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CLINICAL INVESTIGATION **Lung**

SUPPORTIVE USE OF MEGESTROL ACETATE (MEGACE) WITH HEAD/NECK AND LUNG CANCER PATIENTS RECEIVING RADIATION THERAPY

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Purpose: The purpose of this study was to measure the effect of megestrol acetate (MA) on weight loss and quality of life (QOL) in patients with cancer of the lung or head and neck undergoing curative radiation therapy.
Methods and Materials: This was a Phase III, placebo-controlled, double-blind randomized study. Patients received either 800 mg/day of MA (20 milliliters po qAM) or placebo over a 12-week period. Patients received radiation of the head and neck or thorax using a dose of at least 50 Gy, either alone or with chemotherapy. Weight was assessed weekly, whereas QOL was assessed at baseline and at 4, 8, and 12 weeks.
Results: Patient characteristics on the MA arm (16 lung, 12 head/neck; mean age: 60 years) were similar to those on the placebo arm (17 lung, 11 head/neck; mean age: 65.8 years). Patients in the MA group had a mean weight loss over 12 weeks of 2.7 pounds, whereas the placebo group had a mean weight loss of 10.6 pounds. There was a significant time by treatment interaction ($p = 0.001$), with the difference in weight between treatment groups being most pronounced after 6 weeks. Although overall QOL was similar in both arms of the study, several QOL subscale items did differ significantly. Compared to the placebo-treated patients, head-and-neck cancer patients in the MA arm reported the ability to eat as much as they liked ($p = 0.02$ at 12 weeks), and lung cancer patients in the MA arm reported significantly better appetite at 4 weeks ($p = 0.03$) and 8 weeks ($p = 0.001$).
Conclusion: MA used prophylactically is useful as an appetite stimulant; it can help patients maintain weight over the course of curative radiotherapy of the head and neck or lung and can improve specific aspects of QOL.

Quality of life, Megestrol acetate.

INTRODUCTION

Anorexia, cachexia, and weight loss are significant problems among patients with head-and-neck or lung cancer undergoing intensive multimodality treatment (1, 2). Although these problems are often related to the disease, the treatment itself may produce debilitating side effects. For example, radiation therapy (RT) directed toward the aerodigestive tract often impairs appetite, leading to weight loss and compromised nutritional status of patients. Compromised nutritional status is a significant problem, because it can diminish a patient's general sense of well-being and global quality of life (QOL) and impair the body's ability to repair normal-tissue damage.

Megestrol acetate (MA), a progestational agent that promotes weight gain, has been used to help patients maintain appetite and weight during treatment. MA is an orally active synthetic congener of the natural steroid progesterone. It was initially noted to promote weight gain, an unwanted side effect, in women with metastatic breast cancer; it was subsequently used to treat cachexia in patients with human immunodeficiency virus (3–6). The precise mechanism of appetite stimulation and subsequent weight gain is not completely understood. It is thought that cachexia is associated with increased concentrations of tumor necrosis factor α, interleukin-1, and other cytokines. MA may work by downregulating these proinflammatory cytokines (7, 8).

Numerous studies have reported that MA can increase or maintain weight and improve appetite in patients with a variety of malignancies (9–12). Jatoi *et al*. reviewed 15

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studies that were attempts to measure quality-of-life improvements thought to be associated with weight gain (11). In 13 papers, they found that MA administered at various doses resulted in improved appetite. One study by Beller *et al*. reported improvement in global quality of life (13). That study measured QOL with 6 Linear Analog Self Assessment items at randomization and at 4, 8, and 12 weeks in 242 patients with advanced endocrine-insensitive cancer, randomized to placebo or 480 mg/day of MA or 160 mg/day of MA. Overall QOL improved within the first 4 weeks; this trend was sustained throughout the study and was more pronounced at the higher dose. However, Linear Analog Self Assessment measurement is less sensitive and psychometrically sound than some of the validated QOL instruments that are currently available and that provide an overall score.

