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Original Paper

Megestrol Acetate in Advanced, Progressive, Hormone-insensitive Cancer. Effects on the Quality of Life: a Placebo-controlled, Randomised, Multicentre Trial*

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A randomised double-blind placebo-controlled multicentre trial was performed to investigate the effects of megestrol acetate (MA) on the quality of life (QoL), appetite, weight and survival of patients with advanced, incurable, hormone-insensitive cancer. QoL was assessed at the start of treatment and at 4, 8 and 12 weeks, using the EORTC-QLQ-C30 instrument. 255 patients were randomised to 320 mg of MA daily or placebo for 12 weeks. 244 patients were assessable at baseline, 190 at 4 weeks (placebo 94; MA 96), 150 at 8 weeks (placebo 69; MA 81) and 112 at 12 weeks (placebo 55; MA 57). A beneficial effect of MA on appetite loss was observed at week 4 ($P < 0.0001$) and possibly at week 8 ($P = 0.058$). Further weight loss during treatment was significant only in the placebo group. In the first 8 weeks, changes in mean global QoL were small and similar in both groups. By 12 weeks the decrease in mean global QoL was more pronounced in the MA group ($P = 0.028$), which was related to a deterioration in physical function, while psychosocial function was not affected. Survival was not affected by MA, and side-effects were mild. The results show that MA has a beneficial effect on appetite and that it may retard weight loss with no adverse impact on survival and with mild toxicity. However, MA does not appear to improve global QoL as measured by the EORTC QLQ-C30. © **1999 Published by Elsevier Science Ltd. All rights reserved.**

Key words: quality of life, advanced cancer, megestrol acetate
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INTRODUCTION

CACHEXIA AND weight loss [1, 2] are important factors contributing to the impaired quality of life of cancer patients, and more than 50% of cancer patients have cachexia at death [3, 4]. In several controlled studies, treatment with corticosteroids resulted in an improvement in symptoms and the quality of life [5–8]. Cyproheptadine has a mild stimulating effect on appetite [9], and metoclopramide is useful in patients with delayed gastric emptying [10]. Other treatments have not been successful [11–13].

Megestrol acetate (MA) and medroxyprogesterone acetate often cause weight gain as a side-effect in the endocrine treatment of advanced breast cancer [14] and prostate cancer

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[15]. Thus, MA has been tried as a treatment for cancer-related cachexia/anorexia, and uncontrolled studies [16, 17] have shown that this treatment resulted in an increase in appetite and weight.

In an early controlled study, Bruera and associates [18] randomised 40 patients in a double-blind cross-over trial to 480 mg of MA a day versus placebo for 7 days. Appetite, subjective energy level, triceps skinfold measurement and calf circumference improved significantly on treatment with MA. Loprinzi and associates [19] randomised 133 patients into a group treated with 800 mg of MA a day or a group on placebo. Patients assigned to the MA group reported improved appetite and food intake more often. A weight gain of 15 lb or more above the baseline was found in 16% of patients on MA compared with 2% in the placebo group.

To investigate the effects of MA on the quality of life (QoL), appetite, weight and survival, we conducted a double-blind, randomised, multicentre placebo-controlled trial of MA in patients with advanced-stage, incurable, progressive, hormone-insensitive cancer. The primary end-point for the study was QoL. Secondary end-points were survival, weight and side-effects. General aims were to collect data on QoL and study the performance of the QoL instrument.

PATIENTS AND METHODS

Protocol

Patients were included in the trial if the stage of disease was such that no further curative treatment with surgery, radiotherapy, chemotherapy or other medical cancer therapy was indicated. However, palliative treatment including palliative chemo- or radiotherapy was acceptable. The disease had to be in a progressive, symptomatic stage, preferably (although not necessarily) with a history of established anorexia and/or weight loss. The attending clinician had to decide whether pharmacological therapy, for the purpose of improving the patient's QoL, was warranted. Other eligibility criteria were: age more than 18 years; a histological/cytological diagnosis of one of the following types of cancer: lung (small cell or non-small cell), head–neck, oesophagus, gastric, pancreatic, colorectal, biliary, primary hepatic, renal, malignant melanoma, soft tissue sarcoma, hormone-resistant breast and prostate cancer, ovarian, or cervical cancer; an anticipated survival of at least 3 months; a performance status of 0–3 according to the World Health Organization (WHO); and informed patient consent. The exclusion criteria were: hormone-sensitive tumour; treatment with corticosteroids (except as anti-emetics during palliative chemotherapy); curative chemotherapy or radiotherapy; myocardial infarction, deep venous thrombosis or a cerebrovascular lesion less than 6 months old; uncontrolled hypertension or cardiac insufficiency; intolerance of oral treatment; mental or psychiatric infirmity, making QoL assessment impossible. Patients with cancer of the prostate or the breast could be included if tumour progression occurred during endocrine treatment and further such treatment was considered ineffective.

The patients were checked at baseline and at appointments at weeks 4, 8 and 12 with a physical examination, determinations of weight and performance, routine laboratory tests (haematology, electrolytes, renal and hepatic function), determination of the prevalence of chemotherapy or radiotherapy (in the past 4 weeks), prevalence of morphine analgesics, and the extent of in-patient hospital care (number of days in the past 4 weeks). In addition, compliance with the studied treatment, the use of steroids, the prevalence of pleurocentesis/laparocentesis and toxicity were monitored as was the reason for patient refusal or inability to continue the treatment.

