INTRODUCTION

Megestrol acetate (MA) is a synthetic hormone (progestogen) used for the therapy of hormone-dependent cancer, mainly endometrial cancer and less commonly breast cancer. This drug is also used for symptom relief in anorexia-cachexia syndrome (ACS) patients.

OBJECTIVES

To review the effect of megestrol acetate (MA) in patients with ACS.

PATIENTS AND METHODS

To identify eligible studies, systematic review by Lopez et al. (2004) was used, electronic databases (MEDLINE, EMBASE and CENTRAL) were searched and reference lists of included studies were reviewed. The studies were included in the review if they were randomized, enrolled patients with non-hormone-sensitive cancer and ACS and assessed the effects of MA compared with placebo, other drugs or different doses of MA.

RESULTS

The study population is characterized by high mortality and progressive weight loss irrespective of the treatment. Compared to placebo, the effect of MA on survival is similar, but MA increases appetite (number needed to treat [NNT]: 3) and leads to weight gain (NNT: 8) in more patients. The data on other aspects of the quality of life are limited. The comparison of MA and glucocorticosteroids showed no statistical difference in their effect on appetite and weight.

CONCLUSIONS

Compared to placebo, MA reduces the symptoms of ACS, with no effect on survival. The beneficial effect of MA on the overall quality of life has not been confirmed. In identified studies the effect of MA and glucocorticosteroids on anorexia and cachexia is similar. The estimation of the treatment utility in ACS depends on the weight attributed to discomfort caused by symptoms, adverse effects of the drugs and the treatment cost. Because of the low quality of the included studies a new randomized controlled trial is needed for valid assessment of the effects of MA.

KEY WORDS

anorexia-cachexia syndrome, cachexia, cancer, megestrol acetate, neoplasm

INTRODUCTION

Megestrol acetate (MA) is a synthetic hormone (progestogen) used for the therapy of hormone-dependent cancer, mainly endometrial cancer and less commonly breast cancer. This drug is also used for symptom relief in anorexia-cachexia syndrome (ACS) patients. This syndrome that occurs among other things in the advanced stage of cancer or in association with HIV infection, is characterized by weight and appetite loss, decline in muscle and adipose tissue mass, worsening of the performance status and decrease in the quality of life level (well-being).

