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Impact of an oral nutritional supplement enriched in leucine, EPA, DHA, and β-glucans on the increase of muscle mass in patients with cancer and malnutrition: The alisenoc trial

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ABSTRACT

Methods: A randomized, double-blind, parallel-group, controlled, multicenter clinical trial was conducted in patients with cancer and malnutrition during outpatient treatment. Patients were randomized to receive either a specific high-calorie, high-protein ONS enriched with leucine, EPA, DHA, and β-glucans or an isocaloric, isonitrogenous standard ONS for eight weeks. Malnutrition was diagnosed using the SGA and body composition was evaluated using bioimpedance.

Results: 57 patients were recruited and 37 completed the intervention period. After the nutritional intervention, patients who received the enhanced-ONS showed a significant increase in muscle mass, which was not detected with the standard ONS [1.92 (4.31) kg vs −0.68 (1.45) kg); $p = 0.009$)], and there was no significant reduction in the percentage of patients with severe and moderate malnutrition.

Conclusion: An enhanced ONS enriched in EPA, DHA, leucine, and β-glucans increases muscle mass and could promote nutritional and functional status recovery in patients with cancer and malnourishment.

Trial registration: NCT04184713.

1. Background

Disease-related malnutrition (DRM) is a common syndrome in patients with cancer. It is secondary to factors such as insufficient supply of energy and nutrients, increased nutritional requirements, changes in nutrient metabolism, and nutrient digestion and/or absorption disorders. Its prevalence is 15 %–20 % at the time of cancer diagnosis and can be has high as 80 %–90 % in cases of advanced disease (Planas et al., 2016; Bozzetti & SCRINIO Working Group, 2009). The diagnosis of malnutrition in patients with cancer must take into account the presence of weight loss, decreased dietary intake, changes in body composition, and deterioration of functional status (Muscaritoli et al., 2021). Numerous studies have highlighted the consequences of malnutrition in patients with cancer, which include decreased immunocompetence and risk of infections, psychosocial stress, lower quality of life (QoL), increased risk of treatment toxicity, and greater risk of mortality (Rondel et al., 2018).

The pathophysiological basis of the development of DRM in patients

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with cancer is a systemic inflammatory reaction triggered by tumor-host interactions as well as the adverse effects induced by different antitumor treatments. The resulting metabolic disorders include the development of insulin resistance, increased lipolysis, lipid oxidation with loss of body fat, increased protein catabolism with loss of muscle mass, and increased acute-phase protein production. These cytokine-induced metabolic changes hinder nutritional recovery after medical nutritional treatments (Aoyagi et al., 2015). Therefore, attempts to modulate such metabolic changes need to be integrated into the treatment that patients with cancer receive (Arends et al., 2017).

Standard nutritional management for patients with cancer has been proven to have a positive impact on their clinical progress (García-Luna et al., 2023). Nutritional treatment is based on individual dietary advice to meet requirements. If this measure is insufficient, medical nutritional treatment should be prescribed with the main objectives of preventing or correcting nutritional deficiencies, improving tolerance to antineoplastic treatment, and improving QoL (Muscaritoli et al., 2021). Likewise, nutrients or specific bioactive compounds that modulate systemic inflammation and the metabolic changes that accompany it must also be administered. The formulas used by patients with cancer are usually high-protein, high-calorie, and enriched with specific nutrients. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplementation are associated with increases in body weight and lean mass as well as energy and protein intake (Murphy et al., 2011; Sánchez-Lara et al., 2014; Pappalardo et al., 2015; Lu et al., 2022; Izaola et al., 2021). Likewise, supplementation of amino acids such as leucine can increase the patient's anabolic capacity. (Beaudry & Law, 2022; Storck et al., 2020) β-glucans are polysaccharides with immunoregulatory functions. In patients with cancer, their supplementation has been associated with decreased levels of proinflammatory cytokines as well as improvements in symptoms and QoL (Ostadrahimi et al., 2014; Ostadrahimi et al., 2014; Costa Fortes et al., 2010).

This study was designed to assess the effectiveness of a specific ONS enriched in EPA, DHA, leucine, and β-glucans on the nutritional status, functional status, body composition, and QoL of a group of patients with cancer and malnutrition undergoing outpatient cancer treatment.

2. Methods

2.1. Design

This randomized, double-blind, parallel, controlled, multicenter clinical trial was conducted from March 2021 to May 2022. It was registered as Clinical Trial NCT04184713.

2.2. Subjects

Adult outpatients diagnosed with cancer (any type) who had started (or were going to start in the following month) antineoplastic treatment with chemotherapy, immunotherapy, and/or radiotherapy (with or without prior surgery) and who had weight loss >5 % in the last six months were recruited.

