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ORIGINAL ARTICLE

The effect of nabilone on appetite, nutritional status, and quality of life in lung cancer patients: a randomized, double-blind clinical trial

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Abstract

Background Over one half of the patients diagnosed with advanced lung cancer experience anorexia. In addition to its high incidence, cancer-induced anorexia promotes the development of the anorexia-cachexia syndrome, which is related to poor clinical outcomes. Recently, drugs derived from cannabinoids, such as Nabilone, have been recognized for their appetite improvement properties; however, clinical trials to support their use in cancer patients are necessary.

Methods This is a randomized, double-blind, placebo-controlled clinical trial to assess the effect of Nabilone vs. placebo on the appetite, nutritional status, and quality of life in patients diagnosed with advanced Non-small cell lung cancer (NSCLC) (NCT02802540).

Results A total of 65 patients from the outpatient clinic at the National Institute of Cancer (INCan) were assessed for eligibility and 47 were randomized to receive Nabilone (0.5 mg/2 weeks followed by 1.0 mg/6 weeks) or placebo. After 8 weeks of treatment, patients who received Nabilone increased their caloric intake (342-kcal) and had a significantly higher intake of carbohydrates (64 g) compared to patients receiving placebo ($p = 0.040$). Quality of life also showed significant improvements in patients in the experimental arm of the trial, particularly in role functioning ($p = 0.030$), emotional functioning ($p = 0.018$), social functioning ($p = 0.036$), pain ($p = 0.06$), and insomnia ($p = 0.020$). No significant change in these scales was seen in the control group.

Conclusion Nabilone is an adequate and safe therapeutic option to aid in the treatment of patients diagnosed with anorexia. Larger trials are necessary in order to draw robust conclusions in regard to its efficacy in lung cancer patients.

Keywords Anorexia · Orexigenic agent · Energy consumption · Lung cancer · Quality of life

Introduction

Lung cancer patients have the highest rate in cancer mortality worldwide [1], with a poor prognosis and 16% of survival in 5 years [2, 3]. At least a half of the patients with advanced non-small cell lung cancer (NSCLC) experience anorexia (lack of appetite), and this number increases up to 80% as disease progresses [4]. Anorexia is importantly related to a reduced food intake, weight loss, and promotes the cancer anorexia-cachexia syndrome (CACS) [5]. Patients who are identified with anorexia at the time of cancer diagnosis should be treated in a timely manner. Early intervention on patients with anorexia can prevent the onset of CACS, which is a recognized factor for poor prognosis, including a significant decrease in overall survival (OS) and can worsen chemotherapy-derived toxicity [6]; in addition, it is associated with poor quality of life and has a negative impact on family

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members. Most patients with anorexia will further on develop CACS, the treatment of which includes nutritional intervention, physical activity, and pharmacological treatment [7]. Pharmacological intervention for CACS seeks to improve appetite; decrease the inflammatory reaction, related to patient prognosis; and promote anabolic metabolism [7–9]. In spite of its impact in patient overall health and quality of life, a gold standard for treating cancer-associated anorexia has not been established, and the effectiveness of drugs remains controversial or limited to a specific patient subgroup.

Drugs currently under use include megestrol acetate, which increases appetite and weight gain, but its long-term use is limited by the development of potentially serious side effects such as thromboembolic phenomena, edema, and lower response rate to chemotherapy and a trend for inferior survival duration [10]. Other agents whose effectiveness has been tested in NSCLC patients include anamorelin, which has been shown to significantly improve Anorexia/Cachexia Scale (AC/S) score and increase total weight and lean body mass compared to patients assigned to placebo [11]. Anamorelin is a ghrelin receptor agonist but is not readily available worldwide. Other nutritional supplements have also been tested, with limited results [12]. Cannabinoids have been suggested to be a valuable treatment option for improving appetite in patients with anorexia [13]. Among cannabinoids, dronabinol has been found to have antiemetic properties and to stimulate appetite. Several previous studies have shown dronabinol to convey therapeutic benefits in cancer patients who have anorexia and weight loss. However, results have not been conclusive in regard to the mechanisms for appetite stimulation and its impact on weight gain [14]. Nabilone (Cesamet®) is a synthetic analogue of Δ-9 tetrahydrocannabinol (THC), and it has been used in Western Europe and Canada for over 20 years and is approved by the Food and Drug Administration for chemotherapy-induced nausea and vomiting [15, 16]. Nabilone presents several advantages compared to other cannabinoids, such as dronabinol. For example, nabilone has higher bioavailability compared to dronabinol (95% vs. 10–20%), presents a higher duration of action, and is not detected on urine drug tests [17]. The orexigenic effects of THC occur through the inhibition of leptin at the hypothalamic level, [15] and also by palliating dysgeusia, a significant side effect in patients receiving chemotherapy [13, 18]. Although cannabinoids have been associated with appetite stimulation, no clinical trials focused in lung cancer-related anorexia as a primary objective have been conducted to date [16]. A relevant study evaluated the effect of administering nabilone for the management of pain and symptoms experienced by patients with advanced cancer. The patients receiving nabilone showed borderline improvement in appetite compared with those not taking nabilone ($p = 0.0516$) [15]. Moreover, a pilot study in cancer patients determined that delta-9-THC could improve dysgeusia ($p = 0.026$), appetite ($p = 0.05$), and protein intake ($p = 0.008$) and increase quality of sleep ($p = 0.025$) and relaxation ($p = 0.045$) in patients with chemosensory alterations. However, another trial evaluated the administration of delta-9-tetrahydrocannabinol in 65 patients and found a 58% increase in appetite compared to 69% using placebo [19].