It is not easy to define cancer malnutrition. Biochemical, anthropometric and immunologic parameters are used for the diagnosis. The most important biochemical test to diagnose malnutrition is serum albumin levels, and to monitor nutritional status changes levels of proteins with shorter half-lives (prealbumin and transferrin). Among anthropometric tests, the unintended weight loss of >10% of the predicted value during the preceding 3 months is a very good index. Other parameters are: arm circumference (normal range: men >23 cm, women >22 cm) indicating the muscle tissue mass and skin fold thickness over the triceps muscle (normal range: men >10 mm, women >13 mm), an indicator of fat reserves, and the determination of total intracellular potassium using the K42
| Study (author, year) | Population | Intervention | Dose (mg/dl) | Number of participants in groups | Study duration (weeks) |
|---------------------|------------|--------------|--------------|----------------------------------|-----------------------|
| Beller 1997 [8]    | Advanced hormone-insensitive cancer, weight loss | MA | 480 | 81 | 12 |
|                     |            | MA | 160 | 80 |                |
|                     |            | Placebo | 0 | 79 |                |
| Bruera 1990 [6], cross-over trial | Advanced hormone-insensitive cancer, weight loss | MA | 480 | 31 + 9 | 1 |
|                     |            | Placebo | 0 | 31 + 9 |                |
| Bruera 1998 [27], cross-over trial | Advanced hormone-insensitive cancer, (local recurrence or metastases), anorexia | MA | 480 | 84 | 1.5 |
|                     |            | Placebo | 0 | 84 |                |
| Chen 1997 [9]      | Head or neck cancer, full course of radiotherapy, no ACS (prevention only) | MA | 160 | 48 | 8 |
|                     |            | Cisapride | 15 | 41 |                |
|                     |            | Placebo | 0 | 40 |                |
| De Conno 1998 [33] | Advanced hormone-insensitive cancer, diminished appetite or anorexia | MA | 320 | 17 + 4 | 2 |
|                     |            | Placebo | 0 | 16 + 5 |                |
| Erkurt 2000 [32]   | Confirmed cancer, weight loss, progressive anorexia | MA | 480 | 50 | 12 |
|                     |            | Placebo | 0 | 50 |                |
| Farmer 2005 [18]   | Lung, head or neck cancer, treated with radiotherapy | MA | 800 | 20 | 17–19 |
|                     |            | Placebo | 0 | 18 |                |
| Feliu 1992 [30]    | Advanced hormone-insensitive cancer, only palliative care, weight loss >10% or anorexia | MA | 240 | 76 | ≥8 |
|                     |            | Placebo | 0 | 74 |                |
| Fietkau 1997 [10]  | Histologically verified head or neck cancer, radiotherapy, weight loss >5% in 6 weeks or >10% in 6 months | MA | 160 | 31 | 12 |
|                     |            | Placebo | 0 | 30 |                |
| Gambardella 1998 [34] (abstract) | Hormone-insensitive cancer, elderly patients, weight loss >7 kg in last 3 months | MA | 320 | No data | 12 |
|                     |            | Placebo | 0 |                |                |
| Gebbia 1996 [21]   | Advanced hormone-insensitive cancer, irresponsive to chemotherapy | MA | 320 | 60 | 4 |
|                     |            | MA | 160 | 62 |                |
| Giacosa 1997 [28]  | Advanced cancer, weight loss >10% or daily calorie intake of <20 kcal/kg/d | MA + dietary counseling; only dietary counseling | 320 | 10 | 4 |
|                     |            | Placebo | 0 | 8 |                |
| Heckmayr 1992 [23] | Advanced lung cancer | MA | 480 | 33 | 12 |
|                     |            | MA | 160 | 33 |                |
| Jatoi 2002 [15]    | Advanced hormone-insensitive, incurable cancer, weight loss >2.3 kg (5 lbs) in 2 months or daily calorie intake of <20 kcal/kg, weight loss perceived by the patient as a problem, weight gain potentially beneficial for the patient in the physician’s opinion, ECOG performance status 0–2 | MA + placebo | 800 + 0 | 159 | >4 |
|                     |            | Dronabinol + placebo | 5 + 0 | 152 + 2 |                |
|                     |            | Dronabinol + MA | 5 + 800 | 158 |                |
| Jatoi 2004 [14]    | Advanced hormone-insensitive, incurable cancer, weight loss >2.3 kg (5 lbs) in 2 months or daily calorie intake of <20 kcal/kg, weight loss perceived by the patient as a problem, weight gain potentially beneficial for the patient in the physician’s opinion, ECOG performance status 0–2 | MA + placebo | 600 | 140 | 12 |
|                     |            | Eicosapentaenoic acid + placebo | 600 | 141 |                |
|                     |            | MA + eicosapentaenoic acid | 2180 + 2180 | 140 |                |
| Lai 1994 [11]      | Pelvis radiotherapy, anorexia during radiotherapy, no prior treatment for anorexia | MA | 160 | 20 | 3 |
|                     |            | Prednisolone | 30 | 19 |                |
|                     |            | Placebo | 0 | 19 |                |
| Loprinzi 1990 [16] | Advanced, incurable cancer (other than breast or endometrial cancer), weight loss >2.3 kg (5 lbs) in 2 months or daily calorie intake of <20 kcal/kg, weight loss perceived by the patient as a problem, weight gain potentially beneficial for the patient in the physician’s opinion | MA | 800 | 67 + 1 | 10 |
|                     |            | Placebo | 0 | 66 + 1 |                |
isotope, which enables body cell mass assessment. Considering immunological parameters the lymphocyte count (decreased in malnutrition) is most commonly used in practice. In the diagnostic process these above mentioned criteria for ACS are often neglected, which is one of the factors responsible for MA abuse in Poland.

The MA is commonly used in Poland, which is also reflected through its high rank on the list of reimbursed expenses. For ACS in the course of cancer treatment, the form of a suspension and for hormone-dependent cancer the tablets are being reimbursed.

**PATIENTS AND METHODS** The aim of this systematic review with a meta-analysis was the assessment of clinical effects of MA use in advanced stage cancer patients with ACS.

**The study source** For the identification of appropriate studies by systematic review the Lopez et al. was used and the MEDLINE (2002–2007), EMBASE (2002–2007) and CENTRAL (Cochrane Library; Issue 3, 2007) bibliographic databases were searched. Reference lists of the studies included in the analysis have also been reviewed.