Treatment

Eligible patients were stratified by diagnosis and participating centre (the number of centres was 15) and randomised to receive 320 mg of megestrol acetate (Megace®, Bristol-Myers-Squibb, Bromma, Sweden) per day (160 mg twice daily) or placebo. The intended duration of treatment was 12 weeks. However, treatment could be discontinued earlier if the general condition of a patient deteriorated to such a degree that further ('experimental') treatment was deemed inappropriate or impossible, or if serious adverse events occurred. Randomisation was carried out by a telephone call to the secretariate of the co-ordinating centre. Randomly permuted blocks of four were used for generating the randomisation lists. The patients were given tablets containing MA or placebo of the same shape, size, appearance, colour and taste. The code was kept at the hospital pharmacies and could only be broken in case of a serious adverse event. The individual codes were kept secret for all the participants, all clinicians, and the monitors until the study had been closed and all outcome data had been checked and computerised. Treatment compliance was assessed by pill counting at each visit.

Quality of life (QoL)

Quality of life was assessed with the Swedish version of the European Organization for Research and Treatment of Cancer (EORTC) Core Quality-of-Life Questionnaire (EORTC QLQ-C30, version 1) [20]. For purposes specific to the study, three supplementary items were added to the EORTC QoL instrument. Two of the items measured symptoms that could be experienced as side-effects (i.e. sweating and gastrointestinal symptoms such as borborygmi or dyspepsia) of the studied treatment, and one measured the positive range of appetite (in contrast to loss of appetite). A 2-item measure of appetite loss was constructed by calculating the mean of the original QLQ-C30 item score and the reversed response score of the additional item on appetite. The intention was to use this 2-item scale as an outcome measure of appetite loss. QoL assessment was carried out at randomisation and following each 4-week period of treatment (i.e. at 4, 8 and 12 weeks). In the protocol, no further QoL assessment beyond discontinuation of the studied treatment was advocated. However, continuation of QoL assessment at scheduled intervals during the 12-week study period was recommended, even when the studied treatment was discontinued earlier, provided the patients' condition was judged to permit further assessments.

Sample size

The size of the trial was estimated in order to detect a clinically relevant group difference in the mean scores for the global QoL. The scheduled follow-up assessment of the quality of life at 8 weeks was selected for the primary evaluation of group differences. The magnitude of this difference was set at 0.5 standard deviation of the scale score [21], corresponding in this instance to 11 score points. In order to detect such a difference with a type I error (alpha) of 5% and a power of 80%, 65 evaluable patients in each treatment

group were needed. In order to compensate for anticipated patient attrition due to deterioration and death during the initial 8-week period, the number of included patients was increased to at least 120 in each treatment group.

Statistical methods

The internal consistency of the 2-item scale on appetite loss was evaluated with Cronbach's alpha coefficient [22]. An alpha coefficient of 0.7 or better was considered sufficient for group comparisons. The effect of treatment on change over time was evaluated in two ways. First a two-factor repeated measures analysis of variance (ANOVA) was employed, including treatment and possible confounders as independent factors in the model. Second, the numbers of patients in each treatment group who improved, deteriorated, or did not change with respect to QoL variables were compared in contingency tables, and analysed with the chi-square test. For this purpose, an improvement or deterioration was defined as a change of more than ten score points from baseline. Distribution of nominal variables in contingency tables was analysed with the chi-square test or Fisher's exact test where appropriate. The Kaplan–Meier method and logrank test were used [23] for analysis of survival. All *P*-values refer to two-sided tests. The statistical significance level was set at 5%. The trial was approved by the ethical committees at the participating centres (Örebro, Uppsala, Lund, and Göteborg), and by the Swedish Food and Drug Administration.

RESULTS

Participant flow and follow-up

Between May 1992 and November 1995, 255 patients from 15 clinics were included in the trial. Six clinics participated during the whole period and enrolled 131 patients. Three clinics joined the trial after the first year and enrolled 106 patients in 27 months. The remaining 18 patients were included by clinics which participated only for shorter periods of time. The flow of the participating patients with respect to study treatment and QoL assessments is shown in Figure 1.

Patient characteristics at baseline are presented in Table 1. The percentage of men was somewhat larger in the MA group ($P = 0.13$). The mean weight of all patients at baseline was 64.6 kg. The mean weight loss at the start of treatment was 6 kg, corresponding to 8.4% of the premorbid weight. Maximum weight loss was 32 kg, or 40% of the premorbid weight. Thirty-eight percent of the patients had had a weight loss exceeding 10%, whilst in 59 patients (24%) no weight loss was recorded before treatment start. The time elapsing between diagnosis and randomisation was significantly longer in the MA group ($P = 0.0043$). Thirty-three percent ($n = 84$) of the patients had been treated as in-patients at least one day during the 4 weeks preceding randomisation, 65% ($n = 166$) had not, and for 2% ($n = 5$) data were missing.

Quality of life

Mean scores for function and symptom measures at baseline are shown in Table 2. No major differences were found between the two study groups before the onset of treatment. In comparison with a relatively large sample of advanced lung cancer patients ($n = 305$) who were included in the original report on the EORTC QLQ-C30 [20], the patients in the present study reported more pronounced cancer-related symptoms, especially with regard to fatigue, appetite loss and pain, as well as worse physical and social functioning and global QoL, while emotional and cognitive functioning were comparable. 11 patients did not fill in the initial QoL form, including 2 patients who withdrew their consent and 2 patients who deteriorated quickly and died soon after randomisation. For 3 patients who subsequently completed one or more follow-up questionnaires, the initial forms were lost due to administrative error, and the reason is unclear in 4 cases. The alpha coefficient for the internal consistency of the 2-item scale for loss of appetite was 0.86, a figure that satisfied our requirements for group comparisons.

