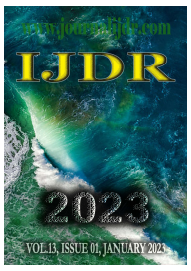
ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 13, Issue, 01, pp. 61380-61384, January, 2023
https://doi.org/10.37118/ijdr.26175.01.2023



RESEARCH ARTICLE OPEN ACCESS

EFFECT OF NANDROLONE IN THE TREATMENT OF CANCER CACHEXIA

Preti Vinicius Basso*, Polakowski, Camila Brandão, Tomasich, Flavio Daniel Saavedra, Trindade, Lilian Cristina Teixeira and Pacheco Jr, Adhemar Monteiro

Faculty of Medical Sciences of Santa Casa de São Paulo. São Paulo- SP, Brazil

ARTICLE INFO

Article History:
Received 27th November, 2022
Received in revised form
30th November, 2022
Accepted 15th December, 2022
Published online 27th January, 2023

KeyWords:
Anabolic steroids, Nandrolone, Cachexia, Neoplasms

Corresponding author:
Preti Vinicius Basso,

ABSTRACT

Introduction: Cancer cachexia has a negative impact on quality of life and survival, and is characterized by proteolysis. Nandrolone may improve protein loss, but requires further study in cancer patients. **Objective:** To compare whether there is an improvement in nutritional parameters and quality of life with the use of anabolic steroid associated with corticosteroids in relation to use alone. **Methods:** A randomized, prospective, double-blind clinical trial was performed. Patients were divided into two groups, where group 1 patients received nandrolone twice a month (2 doses) and dexamethasone (4 mg) once daily and group 2 received dexamethasone (4 mg) for 30 days. Quality of life data (QoL C-30 - EORTC), body composition (BIA) and laboratory tests (RBC, albumin, CRP and transferrin) were compared. **Results:** Thirty patients received nandrolone and 28 patients received dexamethasone alone for 30 days. There was no difference in quality of life ($p = 0.76$); functional ($p = 0.83$) or symptom scales ($p = 0.79$); there was no difference in body composition regarding resistance ($p = 0.74$), reactance ($p = 0.74$) or body mass index (BMI) ($p = 0.88$) and there was no difference in laboratory tests of CRP ($p = 0.10$) and related to the nutritional status of albumin ($p = 0.66$) and transferrin ($p = 0.13$). **Conclusion:** There was no difference between the groups in the treatment of neoplastic cachexia and in palliative treatment in the period of 30 days.

Citation: ***Preti Vinicius Basso, Polakowski, Camila Brandão, Tomasich, Flavio Daniel Saavedra, Trindade, Lilian Cristina Teixeira and Pacheco Jr, Adhemar Monteiro. 2023.*** "Effect of nandrolone in the treatment of cancer cachexia*", International Journal of Development Research*, 13, (01), 61380-61384.

INTRODUCTION

Malnutrition is an aggravating factor of cancer, which affects between 22 and 71% of cancer patients. It can be due either to the effects of the tumor itself or aggravated by the treatment (Fearon, 2011 and Arends, 2017). Malnutrition can progress to neoplastic cachexia, found in up to 80% of cancer patients in the advanced stages of the disease (Sinha-Hikim, 2004). It is a multifactorial syndrome, characterized by a hypercatabolic state and anorexia, in which there is loss of muscle mass, which cannot be reversed by conventional nutritional therapy, leading to functional impairment of the organism (Tuca, 2013) Cachexia has a negative impact on quality of life and is related to higher rates of complications during cancer treatment and lower survival (Oken, 1982). A terapia medicamentosa para a caquexia visa aumentar o apetite, diminuir a inflamação crônica, aumentar a massa magra e promover anabolismo. Alguns medicamentos apresentam evidências comprovada no aumento do apetite e do peso na caquexia neoplásica: os progestágenos, anamorelin e os corticoesteroides (Edge, 2010 and Tremel, 2016). However, anabolic steroids do not stimulate protein synthesis, one of the defining factors of cachexia (Kyle, 2004). They are drugs used in medicine for the treatment of several conditions such as: hypogonadism, cachexia associated with the acquired immunodeficiency virus (HIV), in chronic obstructive pulmonary disease (COPD) and in some cachectic syndromes (European Organization for Research and Treatment of Cancer). Despite its indication in other cachexia syndromes, the literature data are still insufficient to indicate the routine use of anabolic steroids in the treatment of neoplastic cachexia (Kyle, 2014). Multimodal therapy with drug combination, with the aim of improving the symptoms of cachexia, seems to be a promising path (Garcia, 2013). The objective of this study is to compare whether there is an improvement in nutritional parameters and quality of life with the use of anabolic steroid associated with corticosteroids compared to the use of this one alone.