There is anecdotal evidence supporting the hypothesis that global quality of life can be affected by maintaining appetite and weight in the midst of difficult side effects, but there is little in the way of placebo-controlled studies of patients with cancer of the lung or head and neck. Eating behavior and subsequent weight gain is a complex phenomenon. Its impact on global quality of life may be subtle and indirect in the form of enhanced mood, increased opportunities for social relations because of gathering at mealtime, and additional opportunities for social support at celebrations where a meal may be the focal point. Thus, we would expect that if the use of MA were to improve appetite and eating behavior, it might very well influence indirectly a number of other patient behaviors, feelings, and perceptions that could impact global quality of life.

One study of head-and-neck cancer patients examined the effect of MA with intensive combined modality treatment (2). Patients received either placebo or 160 mg of MA daily during chemoradiotherapy and up to 6 weeks thereafter. Patients treated with MA maintained near-baseline values with regard to nutritional parameters. Specifically, weight loss in the MA group during treatment was 0.8 kg vs. 4.1 kg in the placebo control group ($p = 0.0004$). Additionally, global quality of life decreased in the control group, whereas it remained constant in the MA group.

The following is the definition of quality of life used in this paper: Health-related quality of life refers to the extent to which one's usual or expected physical, emotional, functional, and social/family well-being is affected by a medical condition or its treatment (14). This definition incorporates two important elements. First, quality of life is subjective and best rated by patients themselves. Second, the quality-of-life construct is multidimensional, including at least the four dimensions of well-being indicated in the definition above. We hypothesized that enhancing appetite and minimizing weight loss would have a global effect on the four dimensions measured. For example, if appetite improved, emotional well-being could be enhanced by the patient's increased participation in social activities.

The purpose of this study was twofold: (*1*) to improve on research designs used in previous studies by using a well-validated instrument to measure overall QOL, and (*2*) to use MA in a prophylactic setting for patients with head/neck or lung cancer where the impact of MA on nutritional status has not been extensively studied.

METHODS AND MATERIALS

A total of 56 patients were entered into this randomized double-blind, placebo-controlled study. Patients were treated with either head/neck or thoracic RT ($\geq$50 Gy, typically from 50 Gy in 25 fractions to 70 Gy in 35 fractions). Inclusion criteria were as follows: $\geq$18 years of age; squamous cell carcinoma or lymphoepithelioma of the oral cavity or oropharynx, nasopharynx, or larynx; non–small-cell and small-cell lung cancer; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; and greater than 3-month life expectancy. Exclusion criteria included previous or concomitant malignancy with less than a 3-year disease-free interval (except curatively treated carcinoma *in situ* of the cervix or nonmelanotic skin cancer), serious medical or psychiatric illness, physical or functional obstruction of food intake, impaired digestive function, enteral or parenteral nutritional support of patient, significant ascites, pleural effusions, or edema—conditions that could inhibit food intake or invalidate weight determinations. Other exclusion criteria were current or planned treatment with steroid medications, estrogens, or other progestins and, finally, patients who were pregnant or nursing. All patients completed a consent form meeting state, federal, and institutional guidelines before randomization.

Study instruments

The Functional Assessment of Cancer Therapy–General (FACT-G, version 3), head/neck (H/N) and lung (L) subscales (15, 16). The general version of the Functional Assessment of Cancer Therapy (FACT-G) is a 28-item self-report questionnaire that measures QOL in cancer patients. The FACT consists of five subscales measuring physical well-being, functional well-being, social/family well-being, emotional well-being, and satisfaction with the patient-doctor relationship. The FACT can be either self-administered or used in an interview format and is easily completed in 5 to 10 minutes. Patients are asked to rate themselves on how they feel today and over the past 7 days. The FACT-G provides subscale scores and an overall total QOL score. A higher score indicates better QOL. Cronbach's alpha for each subscale has been reported as follows: physical well-being (0.82), functional well-being (0.80), social/family well-being (0.69), emotional well-being (0.74), relationship with the doctor (0.65), and total FACT-G (0.89). Cronbach's alpha for the lung and head-and-neck subscale are 0.68 and 0.63, respectively (16). The FACT was administered at baseline and at 4, 8, and 12 weeks.

