The effect of medroxyprogesterone acetate on weight gain and performance status in patients with lung cancer

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High dose medroxyprogesterone acetate (MPA) used in hormone responsive cancers like breast and prostate is known to improve performance status of cancer patients by increasing appetite. In this study we aimed to evaluate the effects of MPA on body weight, performance status and constitutional symptoms, as well as its toxicity on patients with primary lung carcinoma. Of 70 primary lung carcinoma patients, 19 patients with small cell lung cancer (SCLC) received EC (etoposide-cisplatin), and 51 non-small cell lung carcinoma (NSCLC) patients received MIC (mitomycin-ifosfamide-cisplatin). In addition, patients were divided in two groups. Patients in group A (n=40) additionally received MPA. In Group B (n=30), only chemotherapeutical agents were administered. At the end of therapy, lasting 8 weeks, 70% (28/40) of patients in Group A and 27% (8/30) of patients in Group B gained a body weight of >3 kg. This difference in weight gain was statistically significant (p<0.01). When changes in performance status were evaluated, 52.5% (21/40) of patients in Group A and 27%, (8/30) of patients in Group B showed improvement (p<0.05). An increase in appetite in 52.5% (21/40), a decrease in pain in 70% (28/40) and a better mood in 55%, (22/40) of Group A patients was observed. In Group A five (12.5%) patients had grade 2 headaches, three (7.5%) patients had grade 2 nausea and vomiting and two women had irregular menstruations. It was concluded that MPA in lung cancer patients might be considered to be an effective agent in improving body weight and performance status. The toxicity of MPA was acceptable. [Turk J Med Res 1996; 14(2):74-77]

Key Words: Medroxyprogesterone acetate (MPA), Lung cancer

Anorexia, a symptom of cancer, leads to decreased food intake, weight loss and cachexia (1,2). Cachexia is characterized by anemia, protein depletion and other metabolic abnormalities. These catabolic processes lead to progressive deteration of nutrition, compromise other body functions, lower tolerance to infections, slow healing and aggravate the toxicities of antineoplastic treatments (1,2).

The presence of anorexia, weakness and changes in body image cause considerable distress to both patients and their families. Successful treatment of anorexia can benefit the patient in at least two ways: first, resultant improvement in food intake can prevent or reverse the effects of anorexia on nutrition and second, reversal of the symptom can improve the patient's comfort level.

In small cell lung cancer (SCLC), an apparently small tumor burden may be associated with significant weight loss and a poor prognosis (3). In the same way, the increase in metabolic processes seen in patients with non-small cell lung cancer (NSCLC) like head-neck cancer and colorectal cancer could lead to weight loss, and as a result to regression in performance status (4).

Weight gain has been recognized as a side effect of progestational derivatives, particularly medroxyprogesterone acetate (MPA) and megestreol acetate (MA) used in hormone-responsive tumors such as breast cancer (5,6). There are many investigations concerning effects of MPA in patients with breast and prostate cancer. But there is little information about effects of MPA on body weight in patients with primary lung carcinoma.

The aim of our study was to evaluate the effects of MPA on body weight, performance status and constitutional symptoms as well as its toxicity in patients with primary lung cancer who had lost more than 10% of their preillness body weight.

MATERIALS AND METHODS

Patients with histologically and/or cytologically confirmed primary lung cancer entered this study at Ataturk Chest Diseases Hospital Oncology Ward between April 1992 and December 1993. Patients were required to have adequate hematologic, renal, hepatic functions and ECOG (Eastern Cooperative Oncology Group) performance status <3. Patients were staged according to the New International Staging System (ISS) (7).

After stratification, according to histological type, performance status and extent of the disease, the pa-

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tients were entered sequentially into two groups, until both groups reached 30 patients, then patients were recruited for Group A. That is why the patients of the two groups were not randomized. None of the patients had been treated with chemotherapy or radiotherapy prior to the study. Patients had no hypertension, congestive heart failure, history of coagulation disorders or evidence of diabetes mellitus.