The following key words were employed for the search strategy: neoplasm, cancer, cachexia, anorexia, megestrol acetate. There were no language restrictions on publications. Conference abstracts were also analyzed.

| Study (author, year)  | Population                                                                 | Intervention | Dose (mg/dl) | Number of participants in groups | Study duration (weeks) |
|----------------------|----------------------------------------------------------------------------|--------------|--------------|----------------------------------|------------------------|
| Loprinzi 1994 [26]   | Advanced hormone-insensitive, incurable cancer, weight loss > 2.3 kg (5 lbs) in 2 months or daily calorie intake of < 20 kcal/kg | MA           | 160          | 88                               | 10                     |
|                      |                                                                            | MA           | 480          | 86                               |
|                      |                                                                            | MA           | 800          | 85                               |
|                      |                                                                            | MA           | 1280         | 83                               |
| Loprinzi 1999 [29]   | Advanced hormone-insensitive, incurable cancer, weight loss > 2.3 kg (5 lbs) in 2 months or daily calorie intake of < 20 kcal/kg, weight loss perceived by the patient as a problem, weight gain potentially beneficial for the patient in the physician’s opinion, ECOG performance status 0–2 | MA           | 800          | 158 + 7                          | 4                      |
|                      |                                                                            | Dexamethasone| 3            | 159 + 7                          |
|                      |                                                                            | Flumoxymesterone| 20     | 158 + 7                          |
| Mc Millan 1994 [31]  | Histologically verified cancer of the gastrointestinal tract, only palliative therapy, weight loss of > 5% | MA           | 480          | 12                               | 12                     |
|                      |                                                                            | Placebo      | 0            | 14                               |
| McQuellon 2002 [17]  | Nasopharyngeal, oral, pharyngeal or lung cancer, radiotherapy, without weight loss, ECOG performance status 0–2 | MA           | 800          | 28                               | 12                     |
|                      |                                                                            | Placebo      | 0            | 28                               |
| Pardo 2003 [24]      | Nonmetastatic lung cancer, radiotherapy, anorexia                          | MA           | 600          | 66                               | 4                      |
|                      |                                                                            | MA           | 320          | 64                               |
| Rowland 1996 [7]     | Small-cell extensive stage lung cancer, ECOG performance status 0–2, weight loss of > 5% in 6 weeks or > 10% in 6 months | MA           | 800          | 122                              | 104                    |
|                      |                                                                            | Placebo      | 0            | 121                              |
| Sancho Cuesta 1993   | Advanced cancer, palliative treatment, anorexia, weight loss                | MA           | 160          | 50                               | 12                     |
| (abstract) [20]      |                                                                            | MA           | 320          | 50                               |
| Schmoll 1992 [25]    | Advanced stage cancer, palliative treatment, weight loss of > 5%            | MA           | 480          | 34                               | 8                      |
|                      |                                                                            | MA           | 960          | 29                               |
|                      |                                                                            | Placebo      | 0            | 28                               |
| Tchekmedyian 1992    | Advanced hormone-insensitive cancer, weight loss of > 5%, anorexia          | MA           | 1600         | 49                               | 24                     |
| (abstract) [19]      |                                                                            | Placebo      | 0            | 40                               |
| Ulutin 2002 [22]     | Advanced non-small cell lung cancer, loss of > 10% weight in 6 months      | MA           | 160          | 59                               | 12                     |
|                      |                                                                            | MA           | 320          | 60                               |
| Vadell 1998 [12]     | Incurable cancer, weight loss of > 5%                                      | MA           | 480          | 49                               | 12                     |
|                      |                                                                            | MA           | 160          | 50                               |
|                      |                                                                            | Placebo      | 0            | 51                               |
| Westman 1999 [35]    | Hormone-insensitive cancer, palliative therapy                             | MA           | 320          | 128                              | 12                     |
|                      |                                                                            | Placebo      | 0            | 127                              |
| Zecca 1995 [13]      | Advanced hormone-insensitive cancer, anorexia                              | MA           | 320          | 16                               | 2                      |
| (abstract)           |                                                                            | Placebo      | 0            | 17                               |
Study selection for analysis  The following criteria for study inclusion in the analysis were applied:
1  randomization
2  diagnosis of advanced stage cancer (with the exclusion of hormone-dependent cancer) and ACS
3  intervention: MA in comparison with placebo or other drugs used in practice or in clinical studies in ACS (glucocorticosteroids, cisaprid, dronabinol, eicosapentaenoic acid, fluoxymesterone) or MA in various doses
4  outcomes: survival rate, weight change, performance status (Karnofsky scale, ECOG scale), selected quality of life parameters (appetite, nausea, pain, fatigue, depression, well-being, mood).