Follow-up assessments at 4, 8 and 12 weeks were carried out on 190 (placebo 94; MA 96), 150 (placebo 69; MA 81) and 112 (placebo 55; MA 57) patients, respectively. The change in QoL variables from baseline to follow-up was calculated for each of these subgroups of patients.

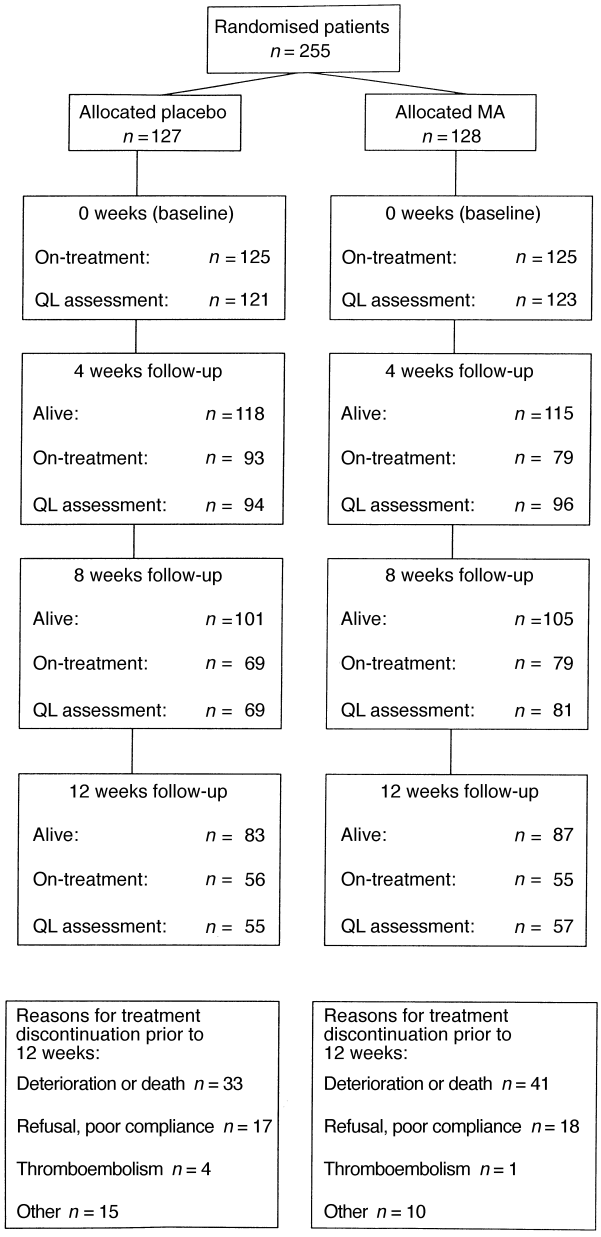

Figure 1. Flow chart of the progress of patients through the trial. Adapted from Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *J Am Med Assoc* 1996, 276, 637–639.

Mean scores for global QoL are shown in Figure 2. In the first 8 weeks there were no major differences between treatment groups with respect to global QoL ratings, and the mean scale score for the entire study population remained essentially unchanged. However, at 4 weeks an interaction was seen in a two-factor ANOVA model between pretreatment weight loss and treatment group ($P = 0.0031$), indicating that the subgroup of patients who had less than 10% weight loss and received MA reported improved QoL. In the final 4 weeks there was a reduction (i.e. deterioration) in the mean score for the subgroup of patients completing all four measurements ($P = 0.041$; repeated measures ANOVA). This reduction was numerically more pronounced in the MA group, although the interaction effect of treatment was significant only in the ANOVA analysis ($P = 0.028$) while a chi-square test of the distribution of patients across categories of change in health status (i.e. improvement, no change, or deterioration) did not show a significant difference between the treatment groups ($P = 0.22$). The interaction effect of treatment on global QoL at 12 weeks remained statistically significant in the ANOVA analysis after inclusion of potential confounders (i.e. the time from diagnosis, pretreatment weight loss, type of cancer, sex, age, performance status, or palliative chemotherapy during the last 4 weeks) in the model.

Table 1. *Baseline characteristics of randomised patients*

	Placebo ($n = 127$)	MA ($n = 128$)
Gender, proportion men	64 (50%)	77 (60%)
Age		
Median (range)	69 (37–85) years	71 (38–89) years
Performance status (WHO)		
0–1	56 (44%)	56 (44%)
2–3	71 (56%)	72 (56%)
Weight loss		
Mean weight loss	5.6 kg (8.1%)	6.3 kg (8.6%)
0% weight loss	31	28
0.1–10%	46	49
10.1–20%	38	40
20.1–30%	6	5
31.1–40%	2	3
Missing data	4	3
Primary tumour site, number		
Colorectal	41	40
Lung	38	36
Pancreas	9	7
Ovary	8	7
Mesothelioma	7	8
Hepatocellular	7	4
Melanoma	4	4
Biliary	3	4
Oesophagus	3	3
Gastric	2	3
Head and neck	1	3
Cervix uteri	2	3
Renal	2	1
Breast	0	2
Urinary bladder	0	2
Leiomyosarcoma	0	1
Lymphoma	0	1
Number of metastatic sites		
0	28 (22%)	23 (18%)
1	55 (43%)	58 (45%)
> 1	44 (35%)	47 (37%)
Time from diagnosis,		
Median (range)	200 (0–3132) days	346* (0–3871) days

*$P = 0.0043$. MA, megestrol acetate; WHO, World Health Organization.