Seventy-eight patients who had lost more than 10% of their regular body weight received either MPA and chemotherapy (in Group A) or chemotherapy alone (in Group B). The patients in Group A received 1000 mg/day p.o. MPA for 8 weeks besides chemotherapy schedules. In both groups the patients with SCLC were given EC schedule, including etoposide 100 mg/m^2-cisplatin 80 mg/m^2 every 3 weeks; the patients with NSCLC were given the MIC schedule including mitomycin 10 mg/m^2-ifosfamide 3 g/m^2-mesna 3 g/m^2-asplatin 50 mg/m^2 every 3 weeks. After 8 weeks, patients in both groups were evaluated for their body weight and performance status changes. The chi square test was used for statistical analysis.

In addition, the patients in the MPA group were asked about their appetite, pain relief and sense of well-being. These subjective responses were assessed as "improved", "no change" or "worsened" as compared to the baseline condition.

Before starting treatment and at the end of 8 weeks physical examination, complete blood count hepatic and renal function tests, serum potassium, cholesterol, lipid, triglyceride levels and ECG were done. All patients were interrogated for the presence of hot flashes, euphoria, vaginal bleeding, nausea and vomiting. The presence of edema was checked by physical examination. Patients were asked whether day had bleeding or evidence of deep vein thrombosis or thromboembolism.

RESULTS

A total of seventy-eight patients were admitted to the study. Eight patients were subsequently withdrawn because of rapid deterioration. Characteristics of both groups are shown in Table 1. Median age of the patients in Group A and Group B was 55 and 64 respectively. Sex ratio (M/F) was 36/4 in Group A and 25/5 in Group B. Median performance status according to ECOG criteria was 2 (range 0-3) and 1 (range 0-2) respectively. Extrathoracic metastasis was seen in 26 patients in Group A and 18 patients in Group B.

At the end of 8 weeks, in Group A, 28 out of forty patients 70% had a weight gain of 3 kg or more, body weight didn't change in 2 patients (5%), while the others (25%) continued to lose weight. Median weight gain in this group was 2.25 kg. Of the 30 patients receiving only chemotherapy (Group B) 8)27%) had a weight gain of 3 kg or more, 12 (40%) had no change in their body weight, meanwhile 10 (33%) of them continued to lose weight. Median weight gain of this group was 2.16 kg. The weight gain ratio was significantly higher in the MPA group (p<0.01) (Table 2).

Table 1. Characteristics of patients

	Group A	Group B
Number of patients	40	30
Male/Female	36/4	25/5
Median age (years)	55	64
Range	30-66	44-75
The initial median performance status	2	[illegible]
Range	0-3	0-2
Stage of disease		
Stage IIIA-IIIB	14	12
Stage IV	26	18
Histology		
SCLC	10	[illegible]
Epidermoid Ca	16	9
Adenocarcinoma	10	8
Large cell Ca	4	3

Table 2. Objective response of patients

	Group A	Group B	
Changes in body weight			
Weight gain	28 (70%)	8 (27%)	p<0.01
Stable weight	2 (5%)	12 (40%)	
Weight loss	10 (25%)	10 (33%)	
Performance status			
Improvement	21 (52.5%)	8 (27%)	p<0.05
Stable	10 (25%)	11 (36.5%)	
Deterioration	9 (22.5%)	11 (36.5%)	

In Group A, performance status improved in 21 (52.5%) patients, remained stable in 10(25%) and became worse in 9(22.5%). In Group B, performance status improved in 8)27%), remained stable in 11 (36.5%) patients. The difference between the improvement of performance status of both groups was significant (p<0.05) (Table 2).

In addition, patients in Group A were asked about their appetite, pain relief and sense of well-being (Table 3). 21 (52.5%) patients apetite whetted, 28 (70%) patients declared reduction of their pain and 22 (55%) patients reported a marked improvement in their sense of well-being. According to WHO criteria, in Group A the adverse effects of MPA were grade 2 headaches in 5 (12.5%) patients, grade 2 nausea-vorniting in 3 (7.5%) and vaginal bleeding in 2 female patients (Table 4).

