Palliative treatment of cancer anorexia with oral suspension of megestrol acetate*

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Megestrol acetate (MA) is a progestational agent, currently known as one of the most effective appetite stimulants in patients suffering from cancer anorexia/cachexia syndrome. Oral suspension of this drug may be particularly useful in patients with far advanced disease, where taking larger amount of pills may lead to the decrease of patient compliance.

The influence of oral MA suspension on quality of life and nutritional status was evaluated in 22 patients with far advanced cancer suffering from anorexia and more than 5 per cent weight loss, all beyond the scope of anticancer treatment. Most patients had lung or gastrointestinal cancer. QLQ-C30 questionnaire, visual analogue scale (VAS) for appetite, anthropometry, maximal handgrip strength and laboratory data were obtained before treatment and then after 2, 4, and 8 weeks of therapy.

Despite of a known high mortality in this prognostically unfavorable group of patients (36% within two months in this study), overall quality of life after the daily dose of 480–840 mg of MA was improved in 63, 56, and 55% of patients remaining on therapy after 2, 4, and 8 weeks, respectively. Appetite was the most successfully influenced parameter with an improvement in VAS in 95% of cases after 2 weeks of therapy (p=0.0001). The drug was well tolerated by the great majority of patients.

Oral suspension of megestrol acetate may be an effective palliative treatment for many patients with far advanced cancer suffering from anorexia/cachexia syndrome.

Key words: Megestrol acetate, cancer cachexia, palliative therapy.

Clinical picture of anorexia and weight loss with fat and muscle tissue wasting and poor performance status is known as anorexia/cachexia syndrome which is common in advanced cancer. Anorexia may be highly distressing to these patients and may not only worsen the patient quality of life but even become the cause of death [5].

Corticosteroids were the first drugs evaluated in clinical trials for alleviation of cancer anorexia/cachexia. Several studies showed temporary improvement in appetite but none of them reported any beneficial effect on body weight [5, 12, 15].

Progestational agents has recently become the important drugs for treatment of cancer anorexia/cachexia syndrome. At least ten randomized controlled trials confirmed the increase of appetite and dietary intake and also weight gain and improvement of well-being after these drugs [3, 4, 6, 14, 15, 18, 23, 25, 27, 28]. Mechanisms of action probably include the reduction of synthesis and release of cytokines and serotonine as mediators of cancer anorexia and cachexia [19, 20].

Megestrol acetate (MA) is currently the most effective and best documented appetite stimulant in patients with advanced cancer and AIDS [18, 30]. Its effect is dose related in the range of 160–800 mg a day [16]. The onset of action usually occurs within the first week, but maximal responses are seen after eight weeks of treatment. Owing to the high morbidity of advanced cancer patients the intake of further tablets may become troublesome for a patient and this may lower patient adherence to the therapy.

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Oral suspension of MA may be advantageous for patients in poor condition [29]. Moreover, bioavailability of this form is about 20 per cent higher as compared with tablets [15]. This work evaluates the effect of MA in oral suspension on appetite, quality of life and nutritional parameters in palliative treatment of cancer anorexia/cachexia syndrome.

Patients and methods

Patients. The total of 22 advanced cancer patients were randomized into two arms with different doses of MA, i.e. fixed dose of 840 mg a day in the arm A, and individual dose of 480 mg initially in the arm B with dose titration to 720 mg and 840 mg a day in the absence of sufficient effect. Inclusion criteria were as follows: confirmed diagnosis of non-hormonal dependent cancer, advanced stage of disease beyond the scope of anticancer treatment, anorexia related weight loss 5–15 per cent of usual body weight, WHO performance status no more than 2, life expectancy of at least 3 months and adequate laboratory hematological, renal and liver findings. Exclusion criteria were presented by concurrent cytostatic or hormonal treatment, preexisting edema, recent history of myocardial infarction or thrombembolic disease and uncontrolled hypertension or diabetes with hyperglycemia. The study was approved by the local Ethical Committee and all patients confirmed informed consent.

One patient did not start the medication by his own decision and two others died due to the rapid progression of cancer. From 19 evaluable patients who had follow-up data, 11 had been randomized into the arm A with the fixed dose while eight others began with the lower dose of 480 mg a day. From the latter group six patients continued on the 480 mg dose a day for one month and only two patients did so for two months, while others had doses adjusted.

Characteristics of 19 evaluable patients are shown in Table 1. Male predominance results from the type of diagnoses. Note that two patients were reclassified later as performance status 3.

