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Original Paper

Megestrol Acetate for Anorexia in Patients with Far-advanced Cancer: a Double-blind Controlled Clinical Trial

F. De Conno, C. Martini, E. Zecca, A. Balzarini, P. Venturino, L. Groff and A. Caraceni

Pain Therapy, Rehabilitation and Palliative Care Division, National Cancer Institute, Via Venezian 1, 20133 Milan, Italy

The aim of this study was to evaluate a low-dose regimen of megestrol acetate (MA; 320 mg/day) on appetite in advanced cancer patients. Out-patients with far-advanced non-hormone responsive tumours and loss of appetite were randomised in a phase III trial, with two consecutive phases: a 14-day double-blind placebo controlled phase (phase A) and a 76-day open phase (phase B). During phase A, patients were treated with MA, two 160 mg tablets/day, or placebo. In phase B, the MA dose was titrated to clinical response in both groups. Appetite, food intake, body weight, performance status, mood and quality of life were evaluated with standardised measures; patients' global judgement about treatment efficacy was also requested. Of 42 patients entering the study, 33 (17 MA and 16 placebo) were evaluable for efficacy. The appetite score improved significantly with MA after 7 days ($P = 0.0023$), and this effect was still significant at 14 days ($P = 0.0064$). Patients judged the treatment with MA effective in 88.2% of cases (14th day), whilst placebo was considered effective by 25% ($P = 0.0003$). None of the other measures showed significant changes during treatment. The remarkable effect on appetite evident after 7 days, without serious side-effects, shows that MA can produce significant subjective effects at a low-dose even in patients with far-advanced disease. © **1998 Elsevier Science Ltd. All rights reserved.**

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

ANOREXIA AND cachexia are major symptoms in 64% of patients with advanced cancer [1] and are already present in 10–12.5% at the detection of the tumour [2]. The mechanisms responsible for this syndrome remain poorly understood, while its aetiology is likely to be multifactorial [3].

Anorexia and weight loss are important for patients' quality of life and indeed they are often a major concern for patients and their families. Several pharmacological agents (corticosteroids, cyproheptadine, hydrazine sulphate) have been tried for the symptomatic treatment of anorexia with only marginal success [4, 5].

Megestrol acetate (MA), a synthetic orally active progestational agent, has been reported to stimulate appetite and weight gain in several controlled randomised studies in patients with non-hormone responsive tumours and anorexia/cachexia syndrome [6–8]. Optimal dose regimens for MA in different indications, such as appetite improvement, patients' sense of well-being, weight gain, are still to be identified.

The aim of this study was to evaluate the safety and symptomatic effectiveness of a 320 mg/day regimen of MA on anorexia defined as loss of appetite. The study included the evaluation of subjective food intake, weight, performance status, mood and quality of life as secondary objectives.

PATIENTS AND METHODS

Patients

Patients were selected according to the following eligibility criteria: (1) diagnosis of advanced non-hormone related tumour; (2) diminished or absent appetite; (3) age 18–75 years; (4) well controlled stable pain; (5) Karnofsky performance status $\geq$ 60; (6) ability to take drugs by mouth; (7) life expectancy > 3 months; (8) no indication for further chemo- or radiotherapy. Patients with heart disease, diabetes mellitus, hypertension not controlled with therapy, and those with previous episodes of thromboembolism were excluded from

Correspondence to F. De Conno.
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the study. Also excluded were patients with severe respiratory distress, ascites and/or important peripheral oedema, concurrent enteral tube or parenteral feeding, active peptic ulcer, primary or metastatic brain tumour, diarrhoea, bowel obstruction, pregnancy or breast feeding, treatment with corticosteroids and/or anabolic drugs. Compliance > 93% was required for data analysis. Compliance was calculated for every patient as follows: percentage ratio equals the difference between the number of tablets delivered and those returned divided by the number of treatment days.

An institutionally approved informed consent form was signed by each patient.

Study design

The trial was divided into two phases for a total duration of 90 days. In the first phase of the study (phase A), each patient was randomised to receive double-blind either MA 320 mg/day orally or placebo for 14 days. In the following phase, all patients were treated with MA and the dosage was titrated according to clinical response for 76 days.