Scale scores for the original QLQ-C30 measures of function during treatment and the change from baseline are shown in Table 3. In the 12 week period, a substantial reduction was noted, in the physical and role function scales, independent of treatment. In the first 4 weeks, mean emotional function scores tended to improve in both treatment groups, but the improvement was not found in subsequent follow-up assessments, and no significant interaction effect from treatment was seen. Changes in cognitive and social function were small and apparently independent of treatment.

There was a marked decrease in the mean score for appetite loss (i.e. an improvement in appetite) in the first 4 weeks (Figure 3). The improvement was significantly more pronounced in the MA group ($P = 0.0012$ for the interaction effect with ANOVA; $P = 0.0026$ with the chi-square test). The significant interaction effect of treatment on appetite loss at 4 weeks remained after inclusion of potential confounders, such as the time from diagnosis, type of cancer, sex, age, performance status, or palliative chemotherapy during the last 4 weeks) in the ANOVA model. At 8 and 12 weeks, the overall improvement from baseline remained, but group differences were smaller and non-significant ($P = 0.0058$ and $P = 0.19$, respectively, for the interaction effect by ANOVA).

Measures of symptoms other than appetite loss are shown in Table 4. For the patient group as a whole, fatigue increased, apparently independent of treatment, at 8 and 12 weeks. Scores for dyspnoea indicated increased symptoms at all follow-up measurements. The increase in reported dyspnoea was somewhat more pronounced in the MA group, but the interaction effect did not achieve statistical significance at any follow-up assessment. Sleep disturbance decreased from baseline to each of the follow-up assessments. At 4 weeks, treatment had an interaction effect in favour of the MA group, but this effect was not found in subsequent measurements.

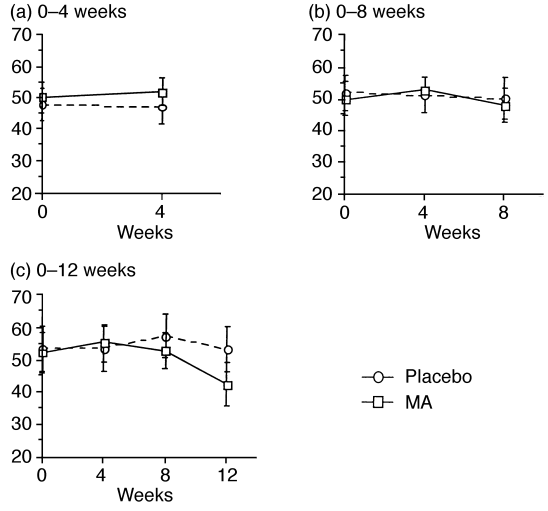

Figure 2. Mean scores for global quality of life at baseline and at (a) 4 weeks ($n = 186$; placebo 91, megestrol acetate (MA) 95); (b) 4 and 8 weeks ($n = 146$; placebo 68, MA 81); or (c) 4, 8 and 12 weeks ($n = 110$; placebo 54, MA 56). Low scores indicate a poor quality of life. Error bars indicate 95% CI.

Weight

The mean weight of the entire study population continued to fall slowly during the studied period of treatment (data not shown; − 0.9 kg by 12 weeks; $P = 0.022$). There was no statistically significant interaction effect for treatment on weight changes ($P = 0.28$). However, when the treatment groups were analysed separately, the continued weight loss was significantly different from zero (− 1.3 kg; $P = 0.0048$) only in the group treated with a placebo, whereas no significant weight loss occurred in the MA group during treatment (− 0.5 kg; $P = 0.45$). Forty-one percent of the MA patients gained weight during the first 8 weeks of treatment, whereas

Table 2. Baseline assessment of quality of life in 244 cancer patients randomised to receive megestrol acetate or a placebo

	Placebo ($n = 121$) Mean ± S.D.	MA ($n = 123$) Mean ± S.D.	Placebo + MA ($n = 244$) Mean ± S.D.
Function scales			
Physical	59.3 ± 27.6	56.0 ± 25.5	57.7 ± 26.6
Role	55.4 ± 38.2	55.3 ± 37.9	55.4 ± 38.0
Emotional	68.7 ± 23.9	70.3 ± 25.4	69.5 ± 24.6
Cognitive	78.0 ± 22.8	80.1 ± 25.7	79.0 ± 24.3
Social	70.4 ± 31.4	71.7 ± 28.4	71.0 ± 29.9
Global quality of life	45.6 ± 24.2	49.3 ± 23.2	47.4 ± 23.8
Symptom scales/items			
Fatigue	56.9 ± 27.5	57.3 ± 26.9	57.1 ± 27.1
Pain	37.7 ± 30.8	37.3 ± 31.0	37.5 ± 30.8
Appetite loss (single item)*	46.8 ± 38.7	48.0 ± 36.1	47.4 ± 37.3
Appetite loss (2-item scale)†	52.2 ± 36.8	54.3 ± 32.4	53.3 ± 34.6
Nausea/vomiting	21.1 ± 24.5	14.1 ± 20.1	17.6 ± 22.6
Dyspnoea	35.5 ± 32.1	39.8 ± 32.4	37.7 ± 32.3
Sleep disturbance	28.9 ± 32.8	34.1 ± 33.7	31.6 ± 33.3
Constipation	22.3 ± 30.2	23.8 ± 32.8	23.0 ± 31.5
Diarrhoea	14.0 ± 23.2	17.6 ± 29.2	15.8 ± 26.4
Other GI‡	25.6 ± 31.0	25.7 ± 28.4	25.7 ± 29.6
Sweating‡	20.9 ± 31.1	16.0 ± 26.1	18.4 ± 28.7
Financial problems	8.3 ± 22.5	7.4 ± 18.9	7.8 ± 20.7

MA, megestrol acetate; S.D., standard deviation. *Original QLQ-C30 item; †2-item scale including original QLQ-C30 item on appetite loss and a study-specific item measuring the positive range of appetite (response score reversed for scale construction); ‡study-specific single-item measures.