METHODS

This was a longitudinal, prospective, randomized, placebo-controlled study. The project was approved by the Research Ethics Committee of Hospital Erasto Gaertner in Curitiba, Brazil, under registration number CAAE 50953415.5.0000.0098. All patients signed the Free and Informed Consent Form.

Study Design: The patients selected for the research were from the chest service and palliative care of Erasto Gaertner Hospital,

Oncological Treatment Center in the municipality of Curitiba, Brazil. The study report followed the Criteria of the Consort - Transparent Reporting of Trials website under the number NCT 03263520. Patients were characterized according to the following data: age, sex, topographic diagnosis of the neoplasm, performance status classification according to the Karnofsky scale and ECOG (Performance scale), clinical stage (7th edition of the International Union for the Fight against Cancer – UICC) (Karnofsky, ?. Oken, 1982 and AJCC). The use of enteral diet, nutritional classification using the PG-SGA (subjective global assessment produced by the patient), weight and BMI (body mass index).

Inclusion criteria were as follows: patients with tumors of the pancreas of the upper gastrointestinal tract who were receiving palliative care without other tumors; patients with moderate or severe malnutrition according to SGA-PPP, patients classified as cachectic according to the criteria of Fearon et al., patients with Karnofsky index equal to or greater than 60%, patients with ECOG scores greater than or equal to two, patients with diet acceptance greater than 70% of caloric requirements; patients who were not using appetite stimulants, anabolic agents, or corticosteroids at the time of the study. In this study, one of the inclusion criteria was exclusive palliative treatment to avoid excessive dosage of dexamethasone as an antiemetic. Only after 30 days without chemotherapy and/or radiotherapy were patients included in the study. In addition, chemotherapy is an isolated factor for malnutrition and to avoid this bias and pharmacological interaction, only patients in exclusive palliative care were included. And those excluded were suspension of oral dexamethasone during the study, for any period; dropped out of treatment; did not return for reassessment appointments; experienced complications with the use of nandrolone and/or dexamethasone.

Intervention: After identifying the candidates, they were referred to a specific consultation for admission to the study. The Free Informed Consent Term (TLCE) was applied. Randomization was performed by electronic drawing using the computer program iGerar®, allocating patients in each group. Both study participants and investigators remained blinded to the division of groups until the end of the study, after statistical analysis. The groups were identified in group 1 (G1) and group 2 (G2), in which patients randomly selected as an odd number were included in group 1 and those with an even number in group 2. Identical boxes with the drug, sealed and packed in boxes identified with 1 or 2, were provided to study participants. After determining which label to dispense with the patient, the samples labeled with G1 and G2 were provided to the principal investigator with guidance and instruction for all patients. In G1, patients received anabolic steroid nandrolone decanoate, at a dose of 50mg for males and 25mg for females, by the intramuscular route applied in the superolateral quadrant of the right gluteal by the same nurse, on the first and fifteenth day after randomization. In addition to the anabolic steroid, the patients used corticosteroids (dexamethasone) at home at a dose of 4mg daily in the morning, for both sexes, for 30 days. And in G2, patients received dexamethasone at a dose of 4 mg a day, for both sexes, for 30 days. At the beginning of the intervention, all patients underwent an assessment of nutritional status, biochemical tests were performed and answered a quality of life questionnaire, repeated 30 days after the intervention. Information on age, sex, primary tumor, clinical staging and use of enteral diet were collected.

