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Omega-3 Supplementation in Combination Therapy for Anorexia Syndrome in Metastatic Breast Cancer

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Abstract **Objective:** To evaluate the efficacy of omega-3 fatty acids combined with megestrol acetate in managing cancer-related weight loss in breast cancer patients. **Material and methods:** A randomized clinical trial was conducted with 111 breast cancer patients experiencing significant weight loss. Subjects were divided into three treatment groups: Group 1 (n=34): Megestrol acetate (800 mg/day); Group 2 (n=35): Prednisolone (30 mg/day); Group 3 (n=42): Combined therapy of megestrol acetate (400 mg/day) plus omega-3 fatty acids (1.6 g/day). Parameters measured: appetite improvement, weight gain, overall quality of life metrics. **Results:** The combination therapy group demonstrated superior outcomes: 73% showed appetite improvement vs. 60-63% in monotherapy groups. 71% achieved significant weight gain. 50% reported enhanced quality of life compared to 20% in other groups. **Conclusion:** The study suggests that combined therapy with omega-3 and reduced-dose megestrol acetate provides more effective weight management with fewer adverse effects compared to standard monotherapy approaches in breast cancer patients. These findings indicate potential therapeutic advantages of incorporating omega-3 supplementation into weight management protocols for cancer patients.

Keywords Breast cancer, Anorexia, Megestrol acetate, Omega-3, Combination therapy

1. Introduction

Anorexia in cancer significantly worsens the quality of life of patients and can shorten its duration, especially in the late stages of cancer. Various drugs have been actively studied to combat this condition [6,7,9].

Corticosteroids were among the first drugs used to treat anorexia in cancer patients. In 1974, Moertel and colleagues conducted the first placebo-controlled study that showed that corticosteroids temporarily improve appetite in patients with advanced cancer [8]. However, subsequent studies have confirmed that these drugs do not contribute to weight gain [10].

In 1990, the first study of the effectiveness of megestrol acetate was conducted. This drug has shown good results in stimulating appetite in patients with anorexia or cachexia caused by cancer or AIDS [4]. Studies with different dosages determined the optimal daily dose of 800 mg. In addition to improving appetite, megestrol acetate contributed to weight gain: in some patients, the weight gain ranged from 9 to 14 kg without signs of fluid retention [2].

Comparative analysis showed that megestrol acetate is more effective than corticosteroids in stimulating appetite. In addition, it has a more favorable security profile. Unlike corticosteroids, megestrol acetate does not cause stomach ulcers, cataracts, myopathy, or glucose tolerance disorders. There was also no suppression of adrenal function, which precludes the need to gradually reduce the dosage after the end of therapy [1,3].

Studies have shown that megestrol acetate has advantages over corticosteroids in the treatment of anorexia and cahex II in acute cancer patients. However, its high cost has become a significant limitation. Treatment with corticosteroids cost less than one dollar a day, while the daily intake of megestrol acetate was several times more expensive. Following a successful trial of megestrol acetate conducted by the North Central Cancer Treatment Group (NCCTG), a survey of oncologists was conducted. The results showed that doctors were divided in their opinions: some preferred megestrol acetate, while others chose more affordable corticosteroids [3,10].

Objective: to determine the most effective method for correcting anorexia syndrome in disseminated breast cancer.

2. Materials and Methods

The study involved adult patients with incurable breast cancer. The selection criteria included losing at least 2.3 kg in 6 months (not due to surgery) or consuming less than 20 calories per kg of body weight per day. Life expectancy was predicted from 6 months and ECOG status to 2.

Patients with ascites, intestinal obstruction, malabsorption, persistent vomiting, on probe or intravenous nutrition were excluded. Patients with brain metastases, thrombosis in the

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last 6 months, poorly controlled hypertension, or heart failure were also excluded. The study did not include pregnant women, nursing mothers, patients with cataracts, insulin-dependent diabetes, stomach ulcers, or opportunistic infections.

The distribution took into account the location of the tumor, the degree of weight loss, ECOG status, planned treatment, and survival prognosis. Patients were divided into three groups: the first group n=34 (n=34patients) received megestrol acetate 800 mg/day, the second (n=35) - prednisone 30 mg/day, the third (n=42) больных- мегестеролmegesterol acetate 400 mg / day and omega-3 1.6 gy/day. If poorly tolerated, the dose could be reduced by half. Indicators of basic characteristics in the compared groups are provided in table 1. In our study, we made several key measurements. When evaluating the effect of treatment on patients ' appetite, the binomial test revealed 75% power, with a difference of 20% between the groups.

Participants ' weight was measured using a two-sample t-test. We found a difference of 0.3 kg between the groups, with a standard deviation of 0.9 kg (30% of the deviation). Thebinomial test was also used to analyze the number of patients who gained more than 10% of the initial weight. The test showed 75% power while revealing a 20% difference between the groups. Ince, tests were performed with a two-sided alternative hypothesis. Considering the three treatment groups and the need for pairwise comparisons, the level of statistical significance was set at 5%. Monthly examinations were conducted with weight measurement and questionnaires on appetite, nutrition, side effects and quality of life. For statistical analysis, Fisher's exact test (for binary indicators), Wilcoxon's test (for rank data), chi-square and Kruskal-Wallis tests (for initial characteristics), and O'Brien's tests (for intergroup differences) were used.