Patients who were participating in other clinical trials were excluded, as were those who were morbidly obese (body mass index (BMI) $\geq$ 40 kg/m^2), those who underwent imminent surgery (or if their oncological treatment had been exclusively surgical), those who required treatment with enteral nutrition or parenteral nutrition, those diagnosed with refractory cachexia, and those who presented with severe infection or an infection that required hospitalization. Patients with other diagnoses such as diabetes mellitus or steroid-induced hyperglycemia in treatment with insulin or whose disease was poorly controlled (HbA1c >8 %) were excluded from the study. Patients with severe renal, cardiac, respiratory, or liver disease; severe and/or active autoimmune diseases; or dementia were also excluded. Patients receiving ONS or artificial nutrition that could not be suspended at least one week before the start of the study were also excluded, as were those who had consumed food supplements or foods fortified with omega-3, arginine, leucine, β-hydroxy β-methylbutyrate (HMB), or nucleotides in the previous month. Lastly, those who refused to take the ONS, pregnant or breastfeeding women, and patients who presented an allergy or intolerance to any of the ingredients of the formulas were excluded.

Patients who required treatment with enteral nutrition or parenteral nutrition at any point during the intervention, those who did not tolerate the product, and those who ingested less than one ONS per day were withdrawn from the study.

2.3. Recorded variables

Three visits were held during the eight-week intervention period. In V1, the baseline visit, the patient information sheet was given, the informed consent form was signed, demographic and clinical variables were recorded, and randomization took place. In V2, held at eight weeks upon completion of the intervention, a nutritional assessment and evaluation of body composition, dynamometry, QoL, biochemical parameters, and physical activity were performed. The following assessments were used to determine the impact of nutritional supplementation.

- Nutritional status: The Subjective Global Assessment (SGA) tool was used to assess nutritional status. The results were divided into SGA-A (well-nourished), SGA-B (moderate malnutrition), and SGA-C (severe malnutrition).
  - o Anthropometric study: weight (current and usual), height, BMI, percentage of weight loss, arm circumference, triceps skinfold thickness, and arm muscle area.
  - o Body composition: A single-frequency (50 kHz) bioimpedance (BIA, Akern®, Akern S.L., Pisa, Italy) analysis which measured resistance, reactance, and phase angle values was used to assess body composition. The appendicular skeletal muscle index, fat mass, lean mass, and body cell mass values were obtained.
  - o Functional status: Hand grip strength was measured by means of dynamometry using a JAMAR HAND® dynamometer. Measurements were taken three times in each hand, alternately, and the mean of these measurements was calculated.
- Quality of life: the scale designed by the Eastern Cooperative Oncology Group (ECOG) was used. The ECOG scale assesses the patient's abilities to perform activities of daily living. The ECOG score ranged from 0 (asymptomatic, without limits) to 5 (dead).
- The biochemical parameters of total protein, albumin, prealbumin, retinol-binding protein, and total cholesterol were measured using the C501 module of the cobas ® 6000 device (Roche Diagnostics S.L., Spain).
- Physical activity: Physical activity was measured using the International Physical Activity Questionnaire (IPAQ) and converted to MET minutes/week.
- Adherence to nutritional treatment: The daily intake of nutritional supplements was evaluated via a self-completed record kept by the patient.

2.4. Nutritional intervention

Patients were instructed to take two packages of an enhanced ONS or standard ONS daily for eight weeks (Table 1).

- Enhanced ONS (Bi1 Alisenoc®; Adventia Pharma, Spain). A polymeric, high-protein, and high-calorie ONS with fiber, EPA, DHA, leucine, and β-glucans.
- Standard ONS (Bi1 control 2.0®, Adventia Pharma, Spain): Standard polymeric, high-protein, high-calorie ONS without fiber.

Additionally, all patients received dietary advice to increase energy and protein intake as well as recommendations on physical exercise, in

Table 1
Composition of macronutrients and ingredients of the formulas under study per 100 ml.

	Enhanced ONS (A)	Standard ONS (B)
Energy (kcal)	200	200
Protein g/TE% (ingredients)	10 g/20 % (whey protein (63 %), caseinate, and vegetable protein)	10 g/20 % (caseinate and whey protein (25 %))
• L-leucine	• 1.6 g	• 0.9 g
Carbohydrates g/TE% (ingredients)	20 g/39.7 % (dextrin and maltodextrin)	18.2 g/46 % (maltodextrin)
• Sugars	• 2.4 g	• 2.1 g
Fat g/TE% (ingredients)	8.6 g/38.5 % (EVOO, canola oil, MCT, and fish oil)	5 g/31 % (canola oil and high-oleic sunflower oil)
• SFA	• 10.9 %	• 4.4 % • 19.1 %
• MUFA	• 18.6 %	• 6.5 %
• PUFA	• 9.0 %	• -
• EPA & DHA	750 mg	
Fiber g/TE% (ingredients)	1.8 g/1.8 % (FOS, acacia fiber, and β-glucans) 100 % soluble	1.5 g/1.5 % (FOS and oat fiber) 60 % soluble – 40 % non-soluble
Osmolarity (mOsm/l)	420	390

