Pergamon

European Journal of Cancer Vol. 33, No. 1, pp. 75–79, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(96)00309-7

Original Paper

Supportive Use of Megestrol Acetate in Patients with Head and Neck Cancer During Radio(chemo)therapy

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To study the supportive effect of megestrol acetate during intensive combined modality treatment, a randomised, double-blind, placebo-controlled study was performed in patients with head and neck cancer. The patients received either 160 mg of megestrol acetate daily or placebo during radio(chemo)therapy and for up to 6 weeks thereafter. The nutritional status as measured by anthropometric and biochemical parameters and the subjective quality of life were assessed prior to therapy, at weeks 1, 4 and 6 of radiotherapy and 12 and 18 weeks from the start of therapy. 61 of 64 patients were evaluable. In the control group ($n = 30$), the nutritional parameters deteriorated during therapy and were fully restored during follow-up. By contrast, the patients treated with megestrol acetate ($n = 31$) could maintain their baseline values. The difference between the groups was most pronounced in patients taking food per mouth (weight loss during treatment: control group: 4.1 kg; megestrol acetate group: 0.8 kg, $P = 0.0004$), but was not significant in patients fed via percutaneous endoscopically guided gastrostomy (PEG). Subjective quality of life remained constant in the megestrol acetate group while it decreased in the control group. However, differences were not statistically significant. Megestrol acetate prevents further deterioration of nutritional status during radio(chemo)therapy and may have an impact on subjective quality of life.

Key words: head and neck cancer, megestrol acetate, radio(chemo)therapy, quality of life, nutritional status

Eur J Cancer, Vol. 33, No. 1, pp. 75–79, 1997

INTRODUCTION

ANOREXIA, CACHEXIA and weight loss are common among patients with head and neck cancer, even prior to therapy [1–3]. Nevertheless, intensive multimodality treatment is essential and may result in further deterioration of the nutritional status [4], which, in turn, may jeopardise implementation of therapy. Thus, supportive care is needed. There is little information on appropriate drug therapy as an adjunct to physical therapy such as inhalations and rinsing of the mouth, and nutritional support via percutaneous endoscopically guided gastrostomy (PEG) [4, 5].

Megestrol acetate is a semisynthetic progestogen that is used in the treatment of hormone-sensitive tumours, particularly breast cancer [6]. The anabolic effect of this agent was initially considered an unwanted side-effect resulting in weight gain [7]. However, based on these experiences, megestrol acetate was successfully used in several prospective studies for the treatment of cancer-associated anorexia and cachexia in patients with hormone-sensitive tumours [8–11]. Megestrol acetate resulted in a significant improvement of appetite [10–12], body weight [10, 11], and quality of life [13–15] in the patients treated. These studies were restricted to advanced stages of cancer that were usually no longer accessible to antitumour therapy.

In contrast, in the present study, megestrol acetate was not tested as a new drug for antitumour therapy, but as an alternative supportive treatment, addressing the question of whether the supportive use of megestrol acetate may improve the tolerability of radiotherapy or simultaneous radiochemotherapy for head and neck cancer.

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Received 23 Feb. 1996; revised 5 Aug. 1996; accepted 12 Aug. 1996.

PATIENTS AND METHODS

Patients

64 patients were entered in this randomised, double-blind, placebo-controlled study between July 1991 and December 1993. Inclusion criteria were histologically verified carcinomas of the head and neck to be treated with radiotherapy as part of a multimodality treatment strategy, age 18 to 75 years, normal ingestion of food by mouth or feeding via PEG, patients informed consent for participation and randomisation, weight loss of 5% over 6 weeks or 10% over the 6 months prior to therapy. Exclusion criteria were distant metastases, history of thromboembolic disease, overt heart failure, wish to become pregnant, intake of oral contraceptives, carpal tunnel syndrome (which may deteriorate on treatment with megestrol acetate), hypersensitivity to megestrol acetate. The exclusion criteria were selected to prevent the well known side-effects of megestrol acetate: oedema, hypertension, thromboembolic complications, nausea and hyperglycaemia.

Stratification and randomisation

Previous studies have demonstrated that weight loss is far less in patients treated with radiotherapy alone compared with simultaneous radiochemotherapy. Alternatively, nutritional support by means of PEG has resulted in significant benefits in terms of weight and quality of life compared with oral nutrition only [5]. Thus, the patients were stratified according to type of treatment (radiotherapy versus radiochemotherapy) and form of nutrition (oral nutrition versus nutritional support via PEG). Afterwards, the patients were randomised to receive placebo (control arm) or megestrol acetate 160 mg daily (treatment arm) for 12 weeks, starting with the onset of therapy. Our radiation and chemotherapy protocols have been described in more detail in previous publications [16–18].