The Eastern Cooperative Oncology Group Performance Status Rating Scale (17). This is a single-item, self-rating of activity level, where 0 = fully ambulatory without symptoms, 1 = fully ambulatory with symptoms, 2 = requiring

bed rest (or equivalent) less than 50% of the waking day, 3 = requiring bed rest (or equivalent) greater than 50% of the waking day, and 4 = bedridden. The ECOG performance status was assessed at baseline and at 4, 8, and 12 weeks.

Procedures

Patients were randomized at the time of study entry and before the initiation of RT to either MA (800 mg per day) or the placebo arm. Patients in the MA arm began using it within 3 days of radiation therapy and continued for a total of 12 weeks. They received 800 mg, 20 mL po qAM. Patients randomized to the placebo arm received a matching oral suspension, 20 mL po qAM beginning within the first 3 days of radiation therapy and continuing for 12 weeks.

All patients underwent a complete history and physical examination before the study entry. A history of the patient's weight change over the preceding 2 months was obtained from the medical record and the patient. Baseline weight was obtained at study entry. Weight was recorded at each clinic visit and approximately weekly over the 12 weeks of the study. The patients were weighed in underwear, hospital gown, or light street clothes, with no shoes. Every effort was made to assure that the patient dressed consistently at each weigh-in and that the same scale was used. The research nurse presented the study questionnaires to patients to complete in conjunction with their clinic appointment. Patient-rated quality of life (FACT) and performance status (ECOG) were assessed at four time points: baseline and at 4, 8, and 12 weeks. Toxicities were recorded on the flow sheet as part of the physician assessment at each of the designated time points. All patients were eligible to receive full supportive care, which included transfusions of blood and blood products, antibiotics, and anti-emetics, as appropriate. Additionally, patients were allowed formal nutritional/dietary consultation. If a patient was seen for consultation by a nutritionist or dietitian, either before or during RT, the date and details of the consultation were recorded on the flow sheets. Patients maintained a medication diary and gave this to the study coordinators at the end of each month.

Statistical analysis

This was a randomized, double-blind, placebo-controlled study. Patients were randomized at the time of study entry and before initiation of radiation therapy. Permuted block randomization within strata defined by the primary disease was used to assign patients to one of two arms with equal probability. Weight was measured at baseline and approximately weekly after randomization. The QOL outcome measure was the overall FACT score. Intent-to-treat analyses were used for all outcome measures; that is, all randomized patients were used in all analyses, whether or not they were actually treated or whether or not they were treated per protocol. Analysis of variance was used to assess the unadjusted group differences in weight and quality of life at 12 weeks post-randomization. When 12-week values were not available, we used the latest recorded values. Analysis of covariance was used to assess the group differences in these measures, adjusting for pretreatment values and patient characteristics such as age, gender, performance status, and disease severity. In addition, to account for the multiple weight and quality-of-life measurements over time for each individual, and to adjust for the fact that not all subjects had 12 weeks of data, a mixed-effects analysis of covariance was used to assess the effect of time (considered continuously as the number of days post-randomization), treatment, and the time × treatment interaction, after adjusting for pretreatment patient covariates. An autoregressive covariance structure was used to model the within-patient correlation over time. The data were analyzed using the SAS Mixed procedure (Proc Mixed; SAS, Cary, NC).

Table 1. Patient characteristics

	MA *n* (%)	P *n* (%)
Total patients	28 (100)	28 (100)
Age (yr)		
Mean (SD)	60.0 (±12.1)	65.8 (±11.6)
Range	38–79 yr	40–89 yr
Gender		
Male	20 (71)	16 (57)
Female	8 (29)	12 (43)
Race		
African-American	5 (18)	4 (14)
White	23 (82)	24 (86)
Diagnosis and treatment		
Lung	16 (57)	17 (60)
RT + chemo	11 (39)	13 (46)
RT only	5 (18)	4 (14)
H/N	12 (43)	11 (40)
RT + chemo	3 (11)	3 (11)
RT only	9 (32)	8 (29)
Performance status		
0	16 (57)	15* (56)
1	11 (39)	10 (37)
2	1 (4)	2 (8)

* One patient did not report performance status.

Abbreviations: MA = megestrol acetate; H/N = head/neck; P = placebo.