EVOO: extra virgin olive oil; FOS: fructooligosaccharides; MCT: medium chain triglyceride; MUFA: monounsaturated fatty acid; ONS: oral nutritional supplement; PUFA: polyunsaturated fatty acid; SFA: saturated fatty acid; STF: standard formula; TE%: percentage of total energy.
A: Bi1 alisenoc®, Adventia Pharma S.L, Spain.
B: Bi1 control 2.0®, Adventia Pharma S.L., Spain.

accordance with the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines (Arends et al., 2017).

Randomization was performed using a number table by the individual responsible for the study's statistical analysis. Each patient received a participant number that assigned him or her to a specific arm to receive one nutritional formula or another (enhanced or standard ONS).

2.5. Statistical analysis

To calculate the sample size, a difference in weight gain of 5 % between the groups was estimated. With a confidence level of 95 %, a power of 80 %, and foreseeing a 10 % loss to follow-up, a sample size of 31 patients per experimental arm was estimated for a total of 62 patients.

The statistical analysis was carried out using the SPSS 25.0 program (IBM). The Kolmogorov–Smirnov Test was used to assess whether quantitative variables followed a normal distribution. These variables were expressed as mean and standard deviation or as median and interquartile range. Student's *t*-test was used to compare quantitative variables and if the distribution was not normal, nonparametric tests were used.

Qualitative variables were expressed as absolute frequencies and percentages. The chi-square test was used to compare these variables.

A p value less than 0.05 was considered significant.

Ethical approval

All procedures were conducted in accordance with the ethical standards of the institutional research committee [La Paz University Hospital (Code 5358, July 2, 2019)] and with the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all individual participants included in the study.

All patients were informed of the conditions for participation in the study and agreed to participate after signing an informed consent form.

3. Results

3.1. Study population

Sixty-three patients were screened, of which 57 met the inclusion criteria and were randomized. Of them, 37 completed the study (Fig. 1). Patients were withdrawn from the study due to a need for enteral nutrition (n = 1) or total parenteral nutrition (n = 5), intolerance to ONS, intake of less than one package of the ONS (n = 6), death (n = 7). No patients were withdrawn for not attending the scheduled appointment (n = 0) (Fig. 1). There were no differences between the groups in regard to patients withdrawn ($p = 0.828$).

There were no differences between the intervention groups in terms of demographic characteristics, toxic habits, tumor type, tumor stage, tumor extent, treatment, and other concomitant diseases (Table 2).

3.2. Nutritional status

In the group as a whole, at baseline, most patients who took part in the study had malnutrition classified as moderate (SGA-B, 77.2 %) or severe (SGA-C, 22.8 %) (Fig. 2). These results were similar to those observed in the nutritional intervention group ($p = 0.350$).

At the end of the nutritional intervention period, there was a reduction in the percentage of patients with severe malnutrition (SGA-C) in the group that received the enhanced ONS, with these patients going on to be classified as SGA-B or even SGA-A. Likewise, the standard ONS group had a smaller reduction in the percentage of patients classified as SGA-B and, to a lesser extent, SGA-C. Nevertheless, analyzing these data according to treatment group did not yield significant differences within the enhanced ONS group ($p = 0.446$) or the standard ONS group ($p = 0.170$) from baseline to the end of the intervention and there were no significant differences between the intervention groups ($p = 0.137$). At the end of follow-up, 21.4 % of the patients in the enhanced ONS group were classified as SGA-A compared to none of those treated with standard ONS ($p = 0.077$) (Fig. 2).

After the intervention was completed, the patients who received the enhanced ONS showed a tendency to return to their body weight at V1 [65.12 (16.14) kg to 66.44 (16.47) kg; $p = 0.091$]. Indeed, there was an increase in body weight observed by the end of the follow-up period compared to a slight decrease in body weight in the standard ONS group [1.32 (4.01) kg vs. −0.51 (2.74) kg; $p = 0.104$], although this difference was not statistically significant. There were no differences in the other anthropometric variables (Table 3).

Regarding changes in body composition (Table 4), it was observed that there was a greater increase in muscle mass in the enhanced ONS group compared to the standard ONS group after the intervention [1.92 (4.31) vs. 0.04 (2.45) kg; $p = 0.014$]. This increase in muscle mass was not related to changes in hand grip strength (Table 3).

Regarding biochemical variables, the parameters analyzed did not show significant changes at the end of the intervention period. No statistical differences were detected when comparing the results according to ONS group (Table 5).