Methods of review – study quality assessment  Identified studies have been initially assessed and selected on the basis of their eligibility for the reviewed topic. Then the validity of selected studies was assessed considering randomization, the intention to treat analysis and the completeness of follow-up.5

The following persons were responsible for defining the clinical question, outcome selection, and assessment of clinical aspects of results: Roman Jaeschke, Maciej Krzakowski and Wiktoria Leśniak.

Available evidence review, methodology assessment, data identification, and their entering into the Review Manager was done independently by 2 persons (Wiktoria Leśniak and Małgorzata Bała or Roman Jaeschke).

Statistical analysis  The results of primary studies were pooled by meta-analysis using the Der-Simonian and Laird method, employing the Review Manager 4.2.10 program. The statistical significance of overall effects was calculated with the use of the Z test, and the homogeneity of results between studies was assessed with the $\chi^2$ and I$^2$ tests.

The results were summarized using the method developed by the GRADE group, which works on the grading of recommendations in clinical practice guidelines.

RESULTS  Description of included studies  Thirty studies have been included in the review, 5 of which were conference abstracts. The studies’ description (population description, drugs compared and their doses, the number of participants, study duration) are shown in TABLE 1 (available in the electronic version of the article). All studies included advanced stage cancer patients with the exclusion of hormone-dependent cancer; most of the studies included patients suffering from various cancers, in several studies lung cancer was the inclusion criterion, in several others head and neck cancer. The shortest duration of follow-up was 1 week$^6$, the longest 2 years$^7$; in the remaining studies the median or mean follow-up period ranged from 2 to 24 weeks.

In the studies in which MA was compared with other drugs or a placebo, the doses of MA ranged from 160 mg/d$^{8-12}$ through 320 mg/d$^{13}$ up to over 480 mg/d (600 mg/d$^{14}$); 800 mg/d$^{7,15-18}$; 1600 mg/d$^{19}$). In the other studies the daily dose ranged 240–480 mg.

In several studies various MA daily doses were compared (160 mg vs 320 mg$^{20-22}$, 160 mg vs 480 mg$^{4,12,23}$, 320 mg vs 600 mg$^{24}$, 480 mg vs 960 mg$^{25}$, 160 mg vs 480 mg vs 800 mg vs 1280 mg$^{26}$).

Two studies with a short duration of drug administration (up to 10 days) were performed as cross-over trials$^{6,27}$, the remaining trials were parallel trials.

The majority of studies were performed with the use of placebo, or with blinding of the alternative intervention in the control group; with the exception of the Giacos et al. study$^{28}$ (lack of placebo, lack of blinding) and the Loprinzi et al. study$^{29}$ (MA vs dexamethasone vs fluoxymesterone).

The methodological quality of studies included in the analysis:
1  the majority of the studies were placebo controlled and blinded
2  the randomization process has not been described in most cases
3  patients who died within the follow-up period were excluded from the analysis in several studies; in the majority of studies the analysis did not include a large number of patients (30–40%), mainly because of their withdrawal
4  in the present analysis, the proportion of patients in whom a certain outcome occurred was calculated, as far as possible, in relation to the number of patients randomized (intention-to-treat analysis); in some original studies the per-protocol analysis was used in which only patients who completed the study were included
5  in several studies the authors did not show the numerical data regarding some predefined outcomes, or presented data were incomplete, which made it impossible to use them in the present meta-analysis; publication bias may be suspected, which lowers the validity of this meta-analysis
6  despite the methodological limitations, studies included in the analysis represent the best available evidence on the effects of MA use in ACS associated with advanced cancer.

Meta-analysis  The estimated effect size for various outcomes is shown in TABLE 2.
1  In comparison with placebo, MA administration:
A  resulted in any weight gain in (a meta-analysis of studies with different weight gain definitions) a statistically significant higher percentage of patients (TABLE 2)$^{7,16-12,18,19,23,30,31}$ (FIGURE 1)
B  resulted in a weight gain of $\pm 5%$$^{12,16,31}$ and weight gain of $\pm 10%$$^{7,16,30,31}$ in a non significantly higher percentage of patients (TABLE 2); heterogeneity for the above mentioned results has not been demonstrated
survival was assessed. The mean difference between groups was 14 mm (95% CI 7–21); a difference of this range for a certain patient is regarded as a clinically significant one, when measuring symptoms and the quality of life. In the meta-analysis of all available studies with an assessment of appetite change from baseline values, standardized mean difference (SMD) expressed in standard deviation (SD) units was 0.44 (95% CI 0.20–0.68), which corresponds to medium effect size in the whole group of patients. It may also correspond to e.g., a large effect size of treatment in every other patient. The presented systematic review according to the GRADE system expressed the effect of MA treatment.