RESULTS

Of the total of 57 patients, 28 were randomized to the MA arm and 29 to the placebo arm. One placebo patient was ruled ineligible after randomization, because positive findings on a bone scan excluded the patient from the analysis. Relevant clinical characteristics for the 56 eligible patients are reported in Table 1. There were no statistically significant differences between the MA and placebo arms for any of these characteristics. There was no difference in the amount of study time for each group: Placebo mean days = 63.1 (±29); MA mean days = 63.6 (±23.1). A total of 16 placebo and 12 MA patients completed the QOL study measure at 12 weeks. Twelve patients on the placebo arm did not complete the study, for the following reasons: toxicity, $n = 1$; protocol violation,

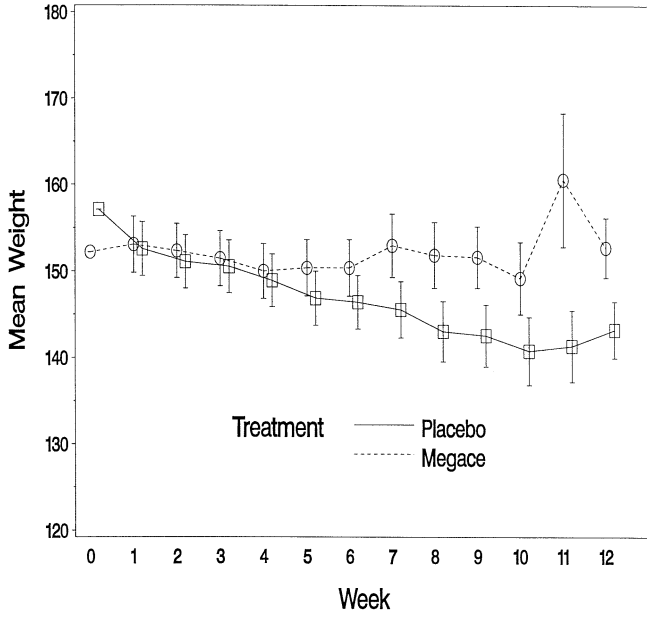

Fig. 1. Least-square mean weight (lbs.) scores (±2 SE) for Megace and placebo patients over the 12-week course of the study.

$n = 1$; patient/physician decision to withdraw, $n = 6$; other, $n = 4$. Sixteen patients on the MA arm did not complete the study, for the following reasons: toxicity, $n = 1$; patient/physician decision to withdraw, $n = 12$; expired, $n = 2$; other, $n = 1$. A review of the research notes in patient charts revealed that two patients, one placebo and one MA, received a feeding tube during the study period.

Change in weight

In the unadjusted analysis (analysis of variance), using an intent-to-treat approach and the final weight recorded as the outcome measure, there was a significant difference between the MA and placebo groups ($p = 0.02$). The patients in the placebo group lost more weight over the course of the study. The MA group had a mean (±SD) weight change of −2.7 lbs. (±13.8 lbs.) with a range from −25 to +37 lbs., whereas the placebo group had a mean weight change of −10.6 lbs. (±10.6 lbs.) with a range of −30 to +13 lbs. Results were similar after adjustment for covariates, including the baseline weights. In addition, the difference between head-and-neck and lung cancer patients was of borderline significance ($p = 0.045$). Head-and-neck patients lost, on average, 7.5 lbs. more than the lung cancer patients did. None of the other covariates (age, gender, race, or performance status) were statistically significant.

Figure 1 shows the mean change in weight over the course of the study. The initial values are actual means, shown for illustration purposes. Weeks 1–12 are least squares means, adjusted for baseline weight, treatment arm, type of cancer (head/neck or lung), gender, and age. The mixed effects model revealed a statistically significant interaction between time and treatment ($p = 0.001$). Changes in weight were most pronounced after 6 weeks, and there was significantly more weight loss in the placebo compared to the MA arm.