The following parameters were obtained at the beginning of the study and at weekly intervals in phase A: physical examination, performance status (Karnofsky), actual, usual and ideal weight, appetite (by means of a numeric scale ranging from 0–10), subjective food intake (evaluated daily by means of a diary on which the patient reported how much had been eaten as, nothing, very little, little, normal or a lot) [9], pain intensity (integrated pain score) [10], previous and current therapy. The patients' global judgement about treatment efficacy ranging from 'not efficacious' to 'very efficacious' was also recorded. In phase B, the same parameters were obtained monthly.

Quality of life was assessed by means of the Therapy Impact Questionnaire (TIQ). This questionnaire comprises a single-item global judgement on health status, three items on functional impairment, six questions on emotional and cognitive status and two items on social interaction and it has been validated for use in advanced cancer patients [11]. This questionnaire was administered at baseline and after 14 days in phase A and monthly in phase B. For each area of quality of life assessment, scores were classified as impaired or not impaired [11].

Psychological distress was evaluated with the Profile of Mood States (POMS). This questionnaire includes 65 descriptors to be rated on a five point scale from 'not at all' to 'extremely'. Six subscale scores can be obtained from the POMS: tension–anxiety, depression–discouragement, aggressiveness–anger, vigour–activity, fatigue–indolence and confusion–bewilderment [12]. The POMS questionnaire was administered only in phase A at baseline and after 14 days of treatment.

Tolerability of treatment was assessed by means of toxicity scores reported on a symptom list according to WHO toxicity classification and on a tolerability sheet prepared *ad hoc* that allowed the quantification of specific symptoms (i.e. gastritis, heartburn, gastrointestinal pain, flatulence, thrombophlebitis, pruritus, sleep disorders, increased sweating, muscle cramps, tremors, nervousness, headache, vaginal spotting, amenorrhoea and libido decrease) as mild, moderate or severe.

Statistical analysis

For the main efficacy variable (appetite), the differences between the 7th day and 14th day scores, respectively, and basal scores were calculated. These differences were considered as the primary variables for the statistical analysis. The same analysis was performed for the POMS subscales, body weight and performance status. Descriptive statistics were computed for each examined variable. In particular, frequency tables were drawn up for nominal and ordinal data, while medians, upper and lower quartiles were used as parameters of location and dispersion for the outcome variables, as it could not be assumed that these variables are distributed, neither normally nor symmetrically. For the same reasons, the two groups of treatment were compared by means of the non-parametric Wilcoxon rank-sum test [13]. The remaining variables were analysed as dichotomous data (i.e. global judgement of efficacy = efficacious versus not-efficacious, food intake = less than normal versus normal or more, and quality of life areas = impaired versus not impaired) and were, therefore, compared by means of Fisher's exact test (one-sided) [14]. This analysis was performed first on patients evaluable for efficacy (analysis per protocol) and then, with confirmative purpose, on patients who received at least one dose of drug following the principle of intention to treat analysis [15, 16]. This type of analysis required the substitution of some missing data relative to the 14th day evaluation (final visit). When there were missing data at the final visit, the data relative to the last available visit were used according to the method called LOCF [16] (last observation carried forward).

RESULTS

Efficacy

In an 18-month period, 42 patients attending the outpatient clinic of our department were enrolled and randomised (21 MA and 21 placebo). There was good homogeneity in the demographic and baseline data in the two groups (Table 1). 33 patients (17 MA and 16 placebo) completed phase A according to the protocol and 9 did not due to protocol violation in 1 case (1 MA) and to 8 withdrawals (3 MA and 5 placebo) for several reasons reported in Table 2. The open phase (76 days of treatment with MA) was concluded by only 6 patients, mainly due to disease progression and subjective factors (Table 2).

The main results are summarised in Table 3, which shows that appetite score was significantly increased after 7 days and that this change was still significant at 14 days. Patients' judgement about treatment efficacy was also significantly in favour of MA against placebo at both 7th day and 14th day assessments. Also, food intake showed a trend for improvement. Body weight slightly increased after 14 days in the MA group. Performance status, mood and quality of life, were not significantly different for patients on MA therapy, although a trend was seen for improvement in the vigour subscale of the POMS and in global health status item of the TIQ.

Toxicity tolerability

No difference in the incidence and severity of toxicity was observed during the double-blind phase. The open phase confirmed the safety profile of MA. The evaluation of the specific symptoms by the *ad hoc* list showed an equal distribution of symptoms between the two groups, attributable to disease progression and/or to side-effects of concomitant medications. Episodes of thrombophlebitis, vaginal spotting or muscle cramp did not appear at all in phase A. In the open phase, two episodes of thrombophlebitis developed after 2 months of treatment with MA.