Table 3. Mean function scale scores by treatment group at different follow-up intervals

		Mean score ± S.D. (mean Δ*T*0)		
Domain	Treatment	4 weeks	8 weeks	12 weeks
Physical	Placebo	55.1 ± 28.9 (− 6.3)	55.9 ± 29.6 (− 6.5)	56.8 ± 32.1 (− 8.5)
	MA	52.8 ± 28.1 (− 6.0)	48.6 ± 26.8 (− 12.6)	46.0 ± 27.8 (− 17.0)
	P_{RM}	0.0003	< 0.0001	< 0.0001
	P_{T*RM}	0.93	0.12	0.099
Role	Placebo	46.1 ± 40.0 (− 12.4)	50.0 ± 42.6 (− 11.2)	53.8 ± 37.8 (− 12.3)
	MA	44.0 ± 38.4 (− 14.1)	41.3 ± 39.6 (− 17.5)	42.0 ± 36.7 (− 19.6)
	P_{RM}	< 0.0001	< 0.0001	< 0.0001
	P_{T*RM}	0.75	0.30	0.27
Emotional	Placebo	72.0 ± 21.3 (2.0)	71.5 ± 23.3 (− 1.0)	75.9 ± 22.9 (4.7)
	MA	75.4 ± 23.7 (4.4)	71.0 ± 26.1 (− 1.3)	69.3 ± 27.0 (− 2.6)
	P_{RM}	0.04	0.52	0.64
	P_{T*RM}	0.44	0.94	0.090
Cognitive	Placebo	77.0 ± 25.7 (− 2.2)	78.7 ± 23.2 (− 2.2)	79.0 ± 23.2 (− 0.9)
	MA	82.3 ± 21.0 (0.5)	76.5 ± 29.7 (− 3.9)	76.8 ± 25.2 (− 4.8)
	P_{RM}	0.63	0.10	0.17
	P_{T*RM}	0.41	0.66	0.36
Social	Placebo	70.5 ± 31.5 (− 0.4)	68.4 ± 32.5 (− 6.6)	74.4 ± 32.0 (0.6)
	MA	70.9 ± 28.6 (− 1.8)	71.4 ± 33.8 (− 3.1)	72.8 ± 31.4 (− 2.8)
	PRM	0.61	0.081	0.73
	P_{T*RM}	0.74	0.51	0.59

Numbers in brackets are mean score changes from baseline (Δ*T*0) within the same subgroup of patients. Positive Δ scores indicate a higher score at follow-up (i.e. improvement), while negative Δ scores indicate a reduction in the mean score (i.e. deterioration). *P*-values refer to repeated measures ANOVA (RM = repeated measure; T*RM = interaction effect of treatment on repeated measure). S.D., standard deviation; MA, megestrol acetate.

22% of patients in the placebo group gained some weight during the corresponding period ($P = 0.014$; Fisher's exact test).

Palliative therapy

The percentage of patients receiving palliative chemotherapy did not differ between the treatment groups (placebo 36/127; MA 38/128). Responses to chemotherapy were not recorded. The percentage of patients receiving palliative radiotherapy was small but significantly larger in the MA group (18/126) than in the placebo group (7/124, $P = 0.023$; chi-square test). There was no significant intergroup difference in the percentage of patients receiving steroid treatment nor in the percentage of patients displaying vaginal spotting. The mean number of hospital days during the treatment time did not differ significantly between the two groups (placebo 8.3 days, MA 9.5 days; $P = 0.49$). 8 MA patients and 5 placebo patients underwent laparo- or thoracocentesis at one or several occasions during the trial.

Compliance with treatment

111 patients completed 12 weeks of treatment (placebo 56; MA 55) as assessed by pill counting at each visit. Treatment was discontinued for 139 patients before the twelfth week, and 5 patients never started treatment. The most frequent reasons for early discontinuation of treatment were deterioration or death due to disease progression (placebo 33,

Table 4. Mean symptom scale and single item scores by treatment group at different follow-up intervals