Evaluation

Nutritional status: Anthropometric data were performed at baseline. Based on height (in meters) and weight (in kg), BMI was determined, classified according to age, being considered elderly over 70 years as recommended. The percentage of weight loss (% PP) was calculated in relation to the patient's current and usual body weight, being considered severe weight loss (% PP) greater than 10% in 6 months, and also used as a diagnosis of cachexia in the criterion of inclusion(Fearon, 2011; WHO, 2000 and Chlebowski, 1986). The body composition of the patients was evaluated with bioelectrical impedance (BIA) estimating the compartments of lean mass (FFM), fat body mass (FM) and total body water (ACT); resistance; reactance and phase angle (PhA). Patients were instructed to fast for four hours, abstain from alcohol for eight hours, not practice physical activity for 12 hours and empty their bladders before the test.8 The device used was the Maltron BF-906® at the frequency of 50Hz.

Quality of life: Patients responded to the EORTC Quality of Life Questionnaire (QoL C-30).9 The QoL C-30 is a multidimensional, self-administered questionnaire. On the symptom scale, the higher the score, the worse the patient's quality of life. Scores range from zero to 100, are expressed as a percentage, and are calculated separately for each scale (Oken, 1982; AJCC).

Laboratory Test: Biochemical tests were requested at the time of the first consultation and at the end of the study. The tests were: hematocrit, albumin, C-reactive protein (CRP) and transferrin. The exams were performed in the clinical analysis laboratory on the same day after the BIA, while the patient was fasting. The first return of all patients occurred within 15 days. Complications were investigated in both groups. We assessed whether dexamethasone was administered as recommended in both groups. If the patient had local complications associated with the intramuscular application of nandrolone, the second dose would not be applied. Thirty days after the first consultation, patients from G1 and G2 returned to the consultation and underwent the same procedures performed in the first consultation: weight assessment, BIA, QL C-30 questionnaire and laboratory tests. Again, it was verified whether any patients had discontinued the use of dexamethasone before the end of the study.
All data were recorded in a specific collection form and exported to the Microsoft Office Excel® Database for Macintosh (Microsoft Corporation, Redmond, Washington, USA, 2016).

Statistical analysis: The sample size calculation was performed by proportional sampling, with a confidence interval of 95% and a risk of error of 2.5%, resulting in an estimated necessary population of 58 patients. The sample was selected consecutively by non-probability sampling during the research period, which was from June 2016 to September 2017. The absolute and relative frequencies of the results obtained were described. Data classified as quantitative / categorical (gender, staging and enteral nutrition) were submitted to the chi-square test. For ECOG and PG-SGA, Fisher's exact test was used. Normally distributed continuous data are expressed as the mean ± standard deviation (SD). For the variables age, Karnofsky performance status, weight, BMI, QL scores C-30, absolute values of BIA and laboratory tests, the Mann-Whitney test was used. For the main objective of the study, the same test (Mann-Whitney) was used to compare the initial and final values of potentially modifiable variables between the groups during the 30-day interval. The variables compared were weight, BMI, QLQ-C30, BIA values and laboratory tests. Statistical analyzes were performed using the Statistical Package for the Social Sciences® (SPSS) version 19.0 for Windows (SPSS Inc, Chicago, IL, USA). Statistical significance was set at 5% ($p < 0.05$), with a confidence interval of 95%.