Assessment schedule

The study variables were recorded seven times during the 12-week study period. Of the measurements, five were taken immediately before and during radiotherapy (at weeks 1, 2, 4, and 6 from start of therapy), and two further measurements were obtained at weeks 12 and 18 after therapy onset. Measurements included anthropometric variables (body weight, upper arm muscle circumference as a measure of muscle mass and triceps skinfold thickness as a measure of fat stores) and biochemical parameters (cholinesterase and transferrin as a measure of serum proteins with short half-life, albumin, serum electrolytes and blood count). The subjective patients well-being was assessed using the modified 'Quality of Life' index [5, 19] as described by Padilla and associates [20]. The patients answered the 13 questions by marking a 10 cm-long undivided line with a cross. Point '0' describes the worst condition of the patient, while point '10' represents his or her individual normal condition. The results were evaluated by measuring the distance in cm between the zero point and the cross. The higher the figure, the better the patient feels. The total index was calculated as the arithmetic mean of all questions. Body weight after 12 weeks (difference from baseline) was prospectively chosen as the primary end-point of the study.

Table 1. Patient characteristics

	Control arm (n = 30)	Treatment arm (n = 31)
Sex		
Male	24 (80%)	25 (81%)
Female	6 (20%)	6 (19%)
Age (years)		
Mean	48.3	52.4
Median	50.5	50
Weight at baseline (kg)		
Mean	63.6	64.2
Median	61.7	63.4
T stage		
T1/T2	6 (20%)	11 (35%)
T3/T4	22 (73%)	20 (65%)
Tx	2 (7%)	
N stage		
N0	7 (23%)	10 (32%)
N1	5 (17%)	8 (26%)
N2	16 (53%)	12 (39%)
N3	2 (7%)	1 (3%)
Radiotherapy	23 (77%)	24 (77%)
Radiochemotherapy	7 (23%)	7 (23%)
PEG	16 (53%)	18 (58%)
RT dose (PT)		
Mean	58.7 Gy	55.5 Gy
Median	60.0 Gy	60.0 Gy

Statistical analysis

Of the 64 patients entered into the study, 61 (30 in the control arm and 31 in the treatment arm) were included in the analysis. In each arm, 1 patient was withdrawn from the study because of suspected side-effects (diarrhoea, impotence). One patient on the control arm refused further participation following randomisation. The major patient, tumour, and treatment characteristics were equally distributed between the treatment arms as shown in Table 1.

The recorded data were reviewed by an independent study monitor. The statistical analysis was performed by Wissenschaftlicher Service Pharma, Monheim, Germany.

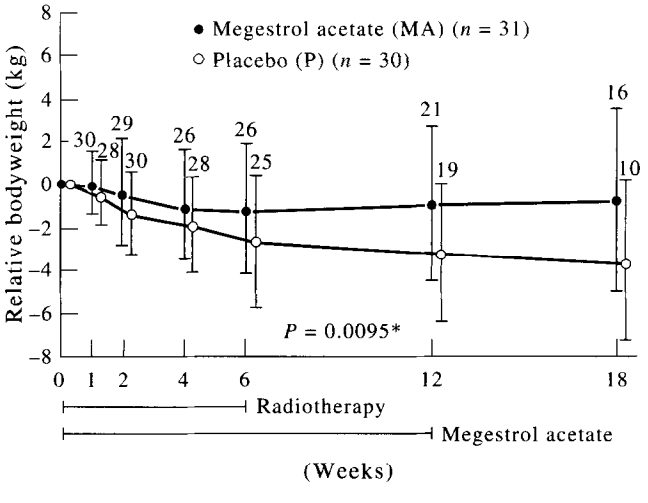

Figure 1. Relative values of body weight in patients of the control group (placebo) and those treated with megestrol acetate. The figures above the bars represent the number of documented patients. For calculation see text (mean + S.D.).

Table 2. Change in body weight; mean and median body weights (kg, ± S.D.)

	Megestrol acetate		Placebo	
	Mean (standard deviation)	Median (*n*)	Mean (standard deviation)	Median (*n*)
Baseline	64.3 (±9.9)	63.4 (31)	63.6 (±10.6)	61.7 (30)
1 week	64.2 (±9.5)	63.2 (30)	63.1 (±10.8)	60.1 (28)
2 weeks	63.7 (±9.5)	63.0 (29)	62.2 (±10.7)	60.0 (30)
4 weeks	63.1 (±9.5)	63.4 (26)	61.7 (±10.4)	60.3 (28)
6 weeks	63.0 (±9.3)	64.0 (26)	60.9 (±9.2)	60.8 (25)
12 weeks	63.4 (±9.6)	64.5 (21)	60.4 (±9.2)	60.6 (19)
18 weeks	63.5 (±10.3)	63.5 (16)	60.0 (±8.2)	59.4 (10)

The Wilcoxon rank test was used for continuous variables. Fisher's exact test was only performed for comparison of the development of body weight after 12 weeks of treatment outcome. According to the hypothesis formulation of the trial, *P*-values are one-sided concerning the primary endpoint (development of body weight). All other *P*-values presented are two-sided. The 'last value option' method [21] was used for extrapolation of data from missed examinations.

