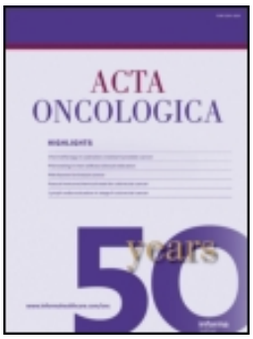

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MEGESTROL ACETATE IN CANCER PATIENTS WITH ANOREXIA AND WEIGHT LOSS

A Hellenic co-operative oncology group (HeCOG) study

DIMOSTENIS-VASILIOS SKARLOS, GEORGE FOUNTZILAS, NICOLAS PAVLIDIS, MARIO BEER, PARIS MAKRANTONAKIS, GERASIMOS ARAVANTINOS, PANAGIOTIS PANTELAKOS, NICOS TSAVARIS, NICOS KARPASITIS and PARIS KOSMIDIS

Fifty-two patients with hormone-independent cancer, who complained of anorexia and of weight loss with at least 10%, received megestrol acetate (MA), 480 mg daily, during 1–21 weeks. Of the 41 patients treated during 4 weeks or longer, 38 experienced weight gain. Monthly subjective evaluation of six parameters using a linear analog self-assessment (LASA) form showed a significant improvement in the patient's rating of appetite, mood, nausea and vomiting, and quality of life; the tumor was progressive in 21, stable in 11 and it regressed in only 9 of these patients. No toxicity was observed; one case of death due to a congestive heart failure remains unexplained. MA at the dose used is a powerful appetite stimulant; it contributes to weight increase and might improve the subjective appreciation of quality of life. MA at lower doses should be compared in a prospective trial to the dose used in this study.

Anorexia and weight loss are frequently associated with cancer and with cancer treatment (1, 2). Multiple and interactive factors are the probable cause of these symptoms, such as direct interference of tumors with food intake, absorption and digestion, treatment complications, changes in smell, taste, energy expenditure etc (1, 3). The impact of these two symptoms on the subjective well-being and the social life of the patients and their families has already been discussed (4).

Megestrol acetate (MA) is used widely in patients with breast cancer and other hormone-sensitive tumors. An increase in appetite and body weight in patients with breast cancer receiving MA at the usual dose (160 mg daily) has been noted as a collateral effect in up to 30% of patients (5); rapid weight gain and increase in appetite were observed when increasing the daily dose of the drug to 480 mg daily (6). Such an effect at different dose levels has been observed also with other gestagens (7). Interestingly enough, the increase in appetite and body weight seemed to be independent of the tumor response to treatment and the disease localization (8). Furthermore, it was reported that one-third of patients with various hormone-independent tumors also increased their body weight and appetite when treated with MA, 160 mg daily (9). This proportion increases in a dose-dependent fashion when the dose is raised to as high as 10 times the conventional level (10). However, the optimal dose of MA for cancer anorexia and weight loss is not yet established (11).

The mechanism of the above effects is imperfectly understood. In vitro adipocyte differentiation is reported; in the human, multifactorial metabolic and hormonal mechanisms have been postulated (12, 4). At daily doses of 480 mg or less, it seems that weight gain is not due to an abnormal distribution of fluids in the different body com-

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partments, and that low doses have a more favorable benefit/toxicity ratio (13).

A series of 29 subjective indicators of quality of life in patients receiving very high doses of MA (1 600 mg/day) has been investigated in a placebo-controlled study of 89 patients, which has shown an improvement in factors related to food intake and in the overall assessment of quality of life after one month of treatment (14).

The question, whether an increase in appetite and weight corresponds to a better quality of life, and the optimal dosage of MA in patients with weight loss can be settled only by large, controlled and preferably blinded comparative studies designed to systematically assess indicators of quality of life, in order to avoid the multiple sources of bias inherent to the heterogeneity of the patient population and the nature of the parameters measured.

Our group performed a non-comparative pilot study designed to test the feasibility, in our patient population with cancer anorexia and weight loss, of supportive treatment with MA at the daily dose of 480 mg, which was chosen based on a review of published trials (4). Some indications of a possible impact of the treatment on different subjective indicators of quality of life emerged during the course of this study.

Material and Methods

From November 1989 to July 1991, 53 consecutive patients were entered into the study in 4 institutions. The requirements for patient selection were the following: confirmed malignant tumor, loss with at least 10% or more of body weight during the last 2 months or a loss of weight since the diagnosis of the tumor, amounting to 10% or more of the ideal body weight (IBW) (15). Patients with tumors considered to be hormone-sensitive (cancer of the breast, ovary, prostate) and those receiving any kind of hormonal treatment were excluded from the study, as well as patients with diabetes, thyroid disease, overt heart failure, history of thromboembolism, serious psychiatric distrubances, pregnancy, obstruction to food intake, or malabsorption. A life expectancy of 3 months or longer, according to the physician's judgement, was required. Treatment consisted of megestrol acetate tablets, 480 mg daily. The 3 tablets of 160 mg each could be given either in a single dose in the morning, or divided in three daily doses. Treatment was to be continued until reaching the ideal body weight; if the patient was still underweight after 8 weeks of treatment, the dose was increased to 640 mg daily; a minimum of 12 weeks of treatment was required. Informed consent by the patients was required according to the local legislation.