Methods. Patients were informed in a printed form how to correctly take the study medication. They took the whole daily dose of MA in the mornings using a syringe. The amount of the drug taken was controlled by measuring of unused suspension in returned bottles. Every effort was made to reveal signs of edema during clinical follow-up. Body weight was measured with the accuracy of 0.1 kg by means of the precise scale regularly set by a technician. Within each visit anthropometric values were obtained by the same well trained physician. Mid arm circumference (MAC, cm) was measured to the nearest millimetre on the left extremity and four skinfold thicknesses were obtained by Harpenden caliper according to Durnin and Womersley with the precision of 0.5 mm [7]. Corrected (bone-free) mid arm muscle area (cMAMA, cm^2) was calculated according to Heymsfield from the following formula [9]:

$$cMAMA = (MAC - \pi.TST)^2 / 4\pi - C$$

where TST, triceps skinfold thickness (cm); C, a constant for the shape of arm and bone area, C=10 cm^2 for men, C=6.5 cm^2 for women. Percentage of body fat was counted from the sum of four skinfolds using appropriate tables.

Blood samples for biochemistry were collected under fasting condition strictly in the mornings up to 9 a.m. Serum cortisol levels were evaluated by fluorescent polarization immunoanalysis, FPIA, with the normal range of morning values 0.17–0.84 μmol/L.

Maximal handgrip strength was measured according to our own method (unpublished) by means of the D.OS-2T dynamometer produced by the Czech manufacturer, Recens company. Four plus four values were obtained from the right and left maximal handgrips. Mean values for each hand were calculated from the best three readings and expressed in percentages of population normals according to the age and gender. Values lower than 85% are supposed to be low and may correspond to malnutrition.

Quality of life (QOL) was evaluated by means of the EORTC Quality of Life Questionnaire QLQ-C30, version 1.0 [1]. The questionnaire was completed under the assistance of a trained dietary nurse, in each case before the examination by a physician, who stayed blind to the results. The same was true for the assessment of appetite by the visual analogue scale (VAS) within the range of 0–100 mm.

Statistics. Evaluation of the results from one centre of this multicentre study does not enable to compare two groups according to the dose of medication. Instead, all patients are evaluated in one group, regarding both doses to be effective. Moreover, most patients were treated with doses close to 840 mg a day, because some patients with the individual dose continued later on adjusted higher doses.

Because of the high drop-out of the patients, that is intrinsic to this patient population, results are evaluated in groups of patients who continued on study medication for two weeks only (19 patients), four weeks (16 patients), eight weeks (12 patients) or even 12 weeks (seven patients). Actuarial significance of differences was calculated by the Student t-test on levels of significance either 1 or 5 per cent. Moreover, percentages of improved patients out of those treated at the time of evaluation as compared to baseline and similarly, out of all evaluable patients by intention to treat analysis, are expressed.

For the evaluation of QOL only four parameters that could directly be influenced by appetite stimulant were chosen, i.e. 1) overall health and quality of life, 2) fatigue, 3) physical functioning, and 4) appetite. Differences from baseline status were assessed by the criteria of clinical significance as opposed to actuarial significance, according to the published experience [1, 2]. Changes were expressed as insignificant (up to 5 points), small (6–10 points), moderate (11–20 points) or big (over 20 points) [24]. Results are pre-

sented in percentages of improved patients out of those treated at the time of evaluation.

Results

Evaluated patients form a selected group of patients with unfavourable prognosis due to far advanced cancer with progressive malnutrition. This corresponded with high mortality in this study. Eight patients (36%) died before completing two months of treatment, one of them without having started medication. In another patient the drug was stopped due to edema and other patient discontinued MA after five weeks by his own decision as not helping him. Thus, only 12 patients were evaluable after eight weeks of therapy. Median time of MA medication was 56 days and median overall survival reached only 63 days. High morbidity is best reflected by the initial performance status (Tab. 1).

Appetite, weight and laboratory changes. Despite of the high morbidity and mortality the most remarkable change after two week therapy was appetite improvement in 18 out of 19 patients (94.7%) with median change +21 mm of VAS, p=0.0001. Continuing therapy led to further improvement of appetite and median changes related to baseline among 12 patients reached +29 mm of VAS after eight weeks, p=0.022 (Tab. 2). Intention to treat analysis shows improvement of appetite in 94.7%, 57.9%, and 47.4% of all evaluable patients after two, four, and eight weeks of MA therapy, respectively.