3.3. Functional status and physical activity

At the beginning of the study, 24.5 % of the population had an ECOG score of 0, 51 % had an ECOG score of 1, 17.5 % had an ECOG score of 2, and 7 % had an ECOG score of 3. No significant differences were observed between the intervention groups. After the intervention period, fewer patients were classified as ECOG 3, the most debilitated state (Fig. 3). This improvement occurred in both intervention groups, with statistically significant changes from the first to the last visit in the

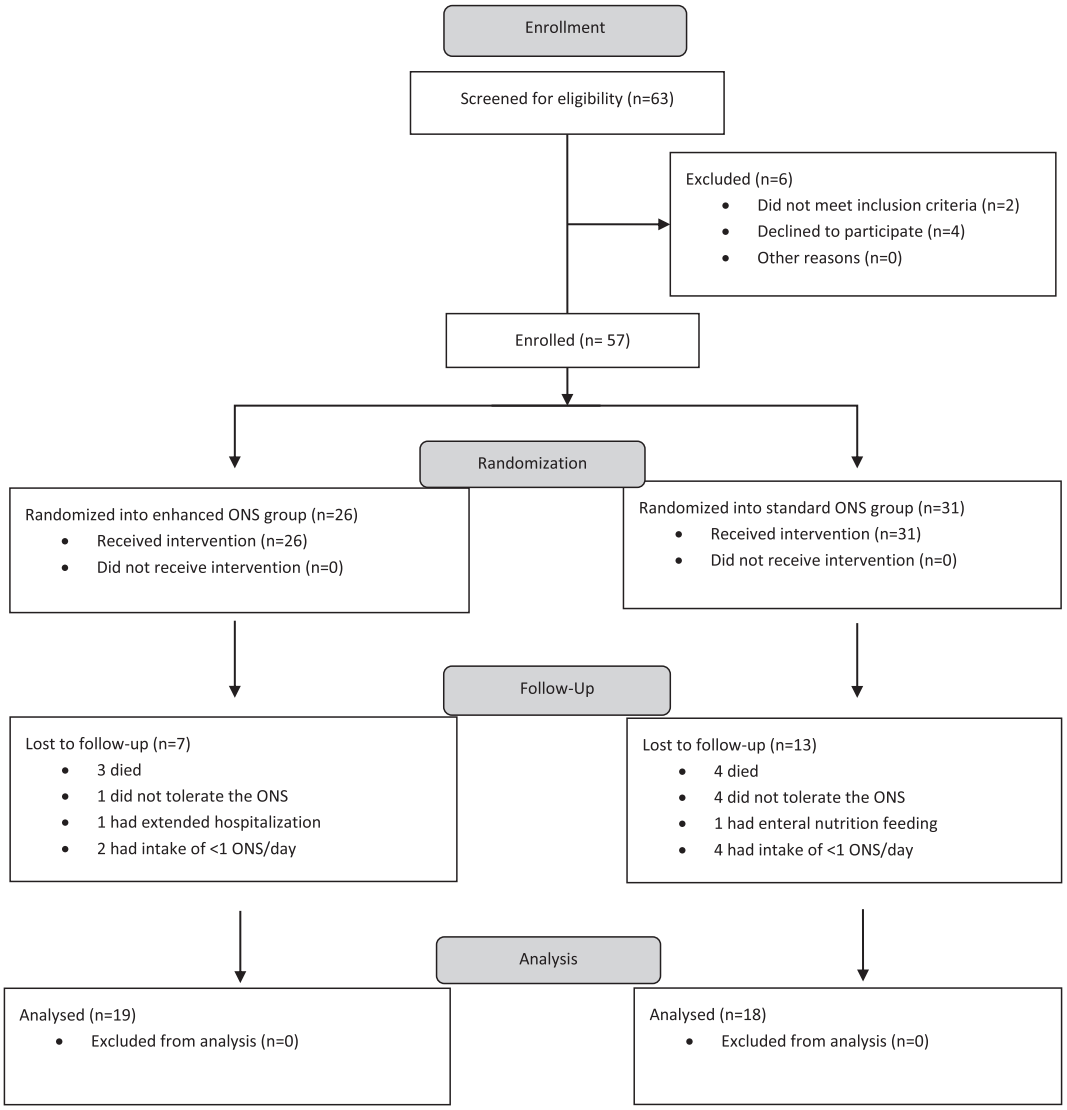

Fig. 1. Flow diagram. ONS: oral nutritional supplement.

enhanced ONS ($p = 0.005$) and standard ONS ($p = 0.001$) groups. At the end of follow-up, 92.3 % of the patients assigned to the enhanced ONS group had an ECOG score of 1 compared to 64.3 % of those in the standard ONS group ($p = 0.08$) (Fig. 3).