Domain	Treatment	Mean score ± S.D. (mean Δ*T*0)		
		4 weeks	8 weeks	12 weeks
Fatigue	Placebo	56.2 ± 27.8 (1.3)	53.8 ± 30.3 (2.9)	52.3 ± 30.0 (3.1)
	MA	56.4 ± 25.3 (1.5)	59.9 ± 27.5 (6.0)	57.9 ± 26.9 (7.5)
	P_{RM}	0.44	0.029	0.065
	P_{T*RM}	0.94	0.46	0.44
Pain	Placebo	38.0 ± 32.4 (1.1)	36.5 ± 31.6 (4.4)	33.3 ± 33.2 (4.6)
	MA	31.1 ± 26.6 (− 4.9)	36.8 ± 34.8 (1.4)	28.4 ± 29.5 (− 2.6)
	P_{RM}	0.36	0.32	0.77
	P_{T*RM}	0.16	0.60	0.25
Nausea and vomiting	Placebo	17.4 ± 23.9 (− 1.4)	15.7 ± 24.8 (− 1.2)	14.5 ± 23.1 (0.6)
	MA	8.6 ± 14.8 (− 4.9)	10.5 ± 20.8 (− 1.9)	11.1 ± 19.8 (− 0.9)
	P_{RM}	0.55	0.46	0.95
	P_{T*RM}	0.30	0.88	0.75
Dyspnoea	Placebo	40.2 ± 33.0 (5.4)	40.7 ± 35.0 (7.4)	34.6 ± 31.3 (3.8)
	MA	51.1 ± 32.7 (12.8)	53.1 ± 33.2 (16.5)	52.0 ± 33.3 (16.4)
	P_{RM}	< 0.0001	< 0.0001	0.0019
	P_{T*RM}	0.081	0.057	0.054
Sleep disturbance	Placebo	29.7 ± 33.3 (0.7)	24.0 ± 33.5 (− 6.4)	20.8 ± 30.8 (− 10.1)
	MA	21.4 ± 28.7 (− 10.5)	26.3 ± 33.0 (− 5.4)	26.3 ± 32.6 (− 5.3)
	P_{RM}	0.046	0.038	0.030
	P_{T*RM}	0.025	0.86	0.49
Constipation	Placebo	23.2 ± 30.8 (1.4)	19.9 ± 30.2 (2.0)	22.2 ± 31.1 (0.6)
	MA	22.3 ± 32.2 (0.4)	23.8 ± 34.9 (4.6)	15.2 ± 23.0 (6.8)
	P_{RM}	0.73	0.27	0.24
	P_{T*RM}	0.83	0.67	0.32
Diarrhoea	Placebo	13.7 ± 23.4 (0.7)	9.5 ± 20.8 (− 4.5)	10.7 ± 23.4 (1.2)
	MA	16.1 ± 27.4 (− 2.2)	16.5 ± 25.5 (− 3.0)	19.3 ± 28.1 (− 6.3)
	P_{RM}	0.71	0.17	0.37
	P_{T*RM}	0.47	0.77	0.17
Other GI	Placebo	28.6 ± 30.7 (3.6)	22.7 ± 26.9 (3.0)	21.6 ± 25.2 (0.6)
	MA	28.7 ± 26.1 (2.8)	27.9 ± 32.0 (2.1)	21.0 ± 29.2 (2.5)
	P_{RM}	0.14	0.31	0.64
	P_{T*RM}	0.86	0.85	0.78
Sweating	Placebo	20.3 ± 30.4 (0.7)	18.1 ± 26.0 (− 0.5)	21.4 ± 29.3 (1.8)
	MA	16.1 ± 27.9 (1.8)	19.8 ± 31.6 (2.9)	18.1 ± 29.6 (2.5)
	P_{RM}	0.53	0.59	0.43
	P_{T*RM}	0.79	0.50	0.89
Financial difficulties	Placebo	11.5 ± 23.5 (2.6)	8.0 ± 19.3 (1.0)	6.2 ± 17.2 (4.2)
	MA	11.0 ± 23.6 (3.9)	10.4 ± 24.6 (3.3)	10.7 ± 23.0 (1.2)
	P_{RM}	0.018	0.12	0.049
	P_{T*RM}	0.63	0.43	0.29

Numbers in brackets are mean score changes from baseline (Δ*T*0) within the same subgroup of patients. Positive Δ scores indicate increased symptom levels at follow-up (i.e. deterioration), whereas negative Δ scores indicate decreased symptom levels (i.e. improvement). *P*-values refer to repeated measures ANOVA (RM = repeated measure; T*RM = interaction effect of treatment on repeated measure). S.D., standard deviation; MA, megestrol acetate.

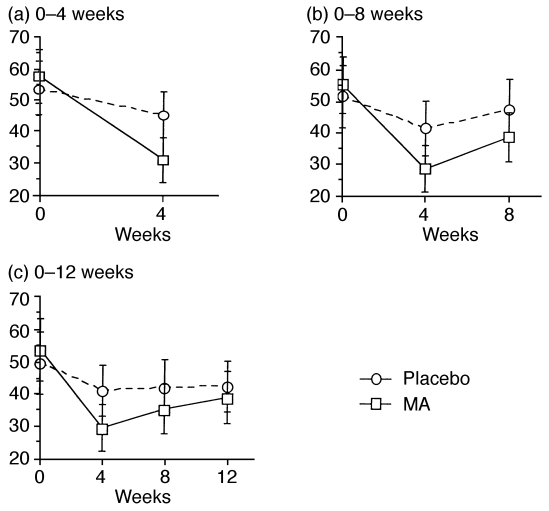

Figure 3. Mean scores for appetite loss (2-item scale) at baseline and at (a) 4 weeks ($n = 187$; placebo 92, megestrol acetate (MA) 95); at (b) 4 and 8 weeks ($n = 149$; placebo 68, MA 81); or (c) at 4, 8 and 12 weeks ($n = 111$; placebo 54, MA 57). Low scores indicate absence of appetite loss (i.e. good appetite).

MA 41), patient refusal or compliance problems (placebo 17; MA 18). 5 cases of thromboembolism (3 pulmonary embolisms and 2 deep venous thromboses) were recorded, 4 of which occurred in the placebo group. Other reasons included oedema (2), gastrointestinal symptoms (2), depression (1), pain (1), treatment with corticosteroids (6), other competitive treatments (2), and administrative error (8). The reason for discontinuation was unclear in three instances. Compliance with instructions on tablet intake ranged from 85 to 89% during the trial period, with no significant difference between treatment periods or treatment groups.