Health-related quality of life

Overall quality-of-life mean scores on the FACT-G are reported in Fig. 2. Repeated measures analyses revealed no significant intragroup differences over time in either of the groups and no significant intergroup differences at any time. Because of their clinical significance, several FACT items were analyzed separately. Comparisons (least-square mean score differences) on the following FACT items were sta-

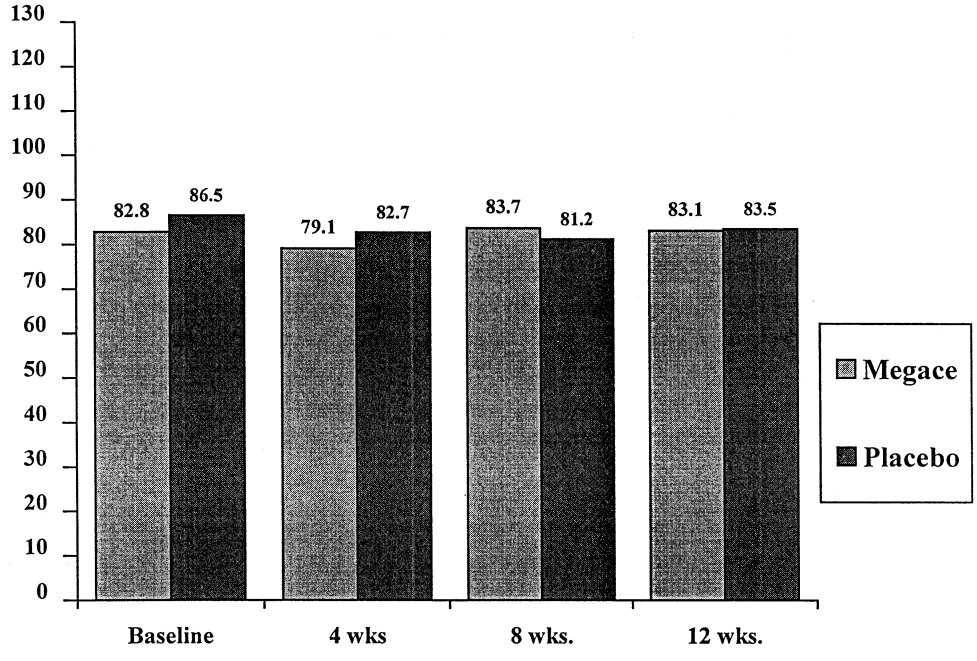

Fig. 2. Functional Assessment of Cancer Therapy (FACT-G) quality-of-life mean scores at four time points.

tistically significant: (*1*) "I am able to eat as much food as I like." Head/neck cancer patients on the MA arm had greater mean scores at 12 weeks ($p = 0.02$, mean [± SE] = 2.0 ± 0.4 MA vs. 0.4 ± 0.4 P). (*2*) "I have a good appetite." Lung cancer patients on the Megace arm reported greater mean scores at 4 weeks ($p = 0.03$, mean [± SE] = 2.9 ± 0.4 MA vs. 1.7 ± 0.3 P) and at 8 weeks ($p = 0.001$, mean [± SE] = 3.5 ± 0.4 MA vs. 1.6 ± 0.3 P). Furthermore, there was a nonstatistically significant trend toward patients on the MA arm reporting higher mean scores (least square) on the item "I am content with the quality of my life right now" at baseline and at 4, 8, and 12 weeks, respectively: MA 2.3 ± 1.4 vs. P 2.1 ± 1.4, MA 2.1 ± 1.4 vs. P 1.9 ± 1.2, MA 2.4 ± 1.1 vs. P 1.9 ± 1.3, and MA 2.6 ± 1.3 vs. P 2.2 ± 1.5.

A total of 24 lung and 6 head/neck cancer patients received chemotherapy as well as RT. There were no statistically significant differences between the patients who received RT plus chemotherapy compared to those who received RT alone on any of the FACT subscales, with the exception of the emotional well-being subscale, which was higher for lung cancer patients receiving RT only ($p = 0.03$). Those patients with head-and-neck cancer receiving RT plus chemotherapy had the lowest scores on the FACT, although the scores were not statistically significant.

The incidence of treatment-associated Grade 1–4 toxicity from either RT + MA (Grade 1 + 2 = 16, Grade 3 + 4 = 0) or RT + Placebo (Grade 1 + 2 = 15, Grade 3 + 4 = 3) was similar. Grade 1–3 nausea was less common on the MA arm ($n = 3$) than on the placebo arm ($n = 6$), whereas Grade 1–2 pulmonary toxicity (dyspnea, cough) was more common on the MA arm ($n = 5, 7$) than on the placebo arm ($n = 1, 2$).

