Original article

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Intramuscular depot medroxyprogesterone versus oral megestrol for the control of postmenopausal hot flashes in breast cancer patients: a randomized study

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Background: Hot flashes are frequent in postmenopausal breast cancer patients, especially when treated with tamoxifen. Estrogen replacement therapy is the most effective treatment for hot flashes, but its use is controversial in breast cancer survivors. Progestins may offer a good alternative for the control of hot flashes in this setting; in particular, oral megestrol acetate has been proven effective in a randomized, placebo-controlled clinical trial. With the aim of further improving these results, we have designed a randomized study comparing oral megestrol acetate with depot intramuscular (i.m.) medroxyprogesterone acetate (MPA) for the control of hot flashes in postmenopausal patients with a history of breast cancer.

Patients and methods: Seventy-one postmenopausal patients were randomized to receive an i.m. injection of depot MPA 500 mg on days 1, 14 and 28, or oral megestrol acetate 40 mg daily for 6 weeks. Patients recorded daily the number and severity of their hot flashes; response was defined as a ≥50% decrease in the number and severity of hot flashes.

Results: At week 6, hot flashes were reduced by 86% on average in the whole group of patients, without significant differences between the two progestins. Response was obtained by 75 and 67% of patients receiving MPA or megestrol, respectively ($P = 0.5$). Responders were followed to assess maintenance of response (without further treatment), which was significantly better with i.m. MPA: in this group, 89% of responders still showed a benefit at week 24, compared with 45% in the megestrol group ($P = 0.03$).

Conclusions: Our study shows that a short cycle of i.m. depot MPA injections provides significant and long-lasting relief from postmenopausal hot flashes in patients with a history of breast cancer, offering an alternative to estrogen replacement therapy or prolonged administration of oral megestrol.

Key words: breast cancer, hot flashes, medroxyprogesterone acetate, megestrol acetate, postmenopausal symptoms, tamoxifen

Introduction

Hot flashes are among the most frequently reported sequelae in breast cancer survivors; their incidence ranges from 55 to 65% in recent surveys [1, 2]. In one study the overall prevalence of hot flashes in breast cancer patients was 65%; 44% of patients reported their hot flashes as 'severely bothersome', and 63% expressed an interest in learning about management strategies [3]. Treatment with the antiestrogen tamoxifen was associated with increased severity and higher prevalence (78%) of hot flashes.

Estrogen replacement therapy is considered the most effective treatment for postmenopausal hot flashes; however, the prescription of estrogens in breast cancer survivors is avoided by many clinicians because of a theoretical increased risk of relapse associated with their use.

The administration of progestational agents is a possible alternative to estrogens, offering good control of hot flashes in most patients. In a placebo-controlled, double-blind randomized study, megestrol acetate reduced hot flashes by 85% in a group of breast and prostate cancer patients when administered at a dose of 40 mg/day orally for 4 weeks [4]. The study

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did not evaluate the duration of response obtained with megestrol acetate; however, the results of a follow-up investigation showed that some patients chose to keep on taking this medication for up to 3 years [5]. This may be interpreted as indirect evidence that long-term treatment with megestrol is necessary to maintain the initial benefit.

Another progestin, medroxyprogesterone acetate (MPA), has been in use for many years for the treatment of hot flashes in healthy postmenopausal women [6]. Intramuscular administration of a depot formulation of MPA has been shown to be effective against hot flashes in randomized, placebo-controlled studies [7, 8]. An interesting characteristic of depot MPA is its long duration of action, due to the fact that progestin is released slowly from the muscle after the injection [9]. In our experience, some breast cancer patients benefit from a dramatic and prolonged reduction of their hot flashes after a short initial cycle of depot MPA injections. Based on these encouraging observations, we designed a randomized trial to compare this treatment modality with oral megestrol acetate in a group of breast cancer survivors.