To facilitate comparisons, absolute values were converted to relative values, i.e. differences from baseline were calculated. A descending curve indicates deterioration, while an ascending curve indicates improvement of a given variable. The figures show means and standard deviations.

RESULTS

Anthropometric parameters

Both during and after radiotherapy (Figure 1) weight loss was less pronounced in the group treated with megestrol acetate. The mean and median body weights are shown in Table 2. At week 12, at completion of therapy with megestrol acetate, the mean decrease in body weight was only 0.6 kg (median 0.3 kg) in this group compared with a mean weight loss of 3.2 kg (median 4.0 kg) in the control group ($P = 0.0095$). This difference was maintained after completion of treatment with megestrol acetate (by 18 weeks from start of therapy). The number (percentage) of patients with increased body weight or weight loss/no change of body weight in each arm is shown in Table 3. At 12 weeks again more patients (14/31; 45%) increased their body weight in the megestrol acetate group compared with 6/30 (20%) in the placebo group ($P = 0.034$; Fisher's exact test).

The effects of megestrol acetate varied with the form of nutrition, the patients without megestrol acetate and with PEG lost a mean of 2.4 kg during the first 12 weeks compared with 0.8 kg weight loss in patients with megestrol acetate and PEG. However, there was a significant difference between megestrol acetate (−0.8 kg) and placebo arm (−4.1 kg) in patients without supportive enteral nutrition via PEG (Table 4).

Similarly, there was no decrease or even a slight increase in the thickness of the triceps skinfold in the megestrol acetate group compared with a continuous decrease in the control group (Figure 2). While fat stores remained constant in the patients treated with megestrol acetate, they steadily decreased in the control group ($P = 0.001$ at week 12 from start of therapy).

Throughout the study, no differences in upper arm muscle circumference were observed between the groups, the lean muscle mass remained constant in either groups.

Laboratory variables

In the patients treated with megestrol acetate, there was no change from baseline in the parameters examined compared with a slight decrease in the control group. However, the differences were not significant for all the parameters.

Subjective well-being

In accordance with the objective parameters of nutritional status, the total Padilla index (Figure 3) remained constant in the patients treated with megestrol acetate, while it decreased continuously until completion of therapy in the control group. However, differences were not statistically significant. The profiles of the individual questions showed a similar behaviour.

Side-effects

One patient in the megestrol acetate arm reported newly developing impotence, and in the control arm unexplainable diarrhoea occurred. The study medication was terminated in

*Table 3. Change in body weight after 12 weeks of treatment (*Fisher's exact test)*

	Megestrol acetate	Placebo	*P** (one sided)
Number of patients with increased body weight	14/31 (45%)	6/30 (20%)	
Number of patients with decreased or unchanged body weight	17/31 (55%)	24/30 (80%)	$P = 0.034$

Table 4. Comparison of weight loss (weight at baseline versus week 12; mean ± standard deviation) with and without administration of megestrol acetate by type of patients feeding (oral versus enteral feeding via PEG)

	Oral nutrition	Enteral nutrition via PEG
Megestrol acetate		
n	13	18
Mean (standard deviation)	−0.8 (±3.0) kg	−0.8 (±4.1) kg
Median	−0.6 kg	−0.1 kg
Placebo		
n	14	16
Mean (standard deviation)	−4.1 (±2.5) kg	−2.4(±3.7) kg
Median	−4.6 kg	−2.0 kg
	$P = 0.004$	$P = 0.14$

both patients, and they were withdrawn from the study. Other megestrol acetate related side-effects were not observed, probably on account of the rigorous exclusion criterias.

DISCUSSION

The supportive use of megestrol acetate was shown to prevent a deterioration of nutritional parameters (body weight, triceps skinfold thickness) and quality of life during radiotherapy.

The data of the control arm confirm previous reports that without adequate supportive care, patients loose 4 to 10 kg of body weight during treatment [3, 4, 22]. However, the effects of megestrol acetate varied with the form of nutrition: there was a significant difference between treatment and control arm in patients with adequate oral food intake compared with a minor difference between groups in patients receiving enteral nutritional support via PEG.