Median changes of body weight related to baseline showed gradual increase from +0.3 kg after 2 weeks up to +3.1 kg after 12 weeks of MA treatment, although without an actuarial significance. After eight weeks nine of 12 patients continuing on therapy had improved weights with median change of +3.4 kg, that remained even after subtraction of four patients with clinical edema. Anthropometric data showed a trend to the increase in body fat mass and no change in bone-free midarm muscle area (Tab. 2).

As expected, the maximal handgrip strength was very low with median value being only 56.9% of population normal among all evaluated patients. After MA there was no significant improvement of this parameter. Median changes after four and eight weeks of MA treatment were +3.6% and –0.1% of population normal, respectively. Despite of that, 60% and 44.4% of treated patients had better handgrip strength relative to baseline after four weeks and eight weeks, respectively.

Laboratory parameters, including albumin, prealbumin, C-reactive protein, glycemia and liver enzymes did not show any significant changes after MA. The only exception was a remarkable decrease of serum cortisol levels from initial median value of 0.66 μmol/L to 0.13 μmol/L after four weeks of therapy, p=0.0004 (Tab. 3). Figure 1 shows changes of cortisolemia in the subgroup of seven patients treated with MA for 12 weeks, p<0.01.

Quality of life. Overall QOL was improved in 12 out of 19 patients (63%) after 2 weeks of therapy with small change in four, moderate in five, and big change in three patients. Five patients worsened with small change in three, and moderate

Table 1. Baseline characteristics of evaluable patients

Number of patients	19
Age, median (range), years	59 (44–78)
Male/Female	15/4
Diagnosis:	
Lung cancer	9
GIT cancer	6
Renal carcinoma	2
Mesothelioma	1
NonHodgkin's lymphoma	1
Time from diagnosis, median, months	9
Nutritional parameters, median (range):	
Actual body weight, kg	60.2 (34.5–96.8)
Body mass index, BMI, kg/m^2	20.1 (13.8–32.7)
Percentage of ideal body weight, %	91.1 (66.9–148.5)
Total weight loss, %	13.2 (4.7–25.4)
WHO performance status (PS):	
PS 1	6
PS 2	11
PS 3	2

Table 2. Nutritional status of 12 patients treated with MA for 2 months

	Initial values mean ±SD	1 month mean ±SD	2 months mean ±SD
Appetite (VAS, mm)	36.8[ab] ±18.7	62.5[a] ±19.7	60.0[b] ±25.5
Body weight (kg)	61.5 ±14.3	63.4 ±14.4	63.8 ±15.2
Midarm circumference, MAC (cm)	24.9 ±3.7	24.7 ±3.5	25.0 ±4.4
Triceps skinfold thickness, TST (mm)	9.3 ±3.9	9.8 ±3.7	10.7 ±4.5
Percentage of body fat (%)	13.3 ±6.6	13.5 ±6.7	14.3 ±7.1
Midarm muscle area MAMA (cm^2)	29.8 ±10	28.9 ±9.1	29.0 ±11.2
Maximal handgrip strength (% of normal)	59.2 ±18.4	62.7 ±22.8	58.4 ±27.4

SD – standard deviation, [a] p<0.01, [b] p<0.05

Table 3. Laboratory values, initial and during MA therapy, 12 patients

	Initial values	1 month	2 months
Albumin g/L, mean ± SD	40.4 ±4.3	40.6 ±4.1	40.5 ±6.4
Prealbumin (g/L, mean ± SD)	0.18 ±0.12	0.21 ±0.1	0.21 ±0.11
C reactive protein (mg/L, mean ± SD)	54.4 ±61	57.7 ±72.9	52.1 ±59.1
Serum cortisol (μmol/L, mean ± SD)	0.81[ab] ±0.33	0.28[a] ±0.37	0.43[b] ±0.59
Serum cortisol (μmol/L, median)	0.7	0.09	0.07

SD – standard deviation, [a] $p<0.01$, [b] $p<0.05$

change in two patients. Fatigue improved in 47% of patients, while physical functioning in only 21%. The most remarkable change was the improvement of appetite in 95% of all evaluable patients.

After eight weeks of therapy, 55% of treated patients had improved overall QOL evenly distributed between small, moderate and big changes, while the rest of patients worsened. Fatiguability was improved in 45%, while 36% of patients worsened with a big change. Physical functioning was only improved in 18% of patients. Again, 82% of treated patients had improved appetite, all with a big change (Fig. 2).