At the first visit, both groups had similar levels of physical activity according to IPAQ [enhanced ONS 754.7 (734.4) MET minutes/week vs. standard ONS 1463.8 (3054.8) MET minutes/week; $p = 0.301$]. At the last visit, there were no significant differences between the two groups [enhanced ONS group 982.9 (795.7) MET minutes/week vs. standard ONS group 1798.7 (2509.0) MET minutes/week; $p = 0.189$] or changes from the initial levels [enhanced ONS 248.4 (880.5) MET minutes/week vs. standard ONS 783.4 (2509.4) MET minutes/week; $p = 0.388$].

Finally, adherence to ONS treatment was high in both groups, exceeding 80 % in both cases: 80.08 % (18.59 %) in the enhanced ONS group vs. 81.94 % (20.62 %) in the standard ONS group, $p = 0.706$.

4. Discussion

Specific nutritional supplementation with leucine, β-glucans, EPA, and DHA significantly increased muscle mass and could improve nutritional status and functional status/QoL in malnourished patients with cancer when compared to an isocaloric and isonitrogenous formula without specific ingredients.

Multiple studies have been conducted on specific omega-3 supplementation in populations of patients with cancer. The latest ESPEN guidelines on the nutritional management of patients with cancer include a recommendation regarding supplementation with omega-3 fatty acids or fish oil in patients with advanced cancer undergoing treatment with chemotherapy who are at risk of weight loss or malnutrition. This recommendation is aimed at stabilizing or improving appetite, food intake, lean mass, and body weight. The effectiveness of this recommendation is not certain; there is a low level of evidence yet a strong degree of consensus (Arends et al., 2017). Some articles have been published on this issue after these guidelines were released. In a 2018 study by Solís Martínez et al., the impact of 2 g EPA supplementation on body composition and inflammation was evaluated in patients with squamous cell carcinoma of the head and neck. The authors observed a positive effect in terms of the regulation of body weight and lean mass, as well as an improvement in QoL (Solís-Martínez et al., 2018). Omega-3 supplementation in patients with pancreatic-biliary cancer undergoing treatment with chemotherapy also appears to be beneficial in terms of improving body composition, as observed in the study by Abe et al. (2018). A 2021 study by Izaola et al. shows that an EPA and DHA supplement regimen favors the recovery of nutritional status and QoL in patients with cancer (Izaola et al., 2021).

The improvement in body composition detected and, more

Table 2
Initial descriptive clinical and demographic variables.

	Enhanced ONS (n = 26)	Standard ONS (n = 31)	*p*
Age (years) (mean (SD))	65.15 (8.29)	62.90 (12.16)	0.427
Sex (female)	10 (38.5 %)	10 (32.3 %)	0.805
Alcohol use	3 (11.5 %)	9 (29 %)	0.107
Tobacco use	3 (11.5 %)	4 (12.9 %)	0.876
Tumor type			0.144
Head and neck	1 (3.8 %)	3 (9.7 %)	
Upper digestive tract (esophagus and stomach)	4 (15.4 %)	4 (12.9 %)	
Lower digestive tract (small intestine, large intestine)	1 (3.8 %)	8 (25.8 %)	
Pancreas	1 (3.8 %)	4 (12.9 %)	
Liver	0 (%)	1 (3.2 %)	
Lung	8 (30.8 %)	7 (22.6 %)	
Gynecological (breast, ovary)	2 (7.7 %)	0 (0 %)	
Urological (bladder, prostate, kidney)	4 (15.4 %)	2 (6.5 %)	
Other (thyroid, neuroendocrine, lymphomas, sarcomas, melanoma, etc.)	5 (19.2 %)	2 (6.5 %)	
Stage			0.665
I	0 (0 %)	1 (2.2 %)	
II	5 (25 %)	4 (16 %)	
III	5 (25 %)	5 (20 %)	
IV	10 (50 %)	15 (60 %)	
Extent			0.696
Invasion	4 (19 %)	4 (14.8 %)	
Metastasis	17 (81 %)	23 (85.2 %)	
Previous cancer surgery	11 (42.3 %)	11 (35.5 %)	0.598
Active cancer treatment	25 (96.2 %)	30 (96.8 %)	0.899
Chemotherapy	14 (53.8 %)	16 (57.1 %)	
Radiotherapy	1 (3.8 %)	0 (0 %)	
Immunotherapy	4 (15.4 %)	2 (7.1 %)	
Combined	7 (26.9 %)	10 (35.7 %)	
Concomitant diseases			0.537
DM	3 (11.5 %)	4 (12.9 %)	
HT	10 (38.5 %)	13 (41.9 %)	
Dyslipidemia	5 (19.2 %)	7 (22.6 %)	
COPD	2 (7.7 %)	6 (19.4 %)	
Gastrointestinal diseases	3 (11.5 %)	3 (9.7 %)	
Thyroid disease	7 (27 %)	4 (12.9 %)	
Other diseases	18 (69.2 %)	17 (54.8 %)	

COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus, HT hypertension, ONS: oral nutritional supplement.

specifically, the increase in muscle mass in patients who received the enhanced ONS may not only be promoted by omega-3 intake, but also by the adequate supply of protein with a high biological value that comes from whey as well as branched-chain amino acids such as leucine, which can also lead to the development of muscle mass (Gielen et al., 2021). Numerous studies have investigated the effects of whey supplementation. One of the most recent studies was published by Cereda et al., who evaluated the impact of supplementation with 20 g/day of whey protein for three months on body composition and toxicity in malnourished patients with cancer and cachexia. These authors detected an increase in muscle mass, an increase in strength, and a reduction in chemotherapy treatment-associated toxicity (Cereda et al., 2019).

Regarding leucine supplementation in patients with cancer, current scientific evidence has assessed its effectiveness in improving muscle mass when accompanied by physical exercise. Storck et al. observed that supplementation with a whey rich in leucine and physical exercise increased hand grip strength, but did not increase muscle mass or change body composition (Storck et al., 2020). These data are in contrast to what was found in our study, although it is true that a multimodal approach including a physical activity regimen was not used in this work. A study by Faccio et al. performed on patients with cancer undergoing chemotherapy or radiotherapy treatment called for nutritional supplementation with whey protein, leucine, and zinc for four weeks. This was then compared to the group that received dietary advice. Differences in body composition were not observed, although increases in total energy and protein intake were detected (Faccio et al., 2021).

Regarding the functional status and QoL evaluation with the ECOG scale, a reduction in the number of patients in the most severe category was observed, especially in patients with cancer who received the enhanced ONS. Studies that include results on the relationship between nutritional status and functional status in patients with cancer measured with the ECOG scale are very recent. A 2020 observational study by Santos et al. detected a positive correlation between the diagnosis of malnutrition and scores on the ECOG scale in patients with cancer, regardless of tumor location (Santos et al., 2021). No studies were found which evaluated the impact of nutritional support on the ECOG scale, a feature which can be considered a strength of this study.

Other main strengths of this study include its randomized, double-blind, multicenter clinical trial design. This study type is of extraordinary methodological quality, which was maintained throughout the study's conduct at all participating sites. Another noteworthy aspect is that the standard ONS formula was isocaloric and isonitrogenous to the enhanced ONS formula. This allows for evaluating the impact of diet on the parameters studied not only in terms of calorie and protein intake, but also in terms of specific components such as protein quality, increased leucine, extra virgin olive oil, and omega-3 from fish oil.

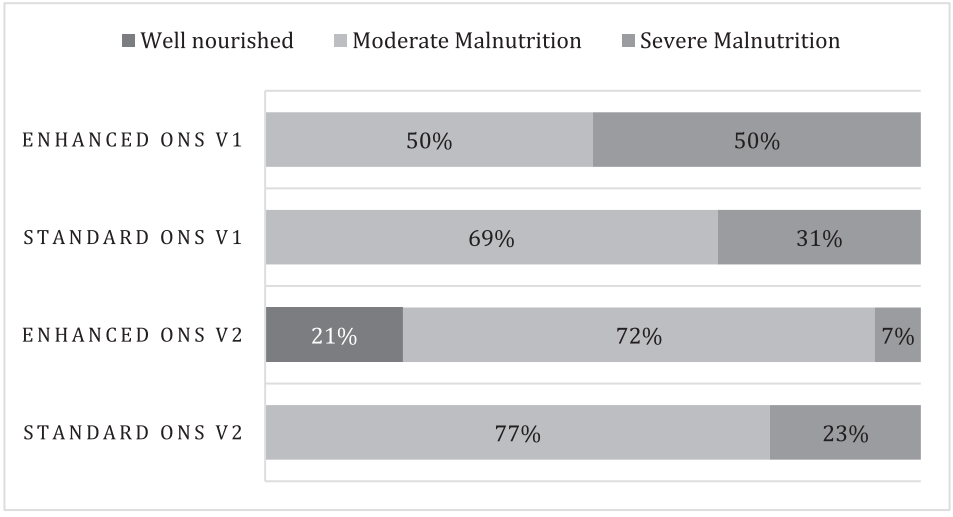

Fig. 2. Evolution of nutritional status by treatment. ONS: oral nutritional supplement.

Table 3
Changes in anthropometric variables according to nutritional intervention group [mean (standard deviation)].