Table 1. *Patients' characteristics at baseline (means and standard deviations are given where appropriate)*

	Enrolled patients		Evaluable	
	Megestrol acetate ($n=21$)	Placebo ($n=21$)	Megestrol acetate ($n=17$)	Placebo ($n=16$)
Sex (m/f)	15/6	16/5	12/5	11/5
Age (years)	63 ± 8	58 ± 12	62 ± 8	60 ± 11
Primary site				
Lung	10	11	8	8
Gastrointestinal	7	3	6	2
Head and neck	1	5	1	5
Others	3	2	2	1
Weight (kg)				
Actual	59 ± 10	62 ± 10	57 ± 8	63 ± 10
Usual	67 ± 11	70 ± 11	65 ± 7	71 ± 11
Ideal	62 ± 10	63 ± 6	62 ± 9	62 ± 6
Height (cm)	168 ± 10	169 ± 6	168 ± 10	168 ± 5
Karnofsky performance status	70 ± 7	74 ± 7	70 ± 7	76 ± 5

Table 2. *Causes of withdrawal. In the open phase, patients are shown in separate groups according to their initial randomisation status*

	Phase A days 1–14		Open phase days 15–30		Open phase days 31–90	
	Megestrol acetate	Placebo	Phase A: megestrol acetate	Phase A: placebo	Phase A: megestrol acetate	Phase A: placebo
Disease progression	1	3	4	4	3	4
Pneumonia	1	–	–	–	–	1
Bowel obstruction	1	–	–	–	–	–
Respitory failure	–	1	–	–	–	–
Compliance < 93%	1	–	–	–	–	–
Gastric ulcer	–	–	1	–	–	–
Heartburn	–	1	–	–	–	–
Arythmia	–	–	1	–	–	–
Patients' decision	–	–	–	–	4	3
Renal failure	–	–	–	–	1	–
Anaemia	–	–	–	–	–	1
Total	4	5	6	4	8	9

Table 3. *Results after* 7 *and* 14 *days of treatment with megestrol acetate or placebo for appetite and secondary outcome measures including subjective food intake, patients' judgement on treatment efficacy, body weight and performance status*

	7th day assessment			14th day assessment		
	Megestrol acetate ($n=19$)	Placebo ($n=19$)	P value	Megestrol acetate ($n=17$)	Placebo ($n=16$)	P value
Appetite (median of the differences from basal score (lower – upper quartiles))	2.00 (1.00–3.00)	0.00 (0.00–1.50)	0.0023	3.00 (2.00–4.00)	0.00 (– 1.00–2.50)	0.0064
Subjective food intake (% ≥ normal)	17.6	0	NS	47	6.2	0.011
Patients' preference (% effective)	70.6	12.5	0.0009	88.2	25	0.0003
Body weight (mean of the difference from basal scores (standard deviation))	0.59 (1.09)	– 0.06 (0.54)	NS	1.06 (1.95)	– 0.34 (1.01)	0.015
Performance status (mean of the difference from basal scores (standard deviation))	– 1.76 (3.93)	– 1.88 (4.03)	NS	– 0.59 (8.27)	– 1.88 (5.44)	NS

NS, not significant.

No relevant toxicity occurred during the study. 3 patients had serious complications which led to withdrawal from the study in phase A: 2 MA patients, 1 had pneumonia and died and another had bowel obstruction which resolved with conservative treatment; 1 patient in the placebo group died due to respiratory failure.

All serious adverse events were related to progression of cancer and not to the drug. Global compliance was very good for phase A: 95.66% ± 5.95 in the MA arm and 95.00% ± 2.98 in the placebo arm.