Table 3. Subjective responses of patients in Group A

	Appetite	Pain relief	Well-being
Improved	21 (52.5%)	28 (70%)	22 (55%)
No change	8(20%)	9(22.5%)	10(25%)
Worsened	11(27.5%)	3(7.5%)	8 (20%)

Table 4. Adverse effects of MPA at patients in Group A

	Grade (WHO)	n (%)
Headache	2	5(12.5%)
Nausea-vomiting	2	3 (7.5%)
Vaginal bleeding	1	2
(Adjustment was made for sex)		

DISCUSSION

Physiopathology of cancer-related cachexia remains poorly understood despite the severity and frequency of the problem. Malnutrition and cachexia in cancer patients due to protein-caloric deficiencies is occasionally seen in clinics as weight loss. Weight loss incidence changes according to the type, stage and therapy response of the tumor. Patients with some type of cancer e.g. lung, prostate, head-neck and gastric cancers are more frequently affected, but the overall incidence ranges between 48% and 61% in the different groups studied. There is no correlation between the tumor extent and weight loss in lung cancer (7).

There is little evidence indicating the suppression of the appetite center in the hypothalamus. However, the adverse effects of chemotherapy and radiotherapy such as bad taste and smell, anorexia and nausea are important factors, that reduce the intake of food (4,7,8). A study in patients with SCLC demonstrated that the mean energy expenditure was 37% above the expected rate in comparable normals (3). The increase in whole body glucose production in patients with NSCLC, head neck cancer and colorectal cancer could consume enough energy to lead to a weight loss of 0.9 kg per month. Results from studies have suggested that increased glucose production in NSCLC patients may increase protein breakdown in order to obtain glycogenic aminoacids (4).

Recently interest has focused on the ability of various cytokines, such as the tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6), and gamma-interferon (γIFN) to produce the metabolic abnormalities associated with malignancy. The suggestion is that TNF, which suppresses the synthesis of lipoprotein lipase in adipocytes, may be the cause of the cathectic state (2,4,7,9,10). Finally, chemicals like toxohormon-L and lipid mobilizing factor (LMF), which are produced directly by tumors, appear to cause severe lipolysis by suppressing food and water intake (2,10).

MA and MPA, synthetic orally active progestins, stimulate the appetite and produce weight gain in patients with breast cancer (5). MA, a derivative of MPA is similar to its parent drug and is widely studied (9,11). According to Willemse et al (5), MPA seems to be marginally more effective than MA and has minor side effects. Improvement in appetite, body weight and intake of food with MPA and/or MA has been shown in many uncortrolled pilot studies and several randomized trials in patients with various advanced malignencies, including breast cancer (8,10-16). In addition to effects of MPA on cancer related cachexia, the effectiveness of its was reported to treat AIDS-related anorexia and cachexia (17,18).

The mechanism of action of MPA is not clearly known. Edema in lower extremities was seen in 30% of the patients, but weight gain was found to be due to an increase of both fat and lean body mass, not fluid retention (6,11-14). Animal models indicate that gonadal steroids affect both energy stores and body weight. The weight gain is composed primarily of fat, lean tissue and water (18). Admitelly, our study was not designed to clearly determine changes in body composition (lean tissue mass vs. fluid) of our patients. Measurement of total body fat, lean tissue mass and water was not feasible in the present setting.

Progesterone receptors are present in various central and peripheral tissues, including the hypothalamic, pituitary and adipose tissues. MPA's effects are likely multiple and interrelated. Lang et al reported that MPA restored and increased the pituitary function of tumor patients resulting in a pituitary function similar to that seen in normal subjects (19). This effect relases to the relief of symptoms and improvement in life quality as seen in patients during high-dose MPA therapy.

The optimal dose of MPA to induce appetite stimulation and weight gain is unknown. Some data from patients with advanced cancer suggest that there is a dose-response effect (6,10,11,20). Heckmayr et al (9), suggested that to achieve weight gain in patients with advanced bronchogenic carcinoma, a high-dose seems to be more effective than a low dose. In this study patients who had received prior chemotherapy were divided into two groups: The first group received low dose of MPA (160 mg/day). Weight gain was shown in the patients who received MPA in the high dose, especially in early stages of disease.