Patients and methods

Eligible patients were postmenopausal women with a history of breast cancer and no evidence of relapse, who had been suffering with bothersome hot flashes for at least 1 month before entry into the study. Hot flashes were defined as 'bothersome' if they occurred at least seven times per week and were sufficiently severe that the patient asked for therapeutic intervention. Postmenopausal status was defined as an absence of regular menses for ≥6 months in patients with an intact uterus; patients with previous hysterectomy but no bilateral oophorectomy were considered postmenopausal if plasma follicle-stimulating hormone, leutinizing hormone and estradiol were in the postmenopausal range. No concurrent or planned treatment with estrogens, androgens, progestins, corticosteroids, clonidine, veralipride or ciclophenile was allowed; patients who had received adjuvant chemotherapy had to have concluded treatment for ≥2 months. Concurrent adjuvant tamoxifen 20 mg/day was allowed if started at least 1 month before entry in to the study and if the planned residual duration of treatment was at least 6 months. Written informed consent was obtained from all patients.

Patients were randomized to one of two groups: group 1 received intramuscular (i.m.) depot MPA (500 mg i.m. on days 1, 14 and 28); group 2 received oral megestrol acetate (40 mg p.o. once daily from day 1 to day 42). Treatment allocation was not double blinded because this would have required the administration of i.m. placebo in group 2, which was judged impractical.

The frequency and severity of hot flashes in the participating patients were monitored through a self-compiled diary, which was started 7 days before the beginning of treatment (to provide baseline data) and continued for 6 weeks thereafter. The diary had columns for each day of the week and rows labeled 'mild', 'moderate', 'severe' and 'very severe'. Patients were asked to record every day the number of hot flashes that they had suffered and their severity, assigning them to one of the four grades detailed above. Choice of grade was subjective—no definition of mild, severe or very severe was given to the patients, who were only asked to be consistent over the duration of the study. At the end of each week, patients were also asked to record in their diary all postmenopausal symptoms, other than hot flashes, or side effects of therapy encountered during the last 7 days. Patients could choose items from a list which included insomnia, fatigue, mood instability, vaginal discharge, dizziness, appetite increase, appetite decrease, dry mouth and fluid retention.

Three main efficacy parameters were evaluated at the end of the sixth week from the start of treatment (i.e. after 6 weeks of daily oral treatment with megestrol acetate or 2 weeks after the last of three i.m. injections of depot MPA), using the average values recorded for that week in comparison to baseline values calculated during the initial week with no treatment. For each group, changes in average number of hot flashes per day and average daily hot-flash score were analyzed using values recorded in the first week (with no treatment) as a baseline. The average daily hot-flash score for each patient was calculated by adding the number of mild hot flashes plus twice the number of moderate hot flashes plus three times the number of severe hot flashes plus four times the number of very severe hot flashes in a week, and then dividing the sum by seven. The third parameter was the proportion of patients who obtained a ≥50% reduction in the frequency of hot flashes and hot-flash score, as compared with baseline values. This value was arbitrarily chosen as a threshold for a clinically significant result, and was used to define 'responding' patients. All patients who achieved a <50% reduction, or who did not complete the treatment for any reason, including side effects or refusal, were defined as treatment failures and withdrawn from the study. Off-study patients, who returned for their normal clinical follow-up, were only asked to report late side effects of treatment such as withdrawal bleeding. Responding patients were asked to continue their diaries for up to a total of 24 weeks from the start of treatment. No maintenance treatment was given in responding patients, who were visited at 2-monthly intervals. When hot flash frequency or score returned to >50% of baseline values, the patient was considered to have lost the initial response and was withdrawn from the study.

Statistical analysis

The primary end point of the study was the proportion of responding patients 6 weeks after the planned start of treatment (7 weeks after randomization). A patient was classified as a responder if she achieved a ≥50% reduction in the frequency of hot flashes and hot-flash score. Sample size was calculated assuming a proportion of responders in group 2 (receiving megestrol acetate) of 70%, and that the treatment with MPA was associated with a 25% absolute increase in the proportion of responders (from 70 to 95%). For an 80% power and a two-sided 5% significance, 90 subjects were planned to detect such a difference. The study was stopped after 71 patients had been randomized over a period of 2 years because of difficulties encountered during patient enrollment.

The proportion of responders was compared by means of the chi-square test [10]. Confidence limits for proportions were estimated according to Fleiss [10].

