The second-line response rate for those who responded to first-line treatment was not significantly different from those who did not respond to first-line therapy (18 versus 9%, $P = 0.27$, Table 4) suggesting that patients who respond (CR/PR) to first-line therapy are not more likely to benefit from second-line therapy than those who did not.

Survival

Overall survival of the two groups is shown in Figure 1. Median survival was 2 years with 5-year survival of 16% (95% CI [10, 22]%), and there was no significant difference between the groups (chi square statistic = 1.90, $P = 0.17$). with median survival of 24 and 32 months for the megestrol acetate and tamoxifen groups, respectively.

Time to treatment failure

Median time to treatment failure (progression, relapse, withdrawal or death) was 9 months for those taking megestrol acetate first and 12 months for those taking tamoxifen first, again with no significant difference between the groups (chi square statistic = 1.68, $P = 0.19$).

Toxicity

Although the toxicity profile of these drugs did differ in both incidence and severity, both treatments were generally well tolerated. However, there was one death possibly attributable to treatment; a patient taking megestrol acetate suffered a pulmonary embolism. Toxicity was more commonly reported by patients taking megestrol acetate with severe/very severe toxicity being recorded in 5 patients (Table 5). In comparison, only 1 case of severe toxicity (weight gain) was reported by patients taking tamoxifen. The commonest side-effects from megestrol acetate were fluid retention, sedation, hyperglycaemia and weight gain and for tamoxifen were hot flushes and nausea (Table 5). As the majority of patients reported toxicity on only one treatment, there is insufficient data to determine whether a patient experiencing toxicity on one drug was likely to also experience toxicity on the other.

Pooled response data

Using Cochran's method to pool the response data for the studies detailed in Table 6 suggested no significant difference between the treatments in terms of response to first-line therapy (chi square statistic = 0.857, $P = 0.35$). This analysis was not repeated for response to second-line treatment because such pooling was invalid in view of the diversity of results from these trials.

Table 3. Response to second-line hormonal therapy in cross-over patients (n = 76)

	Megestrol acetate (%) ($n = 35$)	Tamoxifen (%) ($n = 41$)	Total (%) ($n = 76$)
CR and PR	3 (9%)	6 (15%)	9 (12%)
(95% confidence interval)	(0%, 18%)	(4%, 26%)	
Stable (for >3 months)	10 (29%)	15 (37%)	25 (33%)
Progression	20 (57%)	17 (41%)	37 (49%)
Unknown	2 (6%)	3 (7%)	5 (7%)

Table 4. Response to first- and second-line hormonal therapy in cross-over patients (n = 76)

First-line treatment	Second-line treatment				
	CR and PR	Stable (for >3 months)	No response	Unknown	Total
CR and PR	4	10	6	2	22
Stable (for >3 months)	5	13	16	1	35
No response	0	2	15	2	19
Total	9	25	37	5	76

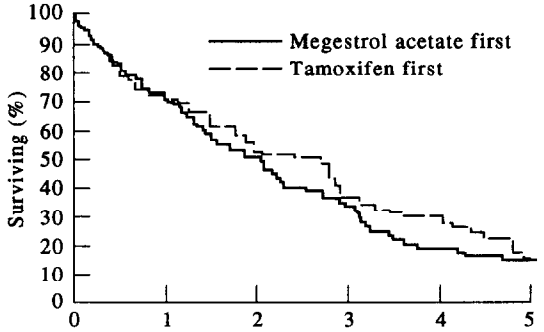
Table 5. Reported incidence of toxicity irrespective of whether given first- or second-line (n = 70)

	Megestrol acetate (*n* = 42)		Tamoxifen (*n* = 28)	
	Mild or moderate	Severe or very severe	Mild or moderate	Severe or very severe
Oedema	9	2	2	–
Sedation	9	–	5	–
Hyperglycaemia	3	1	–	–
Weight gain	4	1	–	1
Hot flushes	1	–	8	–
Nocturia	–	1	–	–
Nausea	1	–	7	–
Vaginal bleeding	1	–	2	–
Other toxic events*	Dry skin, dyspnoea dizziness, hypertension, shortness of breath headaches, congestive cardiac failure, insomnia, pulmonary oedema	–	Dyspnoea, weight loss, anorexia	–
Total	37	5	27	1