The following parameters were recorded 2 weeks after the first visit and at least monthly thereafter: history, physical examination including weight and clinical signs of edema or thrombosis, complete blood count, blood chemistry routine and lipid levels. A linear analog self assessment (LASA) questionnaire was used to record every 4 weeks the patients' subjective assessment regarding their physical well-being, pain level, nausea and vomiting, appetite and quality of life. This form contained 5 horizontal lines, one for each item (16). For each of these items, the patients were requested to make a sign on a 10 cm line, marked at each end with the worst and the best possible adjectives respectively, qualifying a given condition. The patient and the physician were also asked for their general opinion on the change in quality of life ever since the beginning of the study. Standard criteria were used to define tumor evolution or response to antitumor treatment (17).

The collected values for the patients' absolute and percentual weight loss or gain and the sequential measurements on the LASA scale were compared by means of Student's t-test and Wilcoxon's signed rank test for matched pairs, on logarithmically transformed values to correct distribution where required (18). Test power $(1 - Z\beta)$ is reported if inferior to 80% (19).

Results

Patient characteristics. One patient was not eligible (weight loss inferior to protocol requirements), and one patient refused follow-up and could not be assessed. The patient's characteristics are shown in Table 1. Of the 32 patients receiving chemotherapy, 19 had a combination of 3 or more drugs. Two patients had gained weight in the 2 months preceding the start of the study; both were grossly under their ideal body weight, but they complained of anorexia and had tried to force themselves to eat, against their inclinations. Another two patients were over the IBW even after losing more than 10% weight in the last two months; 31 patients had been above their IBW before the diagnosis of their tumor. The mean difference from habitual to ideal body weight was −2% (range −40–+17%). The megestrol study was started 0.7–57 (average 5.4) months following the initial tumor diagnosis.

Treatment. The treatment duration was 1–21 weeks, with a median of 12 weeks. The reasons for its interruption before 12 weeks are shown in Table 2. Most interruptions were due to consequences of disease progression; in 3 cases the physician and in 2 the patient interrupted treatment because of excessive weight. Four other patients felt well and declared no need of medication any more. The prescribed dose increase was performed in 4 cases only. In the other cases of failure to gain weight in the first two months, the patient's general status had worsened by the time the dose should have been increased and the physician was considering a stoppage of treatment within a near future.

Toxicity. No clinical evidence of edema, thrombophlebitis, thrombosis or other adverse effects related to

Table 1

Patient characteristics	*n*
Number entered:	53
Eligible	52
Age	32–82
median	60
Sex	
male	42
female	10
Performance status (W.H.O. scale)	
0	1
1	16
2	23
3	12
Tumor	
lung, non-small cell	13
lung, small-cell	6
head & neck	4
gastric	12
pancreas	1
colorectal	9
bladder	3
non-Hodgkin lymphoma	2
kidney adenocarcinoma	1
unknown primary	1
Stage	
locally advanced	16
metastatic	35
lymphoma, in remission	1
Concurrent anticancer treatment	
none	7
chemotherapy	28
radiation	12
chemotherapy and radiation	4
interferon	1

Percentual change in weight prior to the study

	mean	range
in the last 2 months	−17%	−46–+10
% of habitual weight	−19%	−45–+9
% of ideal weight	−6%	−15–0

MA was noted; no unexpected adverse effects were observed except, possibly, in a case of 62-year-old female patient with gastric cancer, who died of acute congestive heart failure during the fourth week of the study. This patient had no previous history of heart failure or cardiotoxic treatment. No pathologic signs had been evidenced at the routine examination before or during the study; an autopsy could not be performed.

Weight increase. Of the 10 patients who had been in the protocol less than one month, one refused follow-up and 5 had rapidly progressive disease. Four of these patients lost weight from the start, and 5 after having gained some. Forty-one patients were treated for 4 weeks or longer. The body weight of these patients prior to the start of the study was 54.7 kg (95% confidence limits, range 45–64) and 61.3 kg (53–69) at the last control. One of these patients had no change in body weight during the study,

Table 2

Megestrol acetate treatment. Treatment duration, weeks: 1–21, median 12, mean 11

Treatment duration	Number of patients
Treated 12 weeks or longer	26
Stopped before 12 weeks	26
Reasons for stopping:	
early death (tumoral)	1
other disease (congestive heart failure)	1
acute worsening (tumor progression)	1
chemotherapy toxicity	1
overweight (physician's judgement)	3
patient satisfied	6
refusal	5

2 patients lost and 38 gained weight. When evaluating all 49 patients by two or more measurements, i.e. the 41 evaluable patients and 8 patients who were weighed twice in the first month, the difference from the initial weight to the last value during treatment was still significant ($p = 0.02$).