Results

From June 1996 to June 1998, a total of 71 breast cancer patients were randomized to group 1 (i.m. MPA; $n = 37$) or group 2 (oral megestrol acetate; $n = 34$). As can be seen from Table 1, which summarizes the main characteristics of patients in the two groups, the majority of patients in the study were receiving adjuvant tamoxifen ($n = 52$, 73.2%). The median duration of tamoxifen treatment was 10 months (range 1–43);

Table 1. Patients characteristics

	Medroxyprogesterone (group 1; *n* = 37)	Megestrol (group 2; *n* = 34)
Age (years)		
Median (range)	51 (40–67)	53 (42–72)
Months since last period		
Median (range)	21 (1–195)	24 (6–199)
Previous adjuvant chemotherapy		
No. of patients (%)	22 (59.4)	22 (64.7)
Chemotherapy-induced menopause		
No. of patients (%)	13 (35.1)	11 (32.3)
Months from end of chemotherapy		
Median (range)	11 (4–50)	15 (2–66)
Tamoxifen use		
No. of patients (%)	27 (73.0)	25 (73.5)
Months of tamoxifen use		
Median (range)	10 (2–43)	11 (1–39)
Patients on tamoxifen, who also had previous adjuvant chemotherapy		
No. of patients (% of tamoxifen users)	15 (48.4)	16 (51.6)
Months with hot flashes		
Median (range)	11.5 (1–189)	10.5 (1–199)
Months since breast cancer diagnosis		
Median (range)	14 (2–220)	17 (3–137)
Hot flashes number at baseline		
Daily average (mean ± SD)	8.8 ± 4.1	9.2 ± 6.3
Range	2–19	1–30
Hot flashes score at baseline		
Daily average (mean ± SD)	19.3 ± 10.6	20.8 ± 16.7
Range	4–44	2–71

although eligibility criteria allowed patients to be entered after 1 month of tamoxifen treatment, most patients (34 of 52, 65.4%) had been using tamoxifen for at least 6 months.

After randomization, five patients in each group refused to start the assigned treatment and withdrew from the study. Two more patients, both in group 1, were found to be ineligible after randomization (one for medical contraindications to progestin treatment, one not postmenopausal). Six patients did not provide complete diary recordings during treatment (five patients who dropped out before completion for side effects and one who was lost to follow-up).

Reduction of hot flashes

Figure 1 shows changes in the number of daily hot flashes and the daily hot-flash score calculated from diary recordings during the baseline week and the following 24 weeks. The curves are based on all available diary recordings, which were provided by 65 patients (91%) at baseline and 53 (75%) at week 6. The mean number of hot flashes and hot-flash score at baseline did not differ significantly between the two groups. At week 6, the mean number of hot flashes per day was 1.21 [95% confidence interval (CI) 0.65–1.77] in group 1 and 1.42 (95% CI 0.67–1.17) in group 2; the mean scores were 2.08 (range 1.04–3.12) and 2.34 (range 0.99–3.7), respectively. Differences between the two groups at week 6 were not statistically significant. To assess the relative reduction in the number of hot flashes and the hot-flash score between baseline and week 6, we considered the 53 patients who provided complete diary recordings at baseline and at week 6. Overall, the average daily number of hot flashes was reduced by 87.5 ± 16.7% (range 28.6–100) as compared with baseline values, and the average daily hot-flash score was reduced by 89.6 ± 17.1% (range 6.9–100). The differences between the two groups were not significant. Good control of hot flashes by both treatments is also apparent in the reduction of the frequency of