By intention to treat analysis, overall QOL was still improved in 32% out of all evaluable patients after eight weeks of MA therapy.

Side effects. Clinically significant edema was revealed in four out of 19 patients (21%). Three out of the four patients already had slight edema at the beginning of trial which worsened during MA therapy and had to be managed by diuretics. In the fourth patient edema was the reason for withdrawal of the drug after two weeks of therapy. Six other patients had slight pedal edema without clinical importance. There were no other side effects related to MA including laboratory evaluation.

Discussion

The population of advanced cancer patients is notoriously known by its high morbidity and mortality. In this study, only 12 out of 22 randomized patients (55%) could be evaluated after eight weeks of palliative treatment with appetite stimulant, megestrol acetate. The main reason for premature cessation of the study medication was progression of cancer.

Literature data from similar studies also show high proportion of premature cessation of treatment. Tchekmedyian et al [27] was able to evaluate only 53% of patients on MA after two months of therapy. Vadell et al [28] also published high number of patients leaving the study for various reasons, mostly progression of disease, death, and abandonment of treatment, while only 53% continued after eight weeks. Loprinzi et al [14] describes a group of 133 cancer patients with median duration of MA therapy 1.6 months, where only 37% of patients continued beyond the 10th week. Our patients had even lower performance status as compared to these studies probably because of the design of this trial, where concurrent cytostatic treatment was the criterion for exclusion.

From these reasons the main goal of therapy was to improve patients quality of life and their subjective status. Our results confirm literature data showing that MA has a potential to increase appetite even in patients with far advanced disease [6, 28]. Significant benefit in appetite was found by both visual analogue scale and QLQ-C30 questionnaire. During therapy, more than 80% of treated patients had improvement in appetite as compared to initial status.

Subjective evaluation of overall health and QOL by means of the QLQ-C30 questionnaire was improved in 55–63% of treated patients throughout the study and 45–50% of patients presented lower fatigue. On the contrary, physical functioning was improved in only 13–21% of treated patients during the study. The proportion of patients with worsening parameter of physical functioning gradually increased from 32% to 55% during the study. This corresponds to the decreasing performance status from the mean value of 1.8 to 2.2, both probably reflecting the progression of cancer.

Published data on the influence of MA on QOL show improvement of some items of QOL like appetite, food intake, nausea and sometimes mood and well-being of patients [26, 31, 32]. On the other side, most authors have not found higher scores for overall QOL after MA [3, 5, 6, 25, 27]. However, not all authors used standard instruments for the evaluation of QOL and some of them judge methods used not to be sensitive enough for advanced cancer patients. Evaluation of QOL in this study may be influenced by a low number of patients. Despite of that, remarkable improvement of appetite may be perceived favorable by some of our patients and this could be reflected in better mood, higher activity, overall satisfaction and may probably result in the better evaluation of QOL by such patients.

Though nutritional assessment is not a priority in this kind of study, we have evaluated basic nutritional parameters as well. Two thirds of our patients experienced some weight gain during the study with the maximum after eight weeks of therapy, although without an actuarial significance. After subtracting data of four patients with clinical

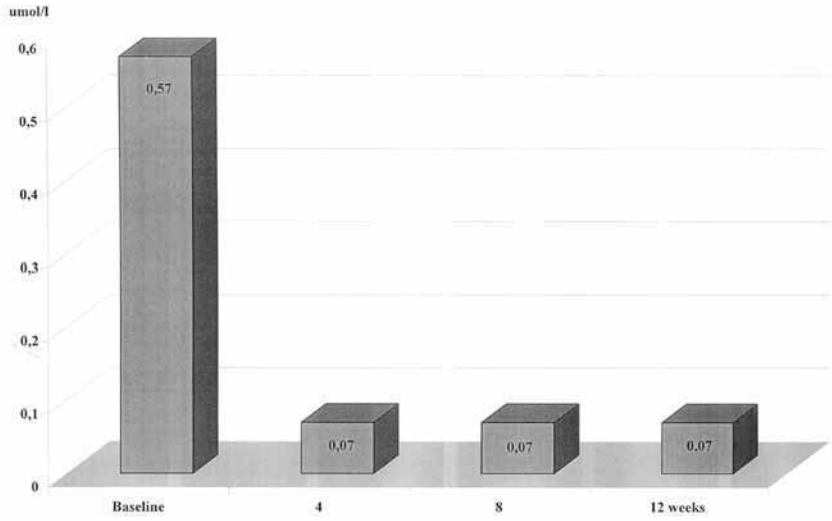

Figure 1. Median serum cortisol levels after MA in the subgroup of patients, n=7, p=0.03.