RESULTS

There were seventy-three patients eligible for the study and referred for the admission consultation. Four refused to participate in the study and six patients did not meet the inclusion criteria, 63 patients were randomized. Of the 32 patients allocated to the nadrolone group, one patient was not allocated to the intervention because he did not understand the C-30 QoL. At follow-up, there was a loss of follow-up in the nadrolone group, as the patient did not return to the consultation on the 15th day. In the nadrolone group, 30 cases were analyzed. Of the 29 cases in follow-up in the dexamethasone group, 28 cases were analyzed because there had been a death during the study. In total, 58 patients were included. The characteristics of the patients' non-modifiable variables during the study are shown in Table 1. There were no significant differences between the groups. There was no significant difference between the nandrolone group and the dexamethasone group in terms of quality of life scores at baseline and at the end of the study, as shown in table 2 ($p \geq 0.36$).

Table 1. Comparison of non-modifiable variables between groups 1 and 2

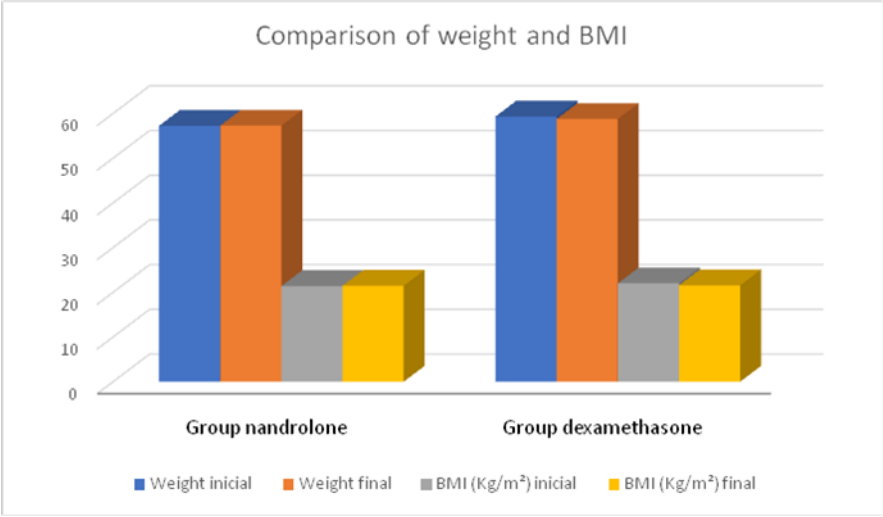
Variable	Subdivision	Group nandrolone (n=30)	Group dexamethasone (n= 28)	*P* Value
Age (years)		64.06 SD of ±7.4	62.96 SD of ± 8.9	0.88
Gender (Male)	Male (n)	22 (73%)	21 (75%)	0.88
Primary tumor	Esophagus (n)	22 (73%)	20 (71.5%)	0.99
	Stomach (n)	4 (13.5%)	3 (11%)	
	Pancreas (n)	4 (13.5%)	5 (17.5%)	
Clinical stage	III (n)	10 (33.5%)	11 (39.3%)	0.63
	IV (n)	20 (66.5%)	17 (60.7%)	
ECOG	1(n)	3 (10%)	2 (8%)	0.99
	2 (n)	27 (90%)	26 (92%)	
Karnofsky	80 (n)	3 (10%)	2 (7%)	0.95
	70(n)	18 (60%)	17 (61%)	
	60 (n)	9 (30%)	9 (32%)	
PG-SGA	B (n)	4 (13.5%)	5 (18%)	0.72
	C (n)	26 (86.5%)	23 (82%)	
Enteral nutrition	Yes (n)	20 (66.5%)	19 (68%)	0.92
	No (n)	10 (33.5%)	9 (32%)	

Source: author data, where (n): frequency in absolute number; ECOG: classification of performance status; PG-SGA: global subjective evaluation produced by the patient; B: moderately undernourished; C: Severely malnourished; SD standard deviation; Statisticallysignificant at p <0.05, 1 group versus group 2. Statistic testes: for age, gender, primary tumor, clincal stage and enteral nutrition was used thechi -squared test ; for ECOG, Karnofsky and PG-SGA was used Fisher's exact test.