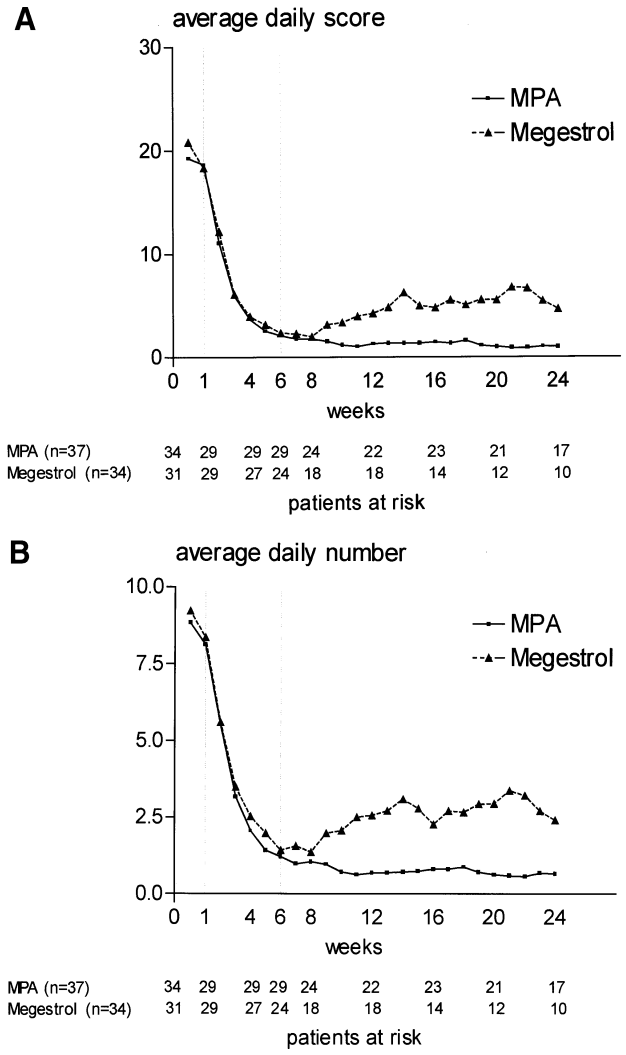

Figure 1. Changes in daily number of hot flashes (**A**) and hot-flash score (**B**) during treatment (first 6 weeks) and up to 24 weeks after randomization in the two treatment groups. The number of patients providing valid diary recordings for each time period is shown under the curves. MPA, medroxyprogesterone acetate.

related symptoms, such as insomnia, mood instability and fatigue, as compared with baseline values (Table 2).

Response rate

Response rate at the end of week 6 was evaluated according to an intention-to-treat criterion on the whole group of 71 randomized patients. Overall, 50 of 71 patients (70.4%; 95% CI 58–81%) achieved a response as previously defined, i.e. ≥50% reduction in hot flashes frequency and hot-flash score; this was often a complete response (total disappearance of hot flashes). Response distribution in the two treatment groups was as follows: 28 of 37 (75.7%; 95% CI 59% to 88%) in group 1, with nine of 37 (24.3%) treatment failures (seven never started for ineligibility or refusal, one was lost to follow

Table 2. Frequency of other menopausal symptoms

	No. of patients (%)	
	Medroxyprogesterone (group 1; n = 37)	Megestrol (group 2; n = 34)
At baseline		
Insomnia	20 (54.1)	18 (52.9)
Mood instability	17 (45.9)	18 (52.9)
Fatigue	18 (48.6)	15 (44.1)
End of treatment		
Insomnia	5 (13.5)	5 (14.7)
Mood instability	4 (10.8)	10 (29.4)
Fatigue	8 (21.6)	9 (26.4)

up and one had a <50% reduction) and 22 of 34 (64.7%; 95% CI 46% to 80%) in group 2, with 12 of 34 (24.3%) treatment failures (five never started for refusal, five stopped early because of side effects, and two had a <50% reduction). Responders in group 2 include one patient who had discontinued megestrol acetate before completion of treatment due to a skin rash, but provided complete recordings in her diary showing >50% reduction of hot flashes frequency and hot-flash score at the end of week 6. No significant difference between the proportion of responders between the two arms was observed (P = 0.567). Table 3 shows the distribution of responses in the two groups according to the number of hot flashes at baseline. The number of hot flashes at baseline was not significantly associated with the proportion of responses (P = 0.188).

Response duration

Maintenance of response in the group of 50 initial responders was assessed at 2-monthly follow-up visits, for 6 months after randomization. However, due to a reduction in the number of patients filling in their diaries during this part of the study, complete diary data were not available for 25 (50%) patients. In these patients, the duration of benefit was assessed by asking, at each visit, whether they thought the initial treatment benefit was still present. When this was not the case, the patient was considered as having lost her response and was withdrawn from the study. We had found during the first part of the study that the correlation between the overall judgement of benefit from treatment, given by patients and their diary recordings was good. Taking into account these limits, a difference between the maintenance of response with MPA and megestrol was observed. Out of 28 responding patients in the MPA group, 25 (89.3%) were still responding at 6 months from randomization. In the megestrol group, only 10 of 22 initial responders (45.4%) were still in response after 6 months. In this latter group, moreover, it was found that four patients had continued to use megestrol tablets, up to a