Appetite and quality of life self-assessment. Forty patients were evaluable for the LASA forms (Table 3 and the figure). When comparing the pretreatment form to the one filled in at the best or worst moment during treatment, significant differences were seen in appetite, nausea and vomiting, overall quality of life, mood, and physical well-being (all p-values < 0.004). The pain level increased during the study; test power was insufficient for the comparison of pain levels. In 9 of the 41 patients who were followed during 4 weeks or longer, the tumor had responded to anticancer treatment before or during the study; it was unchanged in 11 and progressive in 20 patients. Appetite and overall quality of life as indicated on the LASA forms, and weight gain during the study, were tabulated separately for patients with response, stable disease and progression or early death (Table 4). No difference between these groups can be detected with the available numbers. When asked orally for their overall judgement on quality of life, 29 patients expressed the belief that they were generally doing better than before the start of the protocol; 4 were worsened and 7 unchanged. The patients' judgement agreed with their evaluation indicated on the LASA forms in 25 cases. The physician's overall opinion was also recorded. In 11 cases, the patient's overall judgement differed from that of the doctor.

Discussion

The powerful effect of MA as an appetite stimulant was confirmed in our patient population, based on the patient's own evaluation. This result is consistent with the available

Table 3

Change in quality of life self-assessment. (Number evaluable = 40)

	mm. on the LASA scale				Number of patients		
	at start		end study				
	mean	95% c.l.[1]	mean	95% c.l.[1]	better	worse	stable
Appetite	32	7–57	77	38–83	34	4	2
Physical status	38	12–63	51	38–64	28	8	4
Mood	42	19–65	64	45–83	25	8	7
Pain	50	22–78	64	35–93	24	13	3
Nausea/vomiting	31	1–60	13	0–27	23	8	9
Quality of life	41	21–62	60	42–78	26	11	3

[1] 95% confidence limits

Table 4

Percent change in weight and subjective evaluation according to tumor response

	Response n = 9		Stable n = 11		Progression n = 20	
	mean	range	mean	range	mean	range
Weight	10	+7–+15	8.6	−7–+25	9.4	−15–+37
Appetite	30	−5–+70	48	−15–+50	31	−25–+80
Overall quality of life	11	0–+50	30	0–+50	30	−30–+70

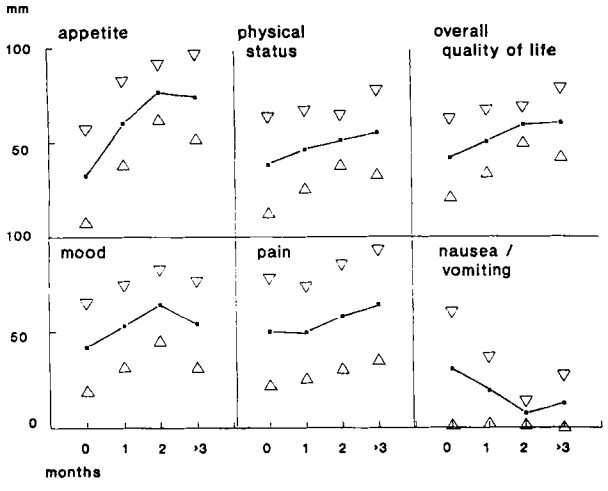

Figure. Subjective assessment, on a scale of 0–100 mm, of different subjective indicators on the linear analog self-assessment form at the start of the study, and after 4 weeks (n = 40), 8 weeks (n = 28), and 12 weeks or later (n = 26); average values and 95% confidence limits.

references on the subject (4). The effect on the patient's weight was also positive and significant, but not quite as marked as on the subjective evaluation of appetite.

Even though most of our patients diseases progressed during the treatment period, the subjective perception of appetite, mood, physical status and overall quality of life were generally better by the fourth week of treatment. The patient's assessment of the severity of nausea and vomiting improved although a majority received concomitant emetogenic treatment. The level of pain increased according to the tumor status. These results generally agree with those of more detailed evaluations (14).

The patient population was highly heterogeneous with respect to tumor diagnosis, general status, previous and present antitumor treatment, and supportive care; most of the assessed indices are entirely subjective and subject to various influences, and the methodology for such assessments is not established and standardized. As a result, carefully blinded comparative studies with sufficient numbers are necessary to overcome the main sources of bias. However, the magnitude of change in the patients' self-assessment of appetite and several other indicators of quality of life in this non-comparative study is a useful hint.

In the present study, megestrol acetate seemed to act as a powerful appetite stimulant and helped most patients to gain weight in the presence of progressive disease. It also helped the patients towards a less negative perception of their quality of life. Even though we observed none of the expected side-effects of MA, a cardiac death was observed. Based on the present study, the daily MA dose of 480 mg cannot be justified before comparing it in a prospective, randomized study to treatment with lower doses (162–320 mg).

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