Table 2. Comparison of QoL C-30 scores

Variable	Timing of measurement	Group nandrolone (n=30	Group dexamethasone (n=28)	Mann Whitney U	*P* Value
QoL C-30 Global	Initial	39.08	42.82	364	0.36
	Final	59.70	58.92	401.5	0.76
QoL C-30 Functional	Initial	50.28	53.07	387.5	0.61
	Final	63.68	63.64	407	0.83
QoL C-30 Symptoms	Initial	42.73	42.39	403.5	0.79
	Final	29.25	30.20	403.5	0.79

Source: Author data, where QoL C-30: quality of life questionnaire, expressed in %. Statisticallysignificant at p <0.05, 1 group versus group 2.



BMI: body mass index; %WL; Statistically significant at p <0.05, 1 group versus group 2.Statistical test: Mann-Whitney

Figure 1. Comparison of weight and BMI

Table 3. Comparison of BIA values

Variable	Timing of measurement	Group nandrolone (n=30)	Group dexamethasone (n= 28)	Mann Whitney U	*P* Value
FFM	Initial	35.98	33.85	348	0.26
	Final	35.96	33.97	347	0.25
FM	Initial	25.27	26.52	404	0.80
	Final	24.73	25.71	405	0.81
TBW	Initial	37.61	30.64	298.5	0.05
	Final	37.54	32.38	316	0.10
PhA	Initial	5.70	5.92	417.5	0.96
	Final	5.02	5.26	410.5	0.88

Source: Author data, where FFM: fat-free mass; FM: fat mass; TBW: total body water; Resistance and Reactance expressed in ohms; PhA: phase angle, expressed in degrees.

Table 4. Comparison of laboratory test values

Variable	Timing of measurement	Group nandrolone (n=30)	Group dexamethasone (n= 28)	Mann Whitney U	*P* Value
Hematocrit	Initial	34.54	35.03	406.5	0.26
	Final	35.21	35.35	415.5	0.25
Albumin	Initial	3.37	3.38	395	0.80
	Final	3.40	3.32	395	0.81
CRP	Initial	3.63	4.79	319.5	0.05
	Final	4.97	6.16	328.5	0.10
Transferrin	Initial	216.63	196.25	323.5	0.66
	Final	219.80	204.93	330.5	0.74

Source: Author data, where CRP: C-reactive protein; Statisticallysignificant at p <0.05, 1 group versus group 2.

In neither of the two groups was there any difference in weight from the beginning of the intervention to the end of the study, and consequently in BMI (Figure 1). Regarding body composition, there was also no significant difference in the values measured between the groups, before and after the intervention, as shown in table 3 (p=0.26). Regarding the BIA data, in both groups there was a difference in resistance: nandrolone group (p=0.003) and dexamethasone group (p=0.023). In the dexamethasone group, where only the corticoid was used, the percentage of water and PA were statistically significant in the studied period. The percentage of fat-free mass and fat mass had no statistically significant difference (p=025). Regarding laboratory tests, there was no difference in the values of albumin and transferrin before and after the intervention. CRP values were higher in both groups at the end of the study (table 4) (p=0.05).