### RESULTS

#### 1. Appetite Improvement

- **A**: A comparable rate of patients with an appetite improvement
- **B**: A comparable rate of patients with weight gain.
- **C**: Fluvastatin was associated with a beneficial trend toward MA regarding the rate of patients with appetite improvement and weight gain.

#### 2. Weight Gain

- **A**: An improvement in the overall well-being (an increase of 8 millimetre [95% CI 0.55–1.09] and lack of the effect on appetite (outcome assessed only in 1 study [25]).
- **B**: An assessment of the quality of data on the effects of MA administration in ACS and a summary of the results are shown in **TABLE 2** according to the GRADE system [26].
- **C**: Dronabinol was associated with a beneficial trend toward MA regarding the rate of patients with appetite improvement and weight gain.

#### 3. Quality of Life

- **A**: A decrease of 10–15 mm in pain perception (an increase of 9 millimetre [95% CI: from a decrease of 4 up to an increase of 22])
- **B**: Lack of a statistically significant difference in depression symptoms (a decrease of 5 millimetre [95% CI: from a decrease of 15 up to an increase of 6])
- **C**: Lack of a statistically significant difference in depression symptoms (a decrease of 5 millimetre [95% CI: from a decrease of 15 up to an increase of 6])
- **D**: An improvement in the overall well-being (an improvement of 8 millimetre [95% CI 1–15]).

#### 4. Side Effects

- **A**: A decrease of nausea of 6 millimetre (95% CI 1–11)
- **B**: Lack of a statistically significant difference in pain perception (an increase of 9 millimetre [95% CI: from a decrease of 4 up to an increase of 22])
- **C**: Lack of a statistically significant difference in depression symptoms (a decrease of 5 millimetre [95% CI: from a decrease of 15 up to an increase of 6])

#### 5. Appetite Improvement

- **A**: A comparable rate of patients with an appetite improvement
- **B**: A comparable rate of patients with weight gain.

#### 6. Weight Gain

- **A**: An improvement in the overall well-being (an increase of 8 millimetre [95% CI 0.55–1.09] and lack of the effect on appetite (outcome assessed only in 1 study [25]).
- **B**: An assessment of the quality of data on the effects of MA administration in ACS and a summary of the results are shown in **TABLE 2** according to the GRADE system [26].
- **C**: Dronabinol was associated with a beneficial trend toward MA regarding the rate of patients with appetite improvement and weight gain.

#### 7. Quality of Life

- **A**: A decrease of 10–15 mm in pain perception (an increase of 9 millimetre [95% CI: from a decrease of 4 up to an increase of 22])
- **B**: Lack of a statistically significant difference in depression symptoms (a decrease of 5 millimetre [95% CI: from a decrease of 15 up to an increase of 6])
- **C**: Lack of a statistically significant difference in depression symptoms (a decrease of 5 millimetre [95% CI: from a decrease of 15 up to an increase of 6])

#### 8. Side Effects

- **A**: A decrease of nausea of 6 millimetre (95% CI 1–11)
- **B**: Lack of a statistically significant difference in pain perception (an increase of 9 millimetre [95% CI: from a decrease of 4 up to an increase of 22])
- **C**: Lack of a statistically significant difference in depression symptoms (a decrease of 5 millimetre [95% CI: from a decrease of 15 up to an increase of 6])

#### 9. Appetite Improvement

- **A**: A comparable rate of patients with an appetite improvement
- **B**: A comparable rate of patients with weight gain.

#### 10. Weight Gain

- **A**: An improvement in the overall well-being (an increase of 8 millimetre [95% CI 0.55–1.09] and lack of the effect on appetite (outcome assessed only in 1 study [25]).
- **B**: An assessment of the quality of data on the effects of MA administration in ACS and a summary of the results are shown in **TABLE 2** according to the GRADE system [26].