	Enhanced ONS			Standard ONS			*p* (between groups)
	V1	V2	Differences	V1	V2	Differences	
Usual weight (kg)	78.32 (21.19)	–	–	76.48 (14.56)	–	–	–
Weight 6 months prior to V0 (kg)	75.16 (18.95)			73.37 (15.13)	–	–	
Weight (kg)	65.12 (16.14)	66.44 (16.47)	1.32 (4.01)	65.7 (13.1)	65.19 (12.2)	−0.51 (2.74)	0.104
Weight loss (%)	−12.95 (6.78)	–	–	10.29 (4.61)	–	–	–
Height (cm)	1.66 (0.08)	–	–	1.65 (0.1)	–	–	–
BMI (kg/m^2)	23.67 (5.49)	24.16 (5.9)	0.49 (1.45)	23.79 (3.86)	23.96 (3.89)	0.17 (1.6)	0.534
Mid arm circumference (cm)	25.63 (4.76)	26.54 (4.26)	0.91 (2.49)	26.62 (4.11)	26.74 (3.87)	0.12 (2.5)	0.336
Tricipital skinfold (mm)	9.48 (5.48)	9.78 (5.44)	0.31 (2.59)	11.06 (3.79)	11.46 (4.07)	0.41 (2.58)	0.603
Muscle area of the upper arm (cm^2)	22.65 (4.94)	23.47 (4.26)	0.81 (2.55)	23.14 (3.88)	23.14 (3.58)	−0.01 (1.95)	0.273
Waist Circumference (cm)	91.81 (14.55)	93.54 (14.63)	6.75 (22.84)	87.82 (11.05)	89.66 (12.3)	1.84 (9.44)	0.452
Calf Circumference (cm)	32.58 (3.9)	32.71 (3.84)	0.13 (2.38)	31.23 (3.91)	32.15 (3.95)	0.93 (3.3)	0.448
Dynamometry (dominant hand) (kg)	24.56 (9.09)	23.68 (8.91)	−0.88 (4.77)	25.79 (11.8)	25.98 (10.73)	0.19 (10.21)	0.220
Dynamometry (non-dominant hand) (kg)	22.5 (9.87)	21.48 (8.92)	−1.02 (5.56)	26.2 (10.29)	26.02 (11.53)	−0.18 (7.93)	0.382

BMI: body mass index; ONS: oral nutritional supplement.

Table 4
Changes in bioimpedance parameters according to nutritional intervention group [mean (standard deviation)].

	Enhanced ONS			Standard ONS			*p* (between groups)
	V1	V2	Differences	V1	V2	Differences	
Resistance (Rz) (ohms)	581.31 (101)	562.63 (91.48)	−16.68 (61.64)	559.62 (72.16)	570.41 (91.56)	10.70 (50.34)	0.121
Reactance (Xc) (ohms)	44.94 (9.11)	48.16 (9.23)	3.23 (5.92)*	49.29 (8.87)	51.85 (10.75)	2.56 (9.9)	0.410
Phase angle (PhA) (°)	4.85 (1.17)	4.6 (0.8)	−0.25 (0.63)	5.11 (1.04)	5.33 (1.59)	0.22 (1.03)	0.185
Total water (L)	35.44 (6.95)	36.17 (6.37)	0.72 (2.96)	35.47 (6.56)	35.05 (6.31)	−0.42 (1.95)	0.190
Extracellular water (L)	18.23 (2.42)	19.14 (3.13)	0.91 (1.62)*	17.98 (2.97)	17.26 (2.42)	−0.72 (1.8)	**0.008**
Intracellular water (L)	17.17 (5.44)	17.03 (3.97)	−0.15 (2.35)	17.41 (4.57)	17.55 (5.62)	0.14 (2.62)	0.735
Appendicular skeletal muscle mass (kg)	18.69 (7.73)	20.61 (8.23)	1.92 (4.32)	20.58 (7.72)	19.9 (7.37)	−0.68 (1.45)	**0.009**
Lean mass (kg)	47.99 (9.24)	48.34 (7.78)	0.35 (3.43)	48.05 (9.03)	47.84 (8.99)	−0.22 (3.17)	0.615
Fat mass (kg)	17.28 (12.71)	18.47 (14.22)	1.19 (3.44)	15.29 (6.68)	15.46 (6.7)	0.16 (2.47)	0.321
Appendicular skeletal muscle mass index (kg)	16.05 (5.4)	16.35 (5.31)	0.3 (1.27)	15.69 (5.46)	15.67 (5.5)	−0.02 (1.11)	0.438

* $p < 0.005$.
ONS: oral nutritional supplement.

Table 5
Changes in biochemical parameters according to nutritional intervention group [mean (standard deviation)].