DISCUSSION

Cancer cachexia treatment aims to improve or alleviate metabolic disturbances and physical performance, reduce interruptions in cancer treatment, and improve quality of life. The ideal drug would promote increased appetite, increase body weight without causing fluid retention and not interfering with the treatment or the tumor. No drug class meets these criteria. The choice of nandrolone was due to its low cost and for having a high anabolic effect when compared to other anabolic steroids, as well as trenbolone, but in Brazil trenbolone still has a higher cost. Corticosteroid alone shows evidence of weight gain effects in cancer patients.[2] Megestrol is used for the purpose of improving appetite and, consequently, promoting weight gain. There is evidence of increased appetite and body weight associated with megestrol compared to the effects of placebo. However, weight gain may be due to water and fat accumulation, not muscle mass. Chlebowski et al, published one of the first series of nandrolone in cancer patients. Patients with advanced lung cancer were randomized to chemotherapy with nandrolone or placebo. The steroid group had less weight loss than the placebo group (12 vs 25%) and longer survival (5.5 vs 8.2 months).[15] Del Fabbro et al, studied testosterone replacement for a period of four weeks in cancer patients with hypogonadism, and showed improvement in fatigue and sexual desire, but no improvement in quality of life, suggesting that more studies should be carried out on the corticosteroid use in this group of patients.[17] Lesser et al, randomized patients on chemotherapy to receive the anabolic steroid oxandrolone or megestrol acetate for 12 weeks. The use of anabolic steroids tended to have greater weight gain than the use of megestrol, but the difference was not significant. However, four weeks after the study ended, the weight gain benefit was no longer evident in the group receiving the anabolic steroids.[17] In our study, nandrolone did not result in weight gain, which we attribute to catabolism due to active and untreated neoplasia at the time of the intervention. The chosen group consisted of patients with tumors of the esophagus, stomach and pancreas due to similar rates of malnutrition and cachexia and similar levels of inflammatory markers.[18-19] In our study, 84.4% of patients were severely malnourished (PG-SGA). Cachexia may result from inadequate treatment of malnutrition and, more often, from the evolution of tumors with no curative possibility, and cannot be reversed with conventional nutritional therapy, 1,29 justifying the choice of a drug intervention as the main objective of the study. According to the latest recommendation from the European Society for Nutrition and Metabolism (ESPEN), the use of corticosteroids for appetite enhancement is highly recommended.[2] For this reason, the study control group used low-dose dexamethasone exclusively. A control group was not assigned to receive no intervention, as all patients had scores equal to or greater than nine according to the PG-SGA classification, which recommends the indication of some type of intervention for the symptomatic improvement of patients. In our study, to measure the increase in lean or fat-free mass, the method used was BIA. This method was chosen because it is a simple, safe, non-invasive, rapid method, suitable for outpatients, has a low cost and, depending on the type of device, can provide segmental composition data.[8-20] As there are no reference values in cancer patients in Brazil, the analyzed BIA values were the result of a sequential evaluation, comparing the data from the beginning to the end of the intervention. Comparison between groups showed no improvement in values. Nandrolone did not have the expected benefit of improving body composition, especially lean mass. At the end of the study, there was a decrease in resistance, and as there was no improvement in PA or lean mass, this decrease in resistance was probably due to the greater amount of water and metabolic changes induced by the neoplasm and not to the improvement in fat-free mass. This may be a result of the nutritional reorientation and water retention that can occur with dexamethasone use.

PhA has been increasingly used as a tool for nutritional diagnosis and prognosis in cancer patients. PhA is dependent on tissue capacitance and is associated with cell membrane quality and integrity.[21] Sarcopenic patients, who are characterized by the predominance of loss of fat-free mass, may have values below 4.5 degrees.20 The lowest PhA value found at the end of the study was 2.1 degrees in both groups. In patients with head and neck cancer, greater PhA was associated with better nutritional status. Nutritional risk and cachexia were identified in patients with minor PhA.[22] Patients with PhA between two and 2.9 degrees had a median survival of 35 days, while patients with an angle above six degrees had a median survival of 220 days.[23] Nenhuma das intervenções do estudo foi capaz de aumentar PhA. This is probably because the study groups were made up exclusively of patients undergoing palliative care and without effective treatment at the time of the intervention. In addition to body composition, one of the study outcomes was the impact on quality of life. Quality of life is related to symptoms and disease progression. C-30 QoL scores that indicated poorer quality of life were directly associated with CRP greater than 10 mg/dL, low albumin, and weight loss greater than 10% in a composite sample of more than 50% of patients with gastrointestinal tract cancer. superior and pancreatic.[24] There was no benefit from using nandrolone on any of the C-30 QOL scales in the control group. However, when each group was evaluated individually, there was a significant improvement in scores at the end of the 30-day period. Corticosteroid use in both groups may be one of the factors that influenced these data. Yennurajalingam et al, demonstrated that dexamethasone used for 15 days was effective in improving symptoms of fatigue, depression and cachexia in cancer patients.[25] The improvement in quality of life scores assessed individually in each group may also be a result of palliative care received by patients. In a randomized series review study, patients in palliative care had better quality of life.[25-26]