DISCUSSION

Clinical benefit from therapies for patients with advanced cancer should be evaluated on the basis of subjective measures of symptoms, quality of life and patients' preference [17, 18]. The main outcome of the present study was the

Table 4. *Mood and quality of life evaluation at* 14 *days*

	Megestrol acetate	Placebo
Mood (POMS subscales)		
Median score differences (upper and lower quartiles)		
Tension–anxiety	0.00 (− 3.00–2.00)	− 0.50 (− 4.00–1.00)
Depression–discourage	− 2.00 (− 4.00–0.00)	− 2.00 (− 3.00–0.00)
Aggressiveness–anger	0.00 (− 1.00–1.00)	− 1.00 (− 6.50–0.00)
Vigour–activity	2.00 (0.00–5.00)	− 1.50 (− 5.00–0.00)
Fatigue–indolence	− 2.00 (− 3.00–0.00)	0.00 (− 0.50–1.00)
Confusion–bewilderment	− 1.00 (− 2.00–0.00)	0.00 (− 1.50–1.00)
Quality of life (TIQ subscales)		
% of patients with scores in the impaired range		
Good health status	0	31.2
Emotional area	0	18.3
Functional impairment	29.4	31.2
Social interaction	0	0

No significant differences were observed. POMS, Profile of Mood States; TIQ, Therapy Impact Questionnaire.

efficacy of MA on anorexia in patients with far-advanced non-hormone dependent tumours. A quick and significant effect on appetite was seen when compared with placebo, even after only 7 days of MA therapy. The clinical significance of this change was confirmed by the patients' judgement on therapy effectiveness. Other variables were also assessed in this study, but firm conclusions cannot be drawn due to the small number of patients involved. However, subjective food intake improved at 14 days of treatment and a trend for weight gain was also observed in the MA group, whilst performance status tended to worsen in both groups, as expected due to the advanced stage of the disease. Quality of life and mood did not show important changes (Table 4).

Different doses of MA have been employed in controlled clinical trials for treatment of anorexia/cachexia in cancer patients [6, 7, 19–22]. Previous studies addressed the efficacy of MA in improving appetite, food intake and weight gain [6, 7, 19–22]. Results are often difficult to compare, because of the differences in design, inclusion/exclusion criteria, absence of placebo control, dose regimen, treatment period and outcome measures.

Bruera and colleagues randomised 40 patients to receive MA at 480 mg daily or placebo for 7 days in a crossover study. Appetite, caloric intake and nutritional status improved significantly for patients on the active drug [6]. Recently, very similar results have been reported by the same authors who also evaluated quality of life, but did not show any significant quality of life changes [19].

Loprinzi and associates reported on 133 patients who were given MA 800 mg/day or placebo. This trial showed that MA stimulates appetite, food intake and weight gain [7]. Another trial comparing four doses of MA (160, 480, 800, 1280 mg) in cancer cachexia was conducted in 342 patients, without placebo control, and demonstrated a positive dose–response effect of MA on appetite stimulation. The optimal dose was 800 mg/day, producing the greatest improvement in appetite and food intake [20].

Tchekmedyian and colleagues reported on 89 patients randomised to MA at 1600 mg daily or placebo. At 1 month, appetite, food intake and pre-albumin level had increased significantly in the treated group. No difference was found in reported side-effects, but 2 cases of deep vein thrombosis (4%) were seen in the MA treated group [21]. However, Loprinzi and associates [7, 20] and Tchekmedyian and colleagues [8, 21] included patients under antineoplastic therapy in their studies.

In the only other placebo-controlled study showing a subjective response with a low MA dose (240 mg/day) [22], this effect was assessed only after 1 month of treatment, which is a significant amount of time in the case of advanced patients. In this study, appetite improved in approximately 45% of patients, but patients' preference about treatment was not assessed.

Our study showed that appetite improvement can be achieved in a shorter period (7 days) with a convenient low dose schedule (160 mg twice a day) and 88% of patients judged MA efficacious. One patient judged the therapy excessively efficacious, suggesting the possibility of lowering the dose to 160 mg/daily. There were very few treatment related side-effects. Results relative to the open phase demonstrated that clinical benefit from the drug can be sustained for at least one month in some patients.

The lack of changes in quality of life measures in our study could also be explained by a lack of sensitivity of the assessment tools employed. The same observation has been recently made using different validated tools for quality of life evaluation [18].

This study shows that advanced cancer patients can have a subjective benefit from MA treatment, even in very late stages of their disease, due to the quick effect on appetite in the absence of relevant objective changes in nutritional status or performance. The dose should be titrated to obtain the desired subjective effects which can be present at doses lower than 320 mg/daily. In cancer patients who are already taking many different drugs, palliative treatment should be administered at the lowest effective dosage in order to avoid undue psychological and/or physical distress. In addition, in Italy, as in the rest of Europe and the U.S.A., a great deal of attention is being paid to reducing health costs, so choosing the lowest effective dosage becomes even more desirable.

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