The total number of patients was 111 patients with disseminated breast cancer in 4 clinical groups. The main criterion for calculating statistical power was the improvement of appetite. All comparisons were made with respect to the megestrol acetate group as a standard treatment.

3. Results

After 3 months of taking megestrol acetate showed better results than prednisone. The effectiveness of prednisone was similar to megestrol acetate, while both groups were statistically inferior to the combination of megestrol acetate+omega-3. In patients who took these two drugs, an improvement in appetite was noted by 60-70% of participants.

When analyzed by the "intent-to-treat" method, a positive effect was observed in 37-42% of all patients. The O'Brien test showed a clear superiority in the combination of megestrol acetate+omega-3 (P = 0.003), and megesterol monotherapy prevailed мегестеролаover prednisone (P = 0.0045).

For the three control measures (weight loss+quality of life+appetite level), the median improvement was: megestrol acetate-4.33, prednisone-4.13 (P = 0.45), and the combination of megesterol+omega-3 – 4.9 (P = 0.0048). Significant improvement in all three parameters was observed in 52% of patients on megestrol+omega3-, 22% on монотерапии megestrol monotherapy (P = 0.003) and 17% on prednisone (P = 0.0041). These results confirm the highest efficacy of megestrol acetate+omega-3.

Table 1. Indicators of basic characteristics in the compared groups

Indicators	1 group n=34	2 group n=35	3 group n=42
Weight loss			
Up to 5%	6 (17,6,6±1,3%)	6 (17,2,2±2,1%)	7 (16,7,7±2,8%)
5-10%	9 (26,5,5±2,2%)	8 (22,9,9±3,1%)	10(23.8,8±3.4%)
More than 10%	19 (55,9,9±4,6%)	21 (60,0±4,7)	25(59,5,5±4,6%)
Quality of life by ECOG			
0-1	18(52,9,9±3,1%)	21 (60±4,9,9%)	23 (54,8,8±3,6%)
2	16(47,1±2,9%)	14(40,0±3,5%)	19(45,2±5,4%)
Age	66±7.1	68±6.2	65±7.7
Weight (kg)	63,2±3,9	66,5±4,1	68,1±4,2
Your appetite level			
is very poor	11 (32,4%)	10(28,6%)	13(31,0%)
Psucker	12(35,3%)	12(34,3%)	15(35,7%)
Satisfactoryый	6(17,6%)	6(17,1%)	7(16,7%)
A good	one 4(11,8%)	5(14,3%)	5(11,9%)
Very good	1(2,9%)	2(5,7%)	2(4,8%)

Table 2. Comparative characteristics of changes by group

Signs	1 group n=34	2 group n=35	3 group n=42
Appetite comparisons before/after (%)			
Worse	10±1.2	11±1.4	6±2.3
Unchanged	27±2.3	28±2.6	22±2.1
Better	63±4.1	60±4.1	73±3.5
Food use before/ after			
Worse	14±1.6	13±1.2	8±3.6
Unchanged	26±1.9	30±1.8	18±4.1
Better	63±3.2	56±3.1	74±5.2
Weight assessment			
Worse	13±1.5	16±2.8	6±3.9
Unchanged	16±1.9	26±3.1	23±2.9
Better	66±2.4	58±3.3	71±2.2

Analysis of the effect of drugs on weight changes in patients

During the study, special attention was paid to the analysis of changes in the weight of patients. Patients with clinical signs of edema and ascites were excluded from the study. In the absence of data on weight after discontinuation of participation in the study, cases were considered as unsuccessful treatment according to the "intent-to-treat" method.

The results showed a tendency to greater weight gain (excluding fluids) in patients taking megestrol acetate+ omega-3 (71%), compared with the monotherapy groups мегестеролаof megesterol (66%) and prednisone (58%), which is statistically significantly dominated by the combined treatment method p=0.047.

Side effects

The study tracked 14 types of toxicity. Statistically significant differences between the three groups were observed in the following cases:

- Myopathy: megestrol acetate-7%, prednisone-19% megesterol+omega-3 -6%, (P = 0.0022)
- Kushingoid changes: 1.2%, 7.7% and 1.8, respectively (P = 0.0048)
- Peptic ulcer disease: 0%, 3% and 0%, respectively (P = 0.04)

Unconfirmed statistical trends were noted:

- In women taking prednisone: hirsutism (9%) and virilization (7%)
- Infectious complications: prednisone-15%, megesterol +omega-3-8%, megestrol acetate-11%
- Thrombosis: megestrol acetate-6%, megesterol+omega -3-2%, prednisone-2%

Additionally, insomnia was noted, mainly in the prednisone group (5.5% vs. 0% for megestrol acetate+omega-3 and 1% for мегестеролемegesterol, P = 0.005).