In our study, we administered chemotherapy and MPA at the same time, especially the last, in a very high dose (1000 mg/day). The patients who received MPA plus chemotherapy had a more advanced stage of disease in comparison with the control group.

Niiranen et al (8), reported that MPA had no significant effect on chemotherapy response, side effects or survival in patients with NSCLC and SCLC; but combining MPA and chemotherapy may result in improved quality of life. Another study suggested that it abrogates drug resistance and increases survival time in melanoma (20). Moreover MPA is used as a bone-marrow protective agent, blocking the hematologic toxicities of chemotherapeutic agents and has antiemetic properties in various malignancies (11,22,23). We did not evaluate the effect of MPA on the chemotherapy response or on the chemotherapy induced side effects.

In our study, 70% of the patients showed a weight gain and 52.5% an improvement in performance status with MPA plus chemotherapy. Improvement in appetite was seen in 52.5%, pain relief in 70% and improvement in sense of well-being in 55% of patients. The median age of the patients who received additional MPA was low, but performance status was worse, and the percentage of advanced stages of disease was higher when compared with the control group. In this study, we didn't use any systematic questionnaire for assessment of the state of life quality.

MPA did not cause thrombotic events or hypertension in any patient. Several studies reported that MPA may induce a hypercoagulable state, but this state does

not directly lead to the development of thrombosis (24,25). MPA's side effects were seen less frequently than expected.

Consequently, MPA may be used to improve weight gain and performance status in patients with primary lung carcinoma who have an acceptable toxicity. Further evaluation of its mechanisms of action, dose-response relationship, effect on patient survival and on life quality are warranted.

Medroksiprogesteron asetatın akciğer kanserli hastalarda kilo ve performans arttırıcı etkisi

Meme ve prostat kanseri gibi hormonal tümörlerde kullanılan yüksek doz metroksiprogesteron asetatın (MPA) iştah artırarak kanserli hastaların performansını düzeldiği bilinmektedir. Çalışmamızda MPA'nın primer akciğer kanserli hastaların vücut ağırlığı, performans durumu, semptomları üzerine etkisini ve ilacın toksisitesini değerlendirmeyi amaçladık. Çalışma grubuna alınan 70 primer akciğer kanserli hastanın 19'u küçük hücreli akciğer kanseri (SCLC), 51'i ise küçük hücreli olmayan akciğer kanseri (NSCLC) idi. SCLC'li hastalara EC (etoposid-sisplatin), NSCLC'li hastalara ise MIC (mitomisin-ifosfamid-sisplatin) kombine kemoterapileri verildi. Tüm hastalar iki gruba ayrıldı. A Grubundaki 40 hastaya kemoterapinin yanısıra MPA, B Grubundaki 30 hastaya ise sadece kemoterapi uygulandı. Sekiz hafta süren tedavi sonunda A Grubundaki hastaların %70 (28/40)'inde, B Grubundaki hastaların %27(8/30)'inde vücut ağırlıklarında >3 kg artış oldu (p<0.01). Performans durumlarına göre A Grubundaki hastaların %52.5 (21/40)'inde, B Grubunda ise %27 (8/30)'unda düzelme görüldü (p<0.05). A Grubunda hastaların %52.5 (21/40)'ı iştahlarında artış, %70(28/40)'ı ağrılarında azalma ve %55(22/40)'ı kendini daha iyi hissettiğini belirtti. A Grubunda 5 (%12.5) hastada grade 2 başağrısı, 3 (%7.5)'ünde grade 2 bulantı-kusma ve 2 kadın hastada menstruasyon düzensizliği gelişti. Buna göre MPA'nın toksisitesinin kabul edilebilir olduğu, primer akciğer kanserli hastaların vücut ağırlığının ve performans durumunun düzeltilmesinde etkili bir ajan olabileceği kanısına varıldı.
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