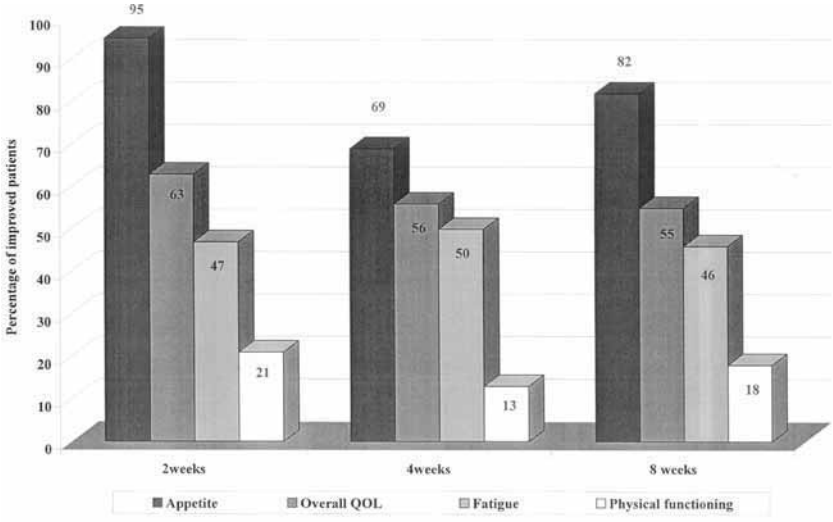

Figure 2. Percentage of patients improved in parameters of QOL after MA compared to baseline.

edema weight gain persists. Our anthropometric measurements confirm published data showing that the main factor of the weight gain probably is an accrual of fat mass [17, 21, 26]. On the contrary, bone-free midarm muscle area calculated from anthropometry by Heymsfield reveals a trend to decreasing values during follow-up.

Maximal handgrip strength measured by dynamometry shows very low initial values, which reflect low arm muscle area and malnutrition found in our patients. Actuarially, these values did not improve after MA. However, there was a proportion of patients (45–70%) with improved handgrip strength during treatment even though further decrease was expected due to progression of disease. In principle the method of handgrip strength depends not only on the size of muscle mass but on muscle functional status as well and may be influenced by mental status and mood of a patient. Hill found improvement in muscle function in malnourished patients as early as on the fourth day of the effective nutritional support, i.e. independent of muscle mass [10]. In any case, an improvement of this parameter may be considered beneficial for an advanced cancer patient.

The remarkable decrease of serum cortisol levels found in our patients corresponds with the previous literature data [13, 22]. Leinung described low morning levels of cortisol after MA therapy in AIDS patients in 1995. He found low levels of ACTH and low adrenocortical response after exogenous ACTH in patients on long-term MA therapy [13]. These findings correspond to central adrenal suppression. MA probably has glucocorticoid properties that may lead to the suppression at the pituitary and/or hypothalamic level. Our results suggest a potential danger of hypoadrenalism that may occur either after cessation of MA or in the period of a concurrent stress.

Oral suspension of MA was well tolerated by our patients without serious side effects, sometimes reported in the literature [8, 11, 14, 15, 25, 27]. There was no case of venous thrombosis or pulmonary embolism in this study.

The results presented here are influenced by the study design enrolling far advanced cancer patients with exhausted possibilities of anticancer therapy. On the other side, maximal positive effects of MA can be expected only after eight weeks of therapy, which is also supported by this study. That is why most authors indicate MA in cancer patients with life expectancy of at least three months, despite of an early onset of action of this drug usually occurring within the first week. Median overall survival of our patients, however, was only nine weeks.

Conclusions

Oral suspension of megestrol acetate is an effective appetite stimulant well tolerated by far advanced cancer patients suffering from anorexia/cachexia syndrome. This therapy may contribute to the improvement in a quality of life in some patients. Besides possible fluid retention, the danger of hypoadrenalism during therapy is recommended

to be taken into account. Hypocorticism could manifest itself not only after cessation of megestrol acetate, but even during the period of a concurrent stress.

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