There were no significant differences in the remaining observed side effects (acne, striae, nausea, vomiting, edema, ascites, and pleural effusion).

Drug efficacy study

When evaluating the toxicity of treatment, differences in side effects were found. Predniolone was more likely to cause heartburn, megesterol+omega-3 was better at reducing abdominal pain, and megestrol acetate was less likely to cause nausea. The effect on the hormonal background was comparable for all drugs.

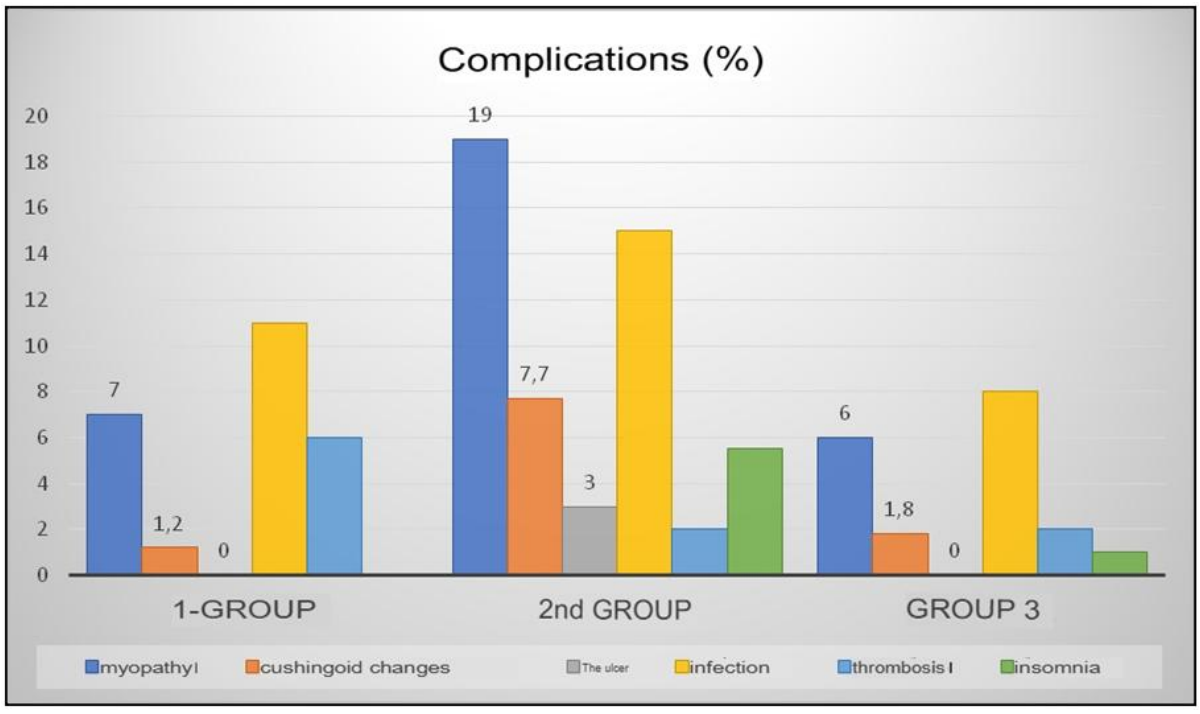

Figure 1. Assessment of complications in the compared groups

The duration of treatment was: megestrol acetate-64 days, megesterol+omega-6-77 days, prednisone-56 days (P = 0.0039). You stopped participating ahead of schedule: 27% of patients мегестролin the megestrol acetate group, 21% -megesterol+omega-3, and 36% - prednisone (P = 0.05).

Maximum quality of life indicators: megestrol acetate - 68 points, prednisone-71 points, megesterol+omega-3-69 points. A gradual decrease in the quality of life was observed in all groups, which confirmed the reliability of the assessment methodology. No statistically significant differences were found between the two drugs.

For short-term treatment (1-2 weeks) of patients with severe condition, corticosteroids are preferred. They quickly increase energy levels and reduce pain, and a short course reduces the risk of complications.

For long-term therapy (several weeks or more), megestrol acetate+omega-3 is recommended. The number of patients who stopped treatment due to side effects is 66% lower compared to the prednisone group. The drug better stimulates appetite and promotes a set of muscle mass.

4. Conclusions

The study showed that the combination of megestrol acetate and omega-3 fatty acids is the most effective treatment for anorexia in patients with disseminated breast cancer. Patients treated with megestrol acetate in combination with omega-3s showed significant improvements in appetite, weight gain, and quality of life compared to groups treated with megestrol acetate or prednisonealone. In addition, combination therapy was characterized by a more favorable safety profile, with fewer side effects, such as myopathy, kushingoid changes and peptic ulcer disease, compared with монотерапией prednisone monotherapy. The results of the study suggest that the addition of omega-3 fatty acids to megestrol acetate may be an effective approach to correcting anorexia in patients with advanced breast cancer.

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