#### DISCUSSION

The presented systematic review and the attempt at summarizing quantitatively the results did not bring unexpected conclusions. Similarly to the previously published meta-analyses, an appetite improvement shown in absolute values (number needed to treat [NNT] c. 3–4) and weight gain (NNT c. 8) can be noticed. In the previously published meta-analyses comparable results regarding weight gain (RB 2.16, 95% CI 1.45–3.21 and relative benefit [RB] 2.14, 95% CI 1.41–3.24) and appetite improvement (RB 2.33, 95% CI 1.52–3.59 and RB 3.03; 95% CI 1.83–5.01) were obtained. For appetite improvement, a difference in favor of MA, shown in the present publication and in the Berenstein and Ortiz review, results from the inclusion of an additional study.
### Table 2: Data quality assessment and results summary according to GRADE system

| Data quality assessment                                      | Results summary |
|--------------------------------------------------------------|-----------------|
| **N° of studies**                                            | **Patient number** | **Effect** | **Abs. weight gain (95% CI)** | **Quality** | **Weight** |
| **Type of studies**                                          | **Megestrol**      | **Relative** | **Abs. weight gain (absolute)** |            |           |
| **Quality of studies**                                       |                  | **(95% CI)** | **Quality** |            |           |
| **Results consistency**                                     |                  | **Weight**   |            |           |           |
| **Other factors**                                            |                  | **Gain**     |            |           |           |
| **Results consistency**                                     |                  | **Rate**     |            |           |           |
| **Other factors**                                            |                  | **Rate**     |            |           |           |
| **Quality of studies**                                       |                  | **Weight**   |            |           |           |
| **Other factors**                                            |                  | **Weight**   |            |           |           |
| **Weight gain (any weight gain, follow up time mean c. 3 months). MA vs. placebo** | **N° of studies** | **Type of studies** | **Quality of studies** | **Results consistency** | **Other factors** | **Patient number** | **Effect** | **Abs. weight gain (95% CI)** | **Quality** | **Weight** |
| 9 Randomized studies                                         | No serious        | Without serious | Doubts (−1) | Dose-effect relation ( +1)    | 179/547 (32.7%) | 83/447 (18.6%) | RR 1.71 (1.24–2.36) | 140/1000 (90–190) | ⊕⊕⊕⊕ High | 6 |
| Weight gain of at least 5%. MA vs. placebo                   | Randomized studies | No serious        | Without serious | Doubts (−1) | None                | 38/187 (20.3%) | 16/136 (11.8%) | RR 1.65 (0.94–2.87) | 80/1000 (0–160) | ⊕⊕⊕ O Mediocre | 6 |
| Weight gain of at least 10%. MA vs. placebo                  | Randomized studies | No serious        | Serious | Discrepancy (−1) | No doubts |                         | 45/286 (15.7%) | 10/280 (3.6%) | RR 3.83 (0.73–20.18) | 100/1000 (20–180) | ⊕⊕⊕ O Mediocre | 6 |
| One-year survival MA vs. placebo                             | Randomized studies | No serious        | Without serious | Discrepancy (−1) | No doubts | High probability of publication selectivity (−1) | 55/250 (22%) | 53/248 (21.4%) | RR 1.02 (0.73–1.42) | 10/1000 (–60–80) | ⊕⊕⊕ O Mediocre | 8 |
| Appetite improvement. MA vs. placebo                         | Randomized studies | No serious        | Serious | Discrepancy (−1) | No doubts | Strong intervention-effect relation ( +1) | 170/301 (56.5%) | 47/262 (17.9%) | RR 3.00 (1.86–4.84) | 380/1000 (160–610) | ⊕⊕⊕⊕ High | 8 |
| Physical status worsening (ECOG, Karnofsky). MA vs. placebo   | Randomized studies | No serious        | Serious | Discrepancy (−1) | No doubts | High probability of publication selectivity (−1) | 103/225 (45.8%) | 107/175 (61.1%) | RR 0.65 (0.39–1.08) | 190/1000 (0–380) | ⊕⊕⊕ O Poor | 8 |
| Absolute weight gain in 1–4 weeks (Higher result indicates a more beneficial effect). MA vs. placebo | Randomized studies | No serious        | Serious | Discrepancy (−1) | Doubts (−1) | Strong intervention-effect relation ( +1) | – | WMD 1.98 kg (0.49–3.48) | ⊕⊕⊕⊕ O Mediocre | 6 |
| Absolute weight gain in 8–12 weeks (higher result indicates a more beneficial effect). MA vs. placebo | Randomized studies | No serious        | Serious | Discrepancy (−1) | Doubts (−1) | Strong intervention-effect relation ( +1) | – | WMD 2.91 kg (–0.06–5.89) | ⊕⊕⊕⊕ O Mediocre | 6 |
| Weight gain – 160 mg/d MA vs. placebo                         | Randomized studies | No serious        | No serious | Discrepancy | Doubts (−1) | None | 34/101 (33.7%) | 22/100 (22%) | RR 1.51 (0.94–2.41) | 120/1000 (–20–260) | ⊕⊕⊕ O Mediocre | 6 |
## Data quality assessment