The elevation of CRP is directly proportional to protein-energy catabolism. In a group of 1,702 patients with advanced cancer, those with CRP levels greater than 10 mg/dL had rates of anorexia, fatigue, and weight loss of 89%, 81%, and 79%, respectively. In those patients with CRP between 5 and 10 mg/dL, the same values were 79%, 75%, and 70%, respectively. Elevated CRP was an independent factor in disease staging and performance status in relation to the accumulation of cachexia symptoms and impact on daily activities.[27] In the present study, in both groups, CRP was high in most patients, and only 6.8% of the sample had normal levels at the beginning of the intervention. In laboratory tests, CRP was the only one that showed a difference at the end of the study when evaluated individually in each group. The intervention group showed no benefit over the control group in lowering CRP levels. The other two laboratory tests for nutritional assessment did not change with the intervention or with the control group. There was no difference between the initial and final mean values of albumin or transferrin.[3] The use of nandrolone with dexamethasone was not superior to the use of corticosteroids alone to improve body composition, quality of life and laboratory nutritional parameters. It was expected that the group that used nandrolone had greater lean mass gain than the control group and, consequently, improved symptoms and quality of life. The nandrolone dosage may also have been too low to cause this gain, as several studies have shown a gain in lean mass with higher doses of anabolic steroids. However, we chose not to use higher doses because they are associated with side effects, which can further harm cancer patients in end-of-life palliative care.

CONCLUSÃO

There was no difference with the anabolic steroid nandrolone associated with dexamethasone to the isolated use of corticosteroids in the treatment of neoplastic cachexia in patients with upper digestive tract and biliopancreatic tumors undergoing palliative treatment within 30 days. It was also not superior in terms of quality of life, body composition and laboratory nutritional markers. In both groups, when evaluated independently, improvement in quality of life scores was observed within 30 days.

Funding: The present study was financed by the authors.

Declaration of conflicting interests: the author declares that there is no conflict of interest.

REFERENCES

AJCC, 7th edition. Cancer Staging Manual. Springer.

Amano K, Maeda I, Morita T, et al. C-reactive protein, symptoms and activity of daily living in patients with advanced cancer receiving palliative care. *J Cachexia Sarcopenia Muscle.* 2017;8(3):457-465.

Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *ClinNutr.* 2017;36(1):11-48.

Chlebowski RT, Herrold J, Ali I, et al. Influence of nandrolone decanoate on weight loss in advanced non-small cell lung cancer. *Cancer.* 1986;58(1):183-186

Costa E.H.S., Krüger J.F., Camargo C.Q., Preti V.B., Hillesheim E., Rabito E.I. Effects of fasting on chemotherapy treatment response: A systematic review of current evidence and suggestions for the design of future clinical trials. *Nutrition and Cancer.* 2021 doi: 10.1080/01635581.2021.1938147

Edge S, Byrd DR, Compton CC, Fritz AG, Greene F, Trotti A. *AJCC Cancer Staging Manual.* New York: Springer; 2010.

El-Jawahri A, Greer JA, Temel JS. Does palliative care improve outcomes for patients with incurable illness? A review of the evidence. *J Support Oncol.* 2011;9(3):87-94.

European Organization for Research and Treatment of Cancer. QLQ-C30-PAL. http://groups.eortc.be/qol/questionnaires_downloads.htm.

Fabbro E Del, Garcia JM, Dev R, Hui D, Williams J. Testosterone replacement for fatigue in hypogonadal ambulatory males with advanced cancer : a preliminary double -blind placebo controlled trial. Support Care Cancer. 2013; 21(9): 2599–607.

Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol.* 2011;12(5):489-495.

Garcia VR, Lopez-Briz E, Sanchis RC, Perales JLG, Bort-Marti S. Megestrol acetate for treatment of anorexia-cachexia syndrome. *Cochrane Database SystRev.* 2013;28(3):CD004310.

Gärtner S, Krüger J, Aghdassi AA, et al. Nutrition in pancreatic cancer: a review. *GastrointestTumors.* 2016;2(4):195-202.

Karnofsky DA, Burchenal JH. The clinical evaluation of chemoterapeutics agents in cancer. In: Macleod CM, ed. Evaluation of Chemotherapeutics Agents.

Kyle UG, Bosaeus I, de Lorenzo AD, et al. Bioelectrical impedance analysis-part II: utilization in clinical practice. *ClinNutr.* 2004;23(6):1430-1453.

Lesser GJ, Case D, Ottery F, et al. A phase III randomized study comparing the effects of oxandrolone (Ox) and megestrol acetate (Meg) on lean body mass (LBM), weight (wt) and quality of life (QOL) in patients with solid tumors and weight loss receiving chemotherapy. *J ClinOncol.* 2008;26(15_suppl):9513-9513

Mulasi U, Kuchnia AJ, Cole AJ, Earthman CP. Bioimpedance at the bedside: current applications, limitations, and opportunities. *Nutr Clin Pract.* 2015;30(2):180-193.

Norman K, Wirth R, Neubauer M, Eckardt R, Stobaus N. The bioimpedance phase angle predicts low muscle strength, impaired quality of life, and increased mortality in old patients with cancer. *J Am Med Dir Assoc.* 2015;16(2):173.e117-122.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern cooperative oncology group. *Am J Clin Oncol.* 1982;5(6):649-655.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden et, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol [Internet]. 1982 ; 5(6):649–55.

Siddiqui NI, Khan SA, Shoeb M, Bose S. Anthropometric predictors of bio-impedance analysis (BIA) phase angle in healthy adults. *J Clin Diagn Res.* 2016;10(6):CC01-CC04.

Sinha-Hikim I, Taylor WE, Gonzalez-Cadavid NF, Zheng W, Bhasin S. Androgen receptor in human skeletal muscle and cultured muscle satellite cells: up-regulation by androgen treatment. *J ClinEndocrinolMetab.* 2004;89(10):5245-5255.

Stegel P, Kozjek NR, Brumen BA, Strojan P. Bioelectrical impedance phase angle as indicator and predictor of cachexia in head and neck cancer patients treated with (chemo)radiotherapy. *Eur J ClinNutr.* 2016;70(5):602-606.

Teunissen SC, Wesker W, Kruitwagen C, de Haes HC, Voest EE, de Graeff A. Symptom prevalence in patients with incurable cancer: a systematic review. *J Pain Symptom Manage.* 2007;34(1):94-104.

Tremel JS, Abernethy AP, Currow DC, et al. Anamorelin in patients with non–small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. Lancet Oncol. 2016;17:519-531. doi:10.1016/s1470-2045(15)00558-6

Tuca A, Jimenez-Fonseca P, Gascon P. Clinical evaluation and optimal management of cancer cachexia. *Crit Rev Oncol Hematol.* 2013;88(3):625-636.

Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: relation to quality of life, exercise capacity and survival in unselected palliative care patients. *Support Care Cancer.* 2013;21(6):1569-1577.

World Health Organization. Obesity: preventing and managing the global epidemic. Report of a World Health Organization Consultation. Geneva: World Health Organization, 2000. p. 256. WHO Obesity Technical Report Series, n. 284.

Yennurajalingam S, Williams JL, Chisholm G, Bruera E. Effects of dexamethasone and placebo on symptom clusters in advanced cancer patients: a preliminary report. *Oncologist.* 2016;21(3):384-390.