Compliance with QoL forms (attrition)

Of the 249 patients that commenced MA/placebo treatment and completed QoL forms at baseline, 16 were dead within 4 weeks (placebo 6, MA 10), 43 within 8 weeks (placebo 23, MA 20), and 79 within 12 weeks (placebo 41, MA 38). Thus, follow-up questionnaire response rates were 190/233 (82%), 150/206 (73%), and 112/170 (66%) at 4, 8 and 12 weeks, respectively, compared with the maximum numbers of theoretically possible responses by patients still alive. The vast majority of cases with missing forms occurred in patients who had also stopped treatment, for reasons discussed above. Based on individual study treatment durations, we expected 735 QoL forms to be filled out by patients still on treatment, whereas 696 were actually completed and collected (95% compliance with on-treatment questionnaire forms). The missing on-treatment forms were due to: a worsening of the patient's general condition (21), patient refusal (6) and administrative errors (8), while in 4 cases the reason for missing forms was not available. There was no intergroup difference in compliance with QoL forms.

Survival

Survival after randomisation did not differ between the groups (data not shown). The range of survival times was 0–139 weeks, with a median survival time of 19 weeks in both treatment groups. Survival after 12 weeks amounted to 66% in both groups, whereas 1-year survival was 14% in the placebo group and 17% in the MA group.

DISCUSSION

In this trial we found appetite improvement in patients with advanced, incurable, hormone-insensitive cancer treated with megestrol acetate. This was also the most consistent finding in other randomised studies of MA [18, 19, 24–30] or medroxyprogesterone acetate [31] listed in Table 5. Moreover, the statistically significant continuous reduction in the mean weight of patients treated with placebo was not seen in patients receiving MA (a subgroup of the latter patients actually gained some weight during the treatment period), although the group differences with regard to weight loss were small and probably of marginal clinical importance. However, compared with lay people or people of the medical profession, cancer patients have been shown to be much more anxious to experience even very small symptomatic improvements [32].

In contrast to the beneficial effects of MA on appetite and weight loss, patients failed to report any such effects on QoL. In fact, patients receiving MA recorded numerically (although not consistently statistically significant) lower mean global QoL ratings at the end of the treatment period than did patients treated with placebo. A similar trend was seen for measures related to the physical domain of QoL, whilst

Table 5. Randomised studies with megestrol acetate (MA) or medroxyprogesterone acetate (MPA)

Reference	No. of patients	Type of trial	Doses (mg/day)	Effects of MA on			Other positive effects
				QoL	Appetite	Weight	
30	98	P	1600	+	+	+	NV
26	240	P,D	160, 480	+	+	NS	Mood
25	122	D	160, 320, 480	NA	+	NS	
27	342	D	160, 480, 800, 1280	NA	+	NS	NV
24	150	P	240	NA	+	NS	
29	34	P	480, 960	NA	NS	NS	
18	31	P, C	480	NA	+	+	Caloric intake
19	133	P, C	800	NA	+	+	NV
28	381	D	160, 625, 1250	NA	+	NS	
Present	255	P	320	(–)	+	NS	
31	206	P	1000 (MPA)	NS	+	+	

P, placebo; D, dose–response; C, cross-over; +, mean positive effect; –, mean negative effect; NS, no significant effect; NA, not assessed; NV, nausea and vomiting.

measures within the psychosocial domain appeared to be less affected by the studied treatment.

The correlation between quality of life and weight changes in cancer patients is probably not very strong. In a study of MA in head-and-neck and lung cancer patients [33], employing the EORTC QLQ-C30 for QoL assessment, weight changes as such did not explain a significant proportion of the variance in QoL ratings. By contrast, changes in global QoL were significantly correlated with changes in fatigue, energy level, and physical functioning, as well as with appetite. In the present study, correlations between the corresponding measures, including appetite loss, and global QoL ratings (data not shown), were all statistically significant. However, in multiple stepwise regression analysis, appetite loss did not enter the equation as a significant explanatory factor, suggesting that the observed overall deterioration in physical performance plays a more important role to the perception of overall well-being in patients with advanced and progressive cancer.

There was no evidence of bias in prognostic factors that could explain a difference in outcome between the treatment groups, which were balanced with regard to pretreatment performance status, sex, age, and distribution of diagnoses. Nor were there any differences in the percentage of patients receiving palliative chemo- or radiotherapy in the period from 8 to 12 weeks in which the intergroup difference in QoL ratings occurred, and compliance with treatment instructions was similar. The only factor that differed between the treatment groups was the time elapsing from diagnosis to randomisation, which was significantly longer in the MA group, despite the randomisation procedure. However, since the inclusion of the time from diagnosis in the ANOVA model did not change the outcome with regard to treatment effects on QoL and appetite loss, and since there were no group differences in patient attrition or survival, the effect of the increased time from diagnosis on other treatment outcomes in MA patients is probably of marginal significance.