The effect of megestrol acetate on weight was not due to water retention. As suggested by the changes in triceps skinfold thickness, the fat stores decreased in the patients of the control group, while they remained constant in the patients

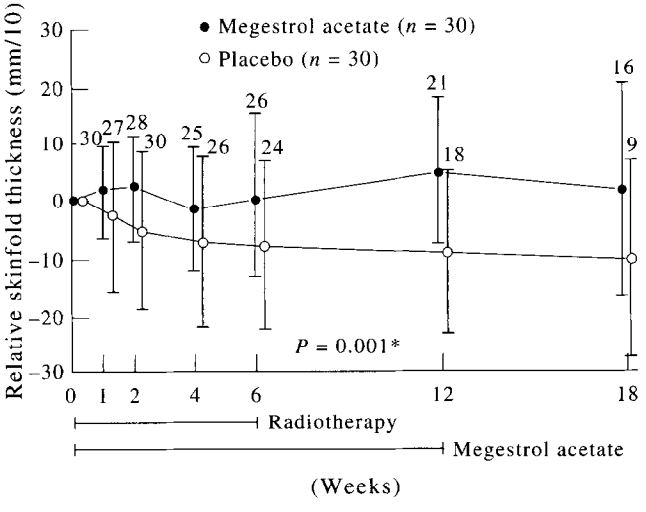

Figure 2. Relative values of triceps skinfold in patients of the control group (placebo) and those treated with megestrol acetate. The figures above the bars represent the number of documented patients. For calculation see text (mean ± S.D.).

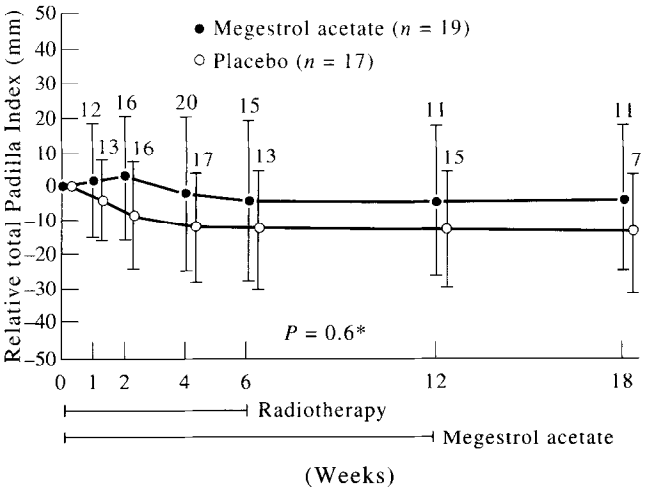

Figure 3. Relative values of total Padilla Index (quality of life) in patients of the control group (placebo) and those treated with megestrol acetate. The figures above the bars represent the number of documented patients. For calculation see text (mean ± S.D.).

treated with megestrol acetate. This is consistent with previous results [8]. Body compartment measurements using bioelectric impedance analysis have shown that weight gain primarily affected fatty tissues, but also lean body mass. Body water remained consistent with the normal distribution [23, 24].

The exact mechanism of action of megestrol acetate in the treatment of tumour anorexia and cachexia is still unknown. In addition to the general anabolic effect, an influence on cytokines is under consideration. *In vitro* studies have demonstrated inhibition of tumour necrosis factor alpha, and megestrol acetate was also shown to stimulate differentiation of pre-adipocytes to fat cells [25].

The improvement of objective nutritional parameters was also reflected in the subjective measurements of quality of life. In contrast to the control group, megestrol acetate was shown to prevent a decrease in the respective values throughout radiation therapy. This is comparable with previously reported results of palliative studies [13–15]. Nevertheless, the differences between the two arms were not statistically different, probably because: (a) the number of patients was very low, when only approximately 60% of the whole study population is taking part in the quality of life questionaire; and (b) it is very difficult to translate a subjective feeling into objective values, as already discussed by other authors [19, 26, 27].

The dosage of megestrol acetate we chose for this study (160 mg/d) proved to be effective. Severe side-effects did not occur. A reduction of the megestrol acetate dose to 60 mg daily may be possible [28]. Although higher dosages (480 to 1600 mg daily) may be expected to result in slightly greater weight gain, they may also cause adverse effects such as oedema, hypertension, thromboembolic complications, nausea and hyperglycaemia [13, 29]. Therefore, patients at risk (coronary heart disease, hypertension, history of thrombosis) were not included in the study.

In conclusion, we have shown that 160 mg of megestrol acetate daily is an appropriate dose when used in the prophylactic setting to prevent radiotherapy-induced weight

loss and may improve subjective well-being in patients with head and neck cancer. Treatment with megestrol acetate 160 mg daily is associated with few side-effects provided that contraindications are observed. Whether or not a further improvement in the nutritional status can be achieved in patients with enteral feeding via PEG remains unclear and should be investigated in future studies.

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Acknowledgement—Supported by Bristol Myers Squibb, München, Germany (megestrol acetate and placebo).