| N° of studies | Type of studies | Quality of studies | Results consistency | Possibility of a clinical reference of the results | Other factors | Megestrol | Relative (95% CI) | Absolute (95% CI) | Quality | Weight |
|---------------|-----------------|--------------------|---------------------|---------------------------------------------------|--------------|-----------|-----------------|-------------------|---------|--------|
| **Weight gain – 160 or 240 mg/d MA vs. placebo** |
| 4 Randomized studies | No serious limitations | No serious discrepancy | Doubts (−1)

### Results summary

| Patient number | Effect |
|----------------|--------|
| 55/177 (31.1%) | 27/174 (15.5%) |
| RR 1.99 (1.09–3.63) | 160/1000 (60–260) |
| ⊕⊕⊕⊕ Mediocre | 6 |

### Other factors

- None

### Applicability score

- Too little evidence (1)

### Sensitivity analysis

- Doubts (−1)

### Results consistency

- No serious discrepancy

### Other factors

- None

### Quality of studies

- No serious limitations

### Results consistency

- No serious discrepancy

### Other factors

- None

### Applicability score

- None

### Sensitivity analysis

- Doubts (−1)

### Results consistency

- No serious discrepancy

### Other factors

- None

### Applicability score

- None

### Sensitivity analysis

- Too little evidence (1)

### Results consistency

- No serious discrepancy

### Other factors

- None

### Applicability score

- None

### Sensitivity analysis

- Doubts (−1)

### Results consistency

- No serious discrepancy

### Other factors

- None

### Applicability score

- None

### Sensitivity analysis

- Too little evidence (1)

### Results consistency

- No serious discrepancy

### Other factors

- None

### Applicability score

- None

### Sensitivity analysis

- Doubts (−1)

### Results consistency

- No serious discrepancy

### Other factors

- None

### Applicability score

- None

### Sensitivity analysis

- Too little evidence (1)

### Results consistency

- No serious discrepancy

### Other factors

- None

### Applicability score

- None

### Sensitivity analysis

- Doubts (−1)
**Results summary**

| Patient number | Megestrol | Relative | Effect | Possibility of a clinical benefit |
|----------------|-----------|----------|--------|-----------------------------------|
| 64/178         | 17/178    | 310      | WMD    | ⊕⊕⊕⊕                             |
| 50/1000        | 50/1000   | 30–70    | 1–1.4  | ⊕⊕⊕⊕                             |

**Data quality assessment**

| Type of studies | Quality of studies | Results consistency | Probability of a clinical benefit | Other factors |
|-----------------|--------------------|---------------------|-----------------------------------|---------------|
| Randomized      | None               | No serious limitations | Doubts (−1)                       |               |
| Randomized      | None               | No serious limitations | Serious discrepancy (−1)           |               |
| Randomized      | No doubts          | No serious limitations | No doubts                         |               |

**Relative Benefit (95% CI)**

| MA vs. glucocorticosteroids – appetite improvement | 1.09 (0.53–2.25) |
| MA vs. glucocorticosteroids – weight gain         | 1.4 (0.7–2.79)   |

**Absolute Benefit (95% CI)**

| Cost of drug administration at the dose of 160 mg/d for 100 days | 20/1000 |
|------------------------------------------------------------------|--------|

**Cost of drug administration**

| Type of studies | Cost of drug administration at the dose of 160 mg/d for 100 days |
|----------------|------------------------------------------------------------------|
| Randomized     | 12/178 (7.1%)                                                   |
| Randomized     | 70/178 (39.3%)                                                  |
| Randomized     | 64/178 (38%)                                                   |

**Implications for clinical practice**

1. The influence of MA on the survival rate in the advanced cancer patients has not been demonstrated.
2. In the majority of patients weight loss progresses independently of treatment, and the drug administration is associated with at least short-term weight gain in additional 10–15% of patients.
3. Although a decrease in appetite or its loss persist in most individuals, the drug administration improves this aspect of the quality of life in c. 30% of patients.
4. Compared with placebo, MA induces weight gain and appetite improvement. In a single study an overall improvement of well-being has been demonstrated.
Because of a low value of available studies, for a more reliable assessment of MA efficacy in cancer-associated ACS it is necessary to perform a randomized controlled trial of high methodological quality.