The dose in treatment with MA has varied in previously published randomised trials (Table 5). Studies comparing different dosages of MA, focusing on weight loss or appetite as target symptoms, did not unequivocally support the superiority of doses exceeding 160–320 mg a day [25, 27, 34]. Gebbia and Testa found that only 2 out of 23 patients gained weight when the MA dose was increased after 30 days from 320 to 480 mg a day, and only 4 out of 23 patients displayed improved appetite [25]. Loprinzi and associates found a dose plateau effect on appetite of 800 mg a day, above which mean weight tended to increase [27]. Nonetheless, a daily dose of 160 mg a day was recommended as the most cost-effective dose. In a study of patients with cancer or AIDS [34] the authors advocated a maintenance dose of 80–160 mg following induction treatment with 320 mg a day. Other studies found higher doses to be more effective [28], and 480 mg a day appears to be the most common dosage used in clinical trials. However, since a majority of the cited studies did not incorporate QoL as an outcome variable, conclusions about the effects of different dose levels are not easily translated into treatment evaluations based on subjective outcomes other than appetite. In the present study we employed a daily dose of 320 mg. Whether an increased dosage may better prevent a deterioration in the QoL has yet to be determined.

The duration of MA treatment for palliation is another issue to be resolved. The most beneficial effects on appetite were seen after 4 weeks, whereas the potentially negative effects on QoL were measured after 12 weeks. Breast cancer studies employing an MA dose of 160 mg a day have shown that the maximum plasma level of MA is reached after a median treatment time of 7 days [35], supporting our observation of an early impact on appetite. Moreover, a delayed treatment response in terms of weight gain in the second or third 4-week period following a weight loss in the first 4-week period of MA treatment only occurred in 3 patients, an observation which is in accordance with previous findings [25]. From this we conclude that the positive effects of MA in most cases are found in the first 4 weeks of treatment, and that no treatment benefits have been shown beyond 8 weeks in palliative settings, especially for patients failing to respond to treatment at an earlier stage. It is interesting to note that beneficial effects also tended to have the same duration in studies employing corticosteroids [5, 7].

One issue that may be of clinical importance is whether any identifiable subgroups of patients benefit from MA treatment more than others. In a recently published study of medroxyprogesterone acetate [31] in cancer patients, it was also suggested that patients losing weight but who were not yet cachectic might benefit more from treatment. In the present study, the ANOVA analysis supported the hypothesis that patients with no or marginal initial weight loss were more likely to benefit from MA treatment during the first 4 weeks. No other objective baseline variable, such as sex, age, performance status, or cancer type, were shown to have any value in predicting changes in QoL during treatment.

The use of QoL as a primary end-point raises a few questions about assessment methods and the size of the study sample. The choice of EORTC QLQ-C30 was justified by its reliability and validity in international cancer settings [20, 36–38], its documented responsiveness to differences in clinical status [20] and its availability in Swedish. However, there was limited experience from use of the instrument in palliative settings, such as the one in the present study, and it was unclear whether the incorporated measures would be capable of capturing any subjective changes induced by MA, if there were any. More recently, the instrument was used for assessing QoL in a randomised trial of medroxyprogesterone acetate in cancer patients [31]. It obtained results similar to ours, except for late impairment in global QoL. Others using combinations of different instruments reached conflicting results [26], and there is no reason for us to believe that other internationally validated questionnaires would yield significantly more reliable results than the EORTC QLQ-C30. As regards the calculation of the study's sample size, the proposed group score difference was based on assumptions of clinical relevance, supported by previously published data [21] and by more recent publications [26, 31].

A potential weakness of the present study is the large number of patient withdrawals, mainly due to general deterioration or death, which seems unavoidable in a population of advanced cancer patients with progressive disease. However, since the survival and compliance data did not point to a systematic treatment-dependent bias, and since the sample size was actually calculated with an expected patient attrition close to that observed, we believe that the group comparisons of QoL are valid and conclusive. For the same reason we did not carry out missing value imputation in the QoL analysis.

There is, of course, the possibility that the observed adverse impact of MA on the QoL in the final 4-week period of treatment did not occur by chance, but, in fact, reflects a genuine adverse impact on the physical well-being of a percentage of patients. A few previous trials indicated that treatment with MA may compromise QoL and even the survival of cancer patients [39–41]. MA causes central suppression of the pituitary adrenal axis and increases insulin demand [42, 43] but this suppression seldom produces clinical manifestations. It has also been suggested [44] that patients treated with MA may need supplementary corticosteroids for stress situations.

The patient population of the present trial was representative of common clinical practice, e.g. with two-thirds of patients being outpatients, and with regard to the distribution of patient-, tumour-, and treatment characteristics, as well as survival. Finally, the patients were recruited from different clinics at three healthcare levels.

The safety aspects of MA treatment were evaluated in terms of survival and treatment side-effects. Survival was virtually identical in both treatment groups, both during the studied treatment period and follow-up, and the results did not suggest that treatment with MA increased the risk of cardiovascular or thromboembolic complications. In fact, there were more thromboembolic episodes in the placebo group (1 pulmonary embolism and 3 deep venous thromboses) than in the MA group (1 pulmonary embolism). Thus, treatment with MA at the proposed dosage and duration was not associated with either increased morbidity or mortality.

In conclusion, the results of this randomised placebo-controlled study lend support to the safety and feasibility of oral MA in palliative cancer settings and confirm the beneficial effects on cancer-related anorexia and weight loss. However, the impact of MA on QoL is apparently not significant, and it cannot be precluded that several months of treatment with MA may have an adverse effect on some physical aspects of the QoL. Therefore, palliative treatment with MA should be carefully monitored if administered for more than 4–8 weeks. Many of the effects of MA parallel those observed in controlled studies with corticosteroids [5–8] and a comprehensive, controlled and comparative study of these treatment options is warranted.

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