	Enhanced ONS			Standard ONS			*p* (between groups)
	V1	V2	Differences	V1	V2	Differences	
Total Cholesterol (mg/dl)	189.22 (38.89)	194.06 (46.19)	4.83 (27.07)	156.41 (31.49)	164.76 (37.6)	−0.22 (49.13)	0.719
Total protein (g/dL)	6.83 (0.4)	6.94 (0.48)	0.11 (0.46)	6.75 (0.43)	6.75 (0.49)	0 (0.52)	0.545
Albumin (g/dL)	4.21 (0.37)	4.28 (0.39)	0.08 (0.3)	4.17(0.54)	4.14 (0.36)	−0.03 (0.48)	0.433
Prealbumin (mg/dl)	22.09 (8.33)	23.52 (8.42)	1.43 (7.85)	20.58 (6.48)	21.89 (6.62)	1.31 (4.66)	0.486
Retinol-binding protein (ng/dl)	4.56 (2.68)	5.26 (2.55)	0.7 (1.91)	3.3 (1.45)	3.51 (1.75)	0.21 (1.07)	0.428

ONS: Oral nutritional supplement.

Lastly, this study not only evaluated changes in nutritional status to assess the effectiveness of the intervention, but also examined specific parameters such as body composition, functional status, and QoL, allowing for elucidating other specific effects that nutritional supplementation with an enhanced ONS may have in patients with cancer.

The main weakness of this study is its small sample size. The study mainly recruited older adult patients (mostly men) with advanced-stage cancer and metastatic disease undergoing chemotherapy or combined treatment with other concomitant diseases such as hypertension and dyslipidemia. This may explain the high mortality rate observed during the intervention period. Lastly, the patients' advanced cancer stages means that these results cannot be extrapolated to other patients with cancer in the initial stages of the disease.

5. Conclusions

In conclusion, this study shows that in addition to reversing malnutrition, a specific ONS enriched in EPA, DHA, leucine, and β-glucans promotes an increase in muscle mass and the recovery of functional status and QoL in malnourished patients with cancer.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Hospital

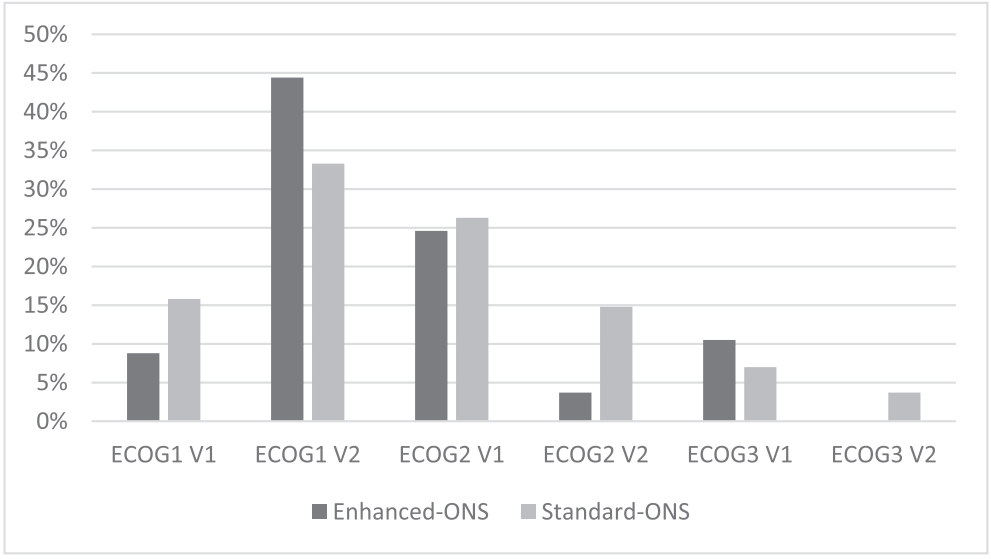

Fig. 3. Changes in the functional status. ECOG: Eastern Cooperative Oncology Group; ONS: oral nutritional supplement.

Universitario La Paz. Informed consent was obtained from all subjects involved in the study.

Consent for publication

Informed consent was obtained from all subjects involved in the study.

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CRediT authorship contribution statement

Alfonso Vidal Casariego: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Pedro P. García Luna:** Writing – review & editing, Investigation, Conceptualization. **Francisco Villazón González:** Investigation, Conceptualization. **Tomás Martín Folgueras:** Investigation, Conceptualization. **Samara Palma Milla:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Juan José López Gómez:** Writing – review & editing, Investigation. **Irene González Navarro:** Investigation. **Alicia Calleja Fernández:** Project administration, Funding acquisition, Conceptualization. **Tamara Casañas Quintana:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Bricia López Plaza:** Formal analysis, Conceptualization. **Daniel A. de Luis Román:** Writing – review & editing, Supervision, Investigation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Hospital Universitario La Paz. Informed consent was obtained from all subjects involved in the study.

ACF and TCQ are employees of Adventia Pharma. The rest of the authors declare no conflicts of interest.

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