**ACKNOWLEDGEMENTS**
The review was supported by the Ministry of Health and Social Welfare in 2006.

**REFERENCES**

1. [Drugs Index by Medycyna Praktyczna]. Medycyna Praktyczna, Kraków 2007: 432. Polish.
2. Nelson KA, Walsh D, Sheehan FA. The cancer anorexia-cachexia syndrome. J Clin Oncol. 1994; 12: 212–225.
3. Szabłowski AW. [Disturbances of nutrition and rules on artificial nutrition for cancer patients]. In: Krzakowski M. (eds). [Clinical Oncology]. Wydawnictwo Medyczne Borgis, Warszawa 2006: 515–532. Polish.
4. Pascual López A, Roqué i Figuls M, Urrútia Cuchi G, et al. Systematic review of megestrol acetate in the treatment of anorexia-cachexia syndrome. J Pain Symptom Manage. 2004; 27: 360–369.

**FIGURE 1** The effects of megestrol acetate use in advanced stage cancer anorexia-cachexia syndrome on weight gain demonstrated, the assessment of other quality of life aspects did not lead to practical implications. Beneficial effects on body weight increased with the dose. However, even the lowest daily dose (160 mg) showed a beneficial trend compared to placebo. A statistically significant influence of a dose increase on appetite improvement has not been demonstrated.

5. A comparison of the effects of MA and glucocorticosteroid administration did not show difference in appetite improvement and weight gain.

6. Lower extremity edema in short-term follow-up, and probably the thromboembolic complications risk increase in long-term follow-up are the adverse effects of MA demonstrated in previous publications.

**FIGURE 2** The effects of megestrol acetate use in advanced stage cancer anorexia-cachexia syndrome on appetite improvement

**Implications for further studies** Further determination of the MA role in ACS syndrome treatment requires determining the relative value (utility) attributed by patients to individual health conditions associated with the drug administration, including appetite improvement and weight gain.

Because of a low value of available studies, for a more reliable assessment of MA efficacy in cancer-associated ACS it is necessary to perform a randomized controlled trial of high methodological quality.

**Comparison: MA vs. placebo**
Outcome: Appetite improvement

| Study or sub-category | MA n/N | Placebo n/N | RR (random) [95% CI] | Weight % | RR (random) [95% CI] |
|-----------------------|--------|-------------|----------------------|-----------|----------------------|
| Erkurt 2000           | 47/58  | 6/57        |                      | 15.94     | 7.70 [3.58, 16.58]   |
| Fietkau 1997          | 38/76  | 10/74       |                      | 18.61     | 3.70 [1.99, 6.87]    |
| Lai 1994              | 11/20  | 4/19        |                      | 12.98     | 2.61 [1.00, 6.80]    |
| Loprinzi 1990         | 24/68  | 16/67       |                      | 20.20     | 1.48 [0.87, 2.52]    |
| McMillan 1994         | 4/20   | 6/18        |                      | 6.59      | 0.60 [0.20, 1.79]    |
| Schmoll 1992          | 37/63  | 6/28        |                      | 16.43     | 2.74 [1.31, 5.74]    |
| Zecca 1995            | 13/16  | 5/17        |                      | 15.84     | 2.76 [1.28, 5.99]    |
| Total (95% CI)        | 301    | 262         |                      | 100.00    | 3.00 [1.86, 4.84]    |

Total events: 170 (MA), 47 (placebo)
Test for heterogeneity: $\chi^2 = 13.46, df = 8 (p = 0.02), I^2 = 62.9%$
Test for overall effect: $Z = 4.51 (p < 0.00001)$
comparing the efficacy of two different doses in 130 patients. Proc Am Soc Col Biol Phys. 2005; 63 (Suppl 1): S77-S78.

ser‑associated wasting: a north central cancer treatment group and Na etate in patients with head and neck cancer during radio (chemo)therapy. J Clin Oncol. 1997; 15: 135–141.

1076–1580.

1067–1072.

1576–1580.

1996; 14: 135–141.

1367–1372.

1367–1372.

1005; 4: 289–300.

1512; 289–300.

1067–1072.

135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.

1996; 14: 135–141.