Table 3. Reduction of hot flashes after 6 weeks, according to the number or hot flashes at baseline, in the two groups

Average number of daily hot flashes at baseline[a]	Number (%) of patients with≥50% reduction of hot flashes	
	Medroxyprogesterone (group 1)	Megestrol (group 2)
1–3	3/4 (75.0)	1/5 (20.0)
4–9	12/17 (70.6)	11/14 (78.6)
≥10	13/13 (100)	10/12 (83.3)

[a]Data not available in six patients.

maximum of 3 months in one patient and 6 months in three patients. None of the patients randomized to MPA received additional injections after the three initial ones. The difference in response maintenance at 6 months after randomization is significantly in favor of MPA, even without removing the four protocol violators from the megestrol group ($P = 0.03$).

Tolerability

Although the treatment in both arms was generally well tolerated, more patients in the megestrol group experienced adverse effects, which in six women (16.6%) led to early discontinuation of therapy (no patient in the MPA group interrupted treatment). Reasons for interruption were skin rashes in two patients (5.9%), dyspnoea in two patients (5.9%), gastric pain in one patient (2.9%) and increased arterial blood pressure in one patient (2.9%). Table 4 shows the other side effects reported during treatment. Withdrawal bleeding after the end of treatment was experienced by two patients (5.4%) in the MPA group and seven (18.9%) in the megestrol group.

Discussion

The management of hot flashes in postmenopausal women with a history of breast cancer is an important part of clinical practice in oncology, especially considering the increasing number of patients who receive adjuvant treatments and have a long life expectancy. Hot flashes may be associated with premature menopause induced by chemotherapy; moreover, they are the most common side effect of treatment with tamoxifen. Since estrogen replacement therapy is usually avoided in women with a history of breast cancer, patients should be informed of the possible alternatives. Among non-hormonal remedies, clonidine [11], vitamin E [12] and soy phytoestrogens [13] have shown either limited or no benefit in placebo-controlled trials. Until recently, the only treatment with proven benefit in this setting was the progestational agent megestrol acetate, which at the dose of 40 mg/day p.o. was superior to placebo in a randomized, double-blind study [4]. Some of the women obtaining control of their hot flashes with megestrol may choose to continue the treatment at a low dose for years, in order to maintain the initial benefit [5]. Although there are no definitive data on the safety of progestin use in women with a history of breast cancer, concerns about its prolonged use may limit the prescription of megestrol acetate for hot flashes.

Table 4. Reported adverse effects during treatment

	No. of patients (%)	
	Medroxyprogesterone (group 1; $n = 37$)	Megestrol (group 2; $n = 34$)
Appetite change		
Increase	3 (8.1)	9 (26.5)
Decrease	7 (18.9)	3 (8.8)
Fluid retention	3 (8.1)	6 (17.6)
Dizziness	5 (13.5)	8 (23.5)
Vaginal discharge	10 (27.0)	9 (26.5)
Dry mouth	12 (32.4)	16 (47.0)

Another progestational agent, MPA, has been in use for some years in healthy postmenopausal women with hot flashes; oral and parenteral formulations have been evaluated in controlled clinical trials [6–8]. To our knowledge, our study is the first were depot i.m. MPA was used for hot flashes in breast cancer survivors, many of whom were concurrently receiving the antiestrogen tamoxifen. Dosages and schedule of MPA in this study were based on previous empirical observations of long-term relief of hot flashes after a short cycle of i.m. injections in some of our patients. Although no definitive conclusions can be drawn from the comparison with oral megestrol, due to the small number of patients recruited and the difficulty in obtaining valid diary recordings from all subjects during treatment and follow-up, our results suggest that depot MPA can be expected to abrogate or substantially reduce hot flashes in most breast cancer patients. Moreover, nearly 90% of patients responding to MPA in our study maintained the initial benefits of treatment for 6 months without further treatment. Thus, when considering progestin therapy for the control of hot flashes in breast cancer survivors, depot MPA can be regarded as a reasonable treatment option. Occasionally a patient does not respond to progestins; in this case,

other treatments should be offered with the aim of obtaining satisfactory control of the symptom. Encouraging results have recently been reported with low-dose antidepressants, such as paroxetine [14] and venlafaxine [15], suggesting that they may play an important role in this field.

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