DISCUSSION

We hypothesized that preventing weight loss or maintaining weight during treatment could have a favorable effect on patient-reported quality of life. We assumed that appetite and weight maintenance would affect nutritional well-being and would be reflected in overall QOL. This seemed likely, because one benefit of maintaining weight (nutritional status) might be improved healing and repair from damage associated with treatment. Improved recovery time may be a possibility, although it was not measured in this study. Although patients in the MA group did lose less weight over the 12-week course of study, weight maintenance did not translate into an improvement in overall QOL.

Several factors may account for these results. First, it could be that maintaining behaviors associated with eating, e.g., gathering at family meals, going out to eat, socializing, etc., are not equally important to individual patients. Whereas one patient might thoroughly enjoy being with her family and friends at a meal, another may prefer noncommunal meals. For the first patient, disruption of appetite may result in a lowered score on the social/family well-being subscale (i.e., "I get emotional support from my family"). She would not experience socially supportive interaction at mealtime, because she would not feel like eating. A lowered score on this subscale would result in a lowered overall score. For the second patient, however, there would not be a lowered score on the social/family well-being subscale, because mealtime interaction was not a source of emotional support. Because the number of patients in each arm is relatively small, several patients with this pattern could influence the overall results.

Second, weight loss may be experienced differently by individual patients. A patient who perceives herself as overweight may in fact welcome a weight loss, whereas the patient who enters RT with the perception of being thin may be highly distressed by weight loss. One assumes that patients with these different attitudes would be distributed evenly across the two study arms, because of the random assignment of each arm. However, because there are relatively few patients in each group, the patients with these different attitudes could affect the overall results of this study.

Third, it is likely that patients with head/neck and lung cancer experience the side effects of treatment differently and may benefit differentially from Megace, given that RT to the mouth may damage taste sensation. Combining these two groups might actually dilute any effect that might be seen in the lung cancer patient group alone. Including them together in this study may have made it more difficult to detect differences. We are conducting ongoing separate studies with head/neck and lung cancer patients to test this hypothesis.

Fourth, there would need to be fairly large differences in overall QOL for them to be detected, because there are only 28 patients in each arm. However, in an unpublished three-center clinical trial with a larger sample of cancer patients, Cella *et al*. tested the effect of liquid formulation megestrol acetate (200 vs. 800 mg/day). They discovered a greater increase in appetite and weight with the use of 800 mg of MA, but did not find statistically significant changes in overall QOL (D. Cella, Center on Outcomes Research and Education, Evanston Northwestern Healthcare, Evanston, IL, personal communication, 2000). The relationships between appetite, eating behavior, weight maintenance, and QOL are complex and yet to be fully understood.

Eating behavior is central to the identity of most human beings. To lose appetite and weight and to experience negative changes in physical appearance as well can be distressing to many, if not most, patients. To lose social relations that accompany eating behavior and activity may also deeply wound some patients, affecting their core sense of who they are. Such an experience may not be adequately reflected on individual items in the overall measurement of life's quality. The present study did not identify a significant QOL beneficial effect of MA with regard to weight loss. However, similar to a previously reported study of head-and-neck cancer (1), weight loss in our study population of lung and head/neck cancer patients receiving curative doses of RT was also approximately 3.5 kg less with the use of

MA. The cost of administering MA at 800 milligrams per day for 2 weeks is at this time approximately $40. This cost may be a wise investment in the patient's overall care.

Most clinicians have had the experience of caregivers seeking to restore eating behavior, and studies have reported on the importance of this phenomenon (18, 19). Appetite stimulation may be good for both the patient and family. Jatoi *et al*. concluded that appetite " . . . is important in its own right—independent of QOL, independent of survival, and independent of any other clinical endpoint" (11). It may be both literally and figuratively true that "I eat; therefore I am." Although individual clinicians may differ on this perspective, it is important to keep attitudes toward appetite, weight, and eating behavior in mind when assessing patient needs and methods that might supply supportive care in the midst of debilitating treatment.

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