* Each occurring in 1 patient

DISCUSSION

Hormone therapy plays a major part in the management of advanced breast cancer. In phase II studies, antioestrogens (e.g. tamoxifen), synthetic progestogens (e.g. megestrol acetate) and aromatase inhibitors (e.g. aminoglutethimide) all show response rates of around 30–40%. Although these treatments have been available for many years, few comparative studies have been published.



Number at risk:						
Tamoxifen	66	45	35	24	20	11
Megestrol acetate	71	51	36	24	14	11

Figure 1. Survival by treatment.

There are also few data on the optimal order in which to give these treatments; information which can only be obtained from cross-over studies.

If the planned recruitment had been achieved, this study would have had an approximately 80% chance of demonstrating that megestrol acetate is of similar efficacy to tamoxifen in these patients, assuming a response rate of 25–35% on either treatment, a significance level of 5% and that a difference in response rates of less than 15% would indicate equivalence. Current clinical opinion would probably require that this difference in response rates was less than 5% before a clinically significant difference could be ruled out. This would require a study with in excess of 1000 patients in each treatment arm which, given the recent changes in clinical practice and consequent shortage of eligible patients, is unlikely to ever be carried out. However, four other small studies have been published [7–10] comparing megestrol acetate with tamoxifen and the response data from these have been combined with the current study in Table 6 to give a total of 543 evaluable patients, with an overall response rate for tamoxifen of 33% and for megestrol acetate of 29%. The response rates for tamoxifen (31–36%) and megestrol acetate (29–34%) first-line were very similar in three [8–10] of these studies with one, Ingle and coworkers [7], reporting a large difference in response rates (tamoxifen 26% versus megestrol acetate 14%) which was not statistically significant. The confidence intervals for the response rates in each of these studies was very wide and

Table 6. Summary of studies comparing tamoxifen with megestrol acetate

[Ref.]	Tamoxifen 1st line	Megestrol acetate 1st line
[7]*	7/27 (26%)	4/28 (14%)
[8]†	17/48 (35%)	14/46 (30%)
[10]	27/79 (34%)	26/77 (34%)
[9]	17/54 (31%)	16/56 (29%)
Current study	22/65 (34%)	18/63 (29%)
Total	90/273 (33%)	78/270 (29%)

* Only assessed perimenopausal or castrated women.
† Interim results only.

none can provide a robust estimate of the response rates for these two treatments nor validly conclude that there is no clinically significant difference between the treatments. Combining the first-line response data from these trials also fails to show a statistically significantly difference between the treatments. The exact power of Cochran's test is difficult to calculate, but since the pooled sample size is still very small (relative to the 2000 plus patients needed in a single trial to prove the optimum order of the treatments) it seems reasonable to conclude that a clinically significant difference can still not be ruled out.

When assessed as second-line therapy, the reports are very mixed. Morgan and colleagues [8] reported no response (0/12) to second-line tamoxifen compared with 17% (4/24) to megestrol acetate second-line, and, although no statistically significant difference was found, concluded that tamoxifen is less effective when used as second-line treatment. This view is supported by Rose and Mouridsen in their review of hormone therapy in advanced breast cancer [1], although this was based on cross-over data to synthetic progestogen therapy in only 22 hormone responsive patients. Most recently, Paterson and colleagues [10] have reported the largest randomised comparison of megestrol acetate and tamoxifen and have reached the opposite conclusion. No responses (0/33) were seen in patients taking megestrol acetate after progressing on tamoxifen while 25% (10/40) responded to tamoxifen after progression on megestrol acetate. This variability is not surprising given that, in each of these studies, a large proportion of patients failed to reach cross-over so that second-line response rates are based on small subgroups of patients. It is also difficult to ensure the comparison of these groups is unbiased because, although second-line hormonal therapy is randomly allocated, the decision whether to proceed with this therapy is not. Based on the above results, the assertion that megestrol acetate should be reserved for second-line use does not appear to be justified.

Another important aspect of endocrine therapy is its toxicity profile. Although most hormone therapies are well tolerated, treatment may be continued for several months during which even mild/moderate toxicities may lead to the impairment of a patient's quality of life. Ingle and coworkers [7] give few data on toxicity but comment that nausea was more comon in patients receiving tamoxifen and affected 30% of patients. Muss and coworkers also give few toxicity data but confirmed that nausea affected approximately a third of patients treated with tamoxifen, but surprisingly no data on weight gain was reported [9]. Conversely, Morgan and colleagues [8] reported that weight gain affected the majority of patients (30/46, 65%) on megestrol acetate, but made no comment on nausea. They also showed that vaginal bleeding was more comon during tamoxifen treatment. Paterson and coworkers [10] reported toxicity in most detail and showed no significant difference in the common side-effects. Hot flushes were, however, more common with tamoxifen and weight gain more common following megestrol acetate. Our study reports a similar pattern, with weight gain more common during treatment with megestrol acetate and nausea and hot flushes more common during tamoxifen. The relevance of these side-effects depends on their severity and on the views of individual patients.

This study has compared megestrol acetate and tamoxifen as hormone therapy for postmenopausal women with advanced breast cancer. It has shown no statistically significant difference between the agents with regard to response rate, response duration or survival. The study is, however, small and does not have the power to exclude a clinically significant difference. Although previous reports have shown conflicting data, particularly with regard to second-line responses, pooled response data suggest the two treatments have broadly similar activity. The toxicity profile of the two drugs is different, but both are generally well tolerated and neither is clearly preferable. For patients who relapse while receiving adjuvant tamoxifen, megestrol acetate would seem a reasonable second-line hormone therapy. For patients who are hormone-therapy naive, either treatment would be appropriate and the choice may depend on patient tolerance.

1. Rose C, Mouridsen HT. Endocrine therapy of advanced breast cancer. *Acta Oncol* 1988, **27**, 721–728.
2. Willemse PH, van Ploeg dPE, Sleijfer DT, Tjabbes T. A randomized comparison of megestrol acetate (NMA) and medroxyprogesterone acetate (NMPA) in patients with advanced breast cancer. *Eur Cancer* 1990, **26**, 337–343.
3. Gregory EJ, Cohen SC, Oines DW. Megestrol acetate therapy for advanced breast cancer. *J Clin Oncol* 1985, **3**, 155–160.
4. Lundgren S. Progestins in breast cancer treatment. A review. *Acta Oncologica* 1992, **31**, 709–722.
5. Kalbfleisch JD, Prentice FL. *The Statistical Analysis of Failure Time Data*. New York, John Wiley & Son, 1980.
6. Cochran WG. Some methods for strengthening the common χ^2 tests. *Biometrics* 1954, **10**, 417–420.
7. Ingle JN, Cregan ET, Ahmann DL, *et al.* Randomized clinical trials of megestrol acetate versus tamoxifen in paramenopausal or castrated women with advanced breast cancer. *Am J Clin Oncol* 1982, **5**, 155–160.
8. Morgan L. Megestrol acetate v tamoxifen in advanced breast cancer in postmenopausal patients. *Semin Oncol* 1985, **12**, 43–47.
9. Muss HB, Pascold EH, Black WR, *et al.* Megestrol acetate v tamoxifen in advanced breast cancer: a Phase III trial of the Pidmont Oncology Association (POA). *Semin Oncol* 1985, **12** (Suppl. 1), 55–61.
10. Paterson AHG, Hanson J, Pritchard KI, *et al.* Comparison of antiestrogen and progestogen therapy for initial treatment and consequences of their combination for second-line treatment of breast cancer. *Semin Oncol* 1990, **17** (Suppl. 9), 52–62.

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