In this randomized, double-blind, placebo-controlled pilot study, we sought to evaluate the effect of nabilone vs. placebo in lung cancer patients diagnosed with anorexia using the AC/S of the Functional Assessment of Anorexia Cachexia Therapy (FAACT) tool [20].

Materials and methods

This was a randomized, double-blind, placebo-controlled pilot study to evaluate the effect of nabilone vs. placebo during 8 weeks of treatment in stage III and IV NSCLC patients from the outpatient clinic of the Thoracic Oncology Unit at the Instituto Nacional de Cancerología (INCan) in México City. The study received approval by the Institutional Review Board and Ethic Committee (014/005/ICI)(CEI 883/14) and was registered at Clinicaltrials.gov (NCT02802540).

Eligibility criteria

Patients diagnosed with histologically confirmed advanced NSCLC, regardless of current therapeutic scheme, with a good performance status (Eaestern Coperative Oncology Group score [ECOG] 0–2), diagnosed with anorexia according to the AC/S were screened for inclusion. The visual analogue scale (VAS) for loss of appetite and weight loss were registered. Patients were informed of the objective of the study and were invited to participate and sign an informed consent form. Exclusion criteria for this study included patients who withdrew their informed consent and did not wish to continue in this study, patients who only underwent the baseline evaluation and did not attend the rest of the follow-up, patients who decided to stop taking the medication after they had agreed to enter the study, patients with a known allergy and/or contraindication for receiving cannabinoids, patients who had previously received treatment with cannabinoids, and patients who had previously received any other pharmacological treatment for anorexia.

Stratification and randomization

After baseline assessment, patients were randomized by the protocol coordinator in a double-blind manner to receive capsules for oral administration of 0.5 mg daily of nabilone or placebo for 2 weeks, as administration of this agent must initiate with an induction dose as per regulatory indication. Subsequently the dose was increased to 1 mg daily for the

next 6 weeks. Patients were evaluated at the time of inclusion, and 4 and 8 weeks after randomization.

Nutritional assessment

The presence of anorexia was identified using the AC/S-12 section of the FAACT tool [20]; patient perception of loss of appetite was evaluated using a unidirectional VAS. Body weight and height were measured. The body mass index (BMI) was calculated as body weight/height squared. A subjective global assessment (PG-SGA) was used to assess and classify patients as having moderate or severe malnourishment (B or C) or as being well nourished (A). Food intake was measured using the SNUT program, which calculates calories, proteins, carbohydrates, fats, and micronutrients, including iron and zinc [21].

Biochemical parameters

The biochemical data evaluation included an analysis of the serum albumin level and a complete blood cell count. Venous blood samples were drawn from patients after an overnight fast. All laboratory values were determined using routine automated analyzers at the Department of Clinical Chemistry at the INCan.

NLR was defined as absolute neutrophil count divided by absolute lymphocyte count, whereas PLR was described as absolute platelet count divided by absolute lymphocyte count. NLR ≥ 5 and PLR ≥ 150 were considered to indicate systemic inflammatory response (SIR) [22].

HRQL evaluation and toxicity

The Health-related quality of life (HRQL) evaluation was assessed using the validated Mexican-Spanish version of the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaires specific for cancer and for LC (EORTC-QLQ-C30 and QLQ-LC13, respectively) [23, 24]. Scores for the multi-item functional, symptom scales and the single-item scales were calculated using a linear transformation of raw scores to produce a range from 0 to 100, as described by EORTC. In this scale, the best score is 100 for the global health status and functional scales, while scores nearing 0 represent lesser symptoms. Chemotherapy toxicity was evaluated using the Common Terminology Criteria for Adverse Effects (CTCAE).

Statistical analysis

For descriptive purposes, continuous data were summarized as arithmetic means and standard deviation (SD), whereas categorical variables were summarized as proportions. Square chi and student t test were performed to analyze baseline differences between groups. Among each group, differences over time were analyzed using a paired t test for nutrimental and biochemical variables (baseline–4 weeks, baseline–8 weeks) and Friedman for Quality of life scales (baseline–4 weeks–8 weeks). Overall survival (OS) was defined as the time from randomization until death or loss to follow up. OS was analyzed using the Kaplan-Meier method, and comparisons among median values were performed using the Log-rank test. A p value of 0.05 (two-sided) or lower was considered significant. SPSS for MAC version 20 was employed to perform all analyses (IBM, Corp., Armonk, NY, USA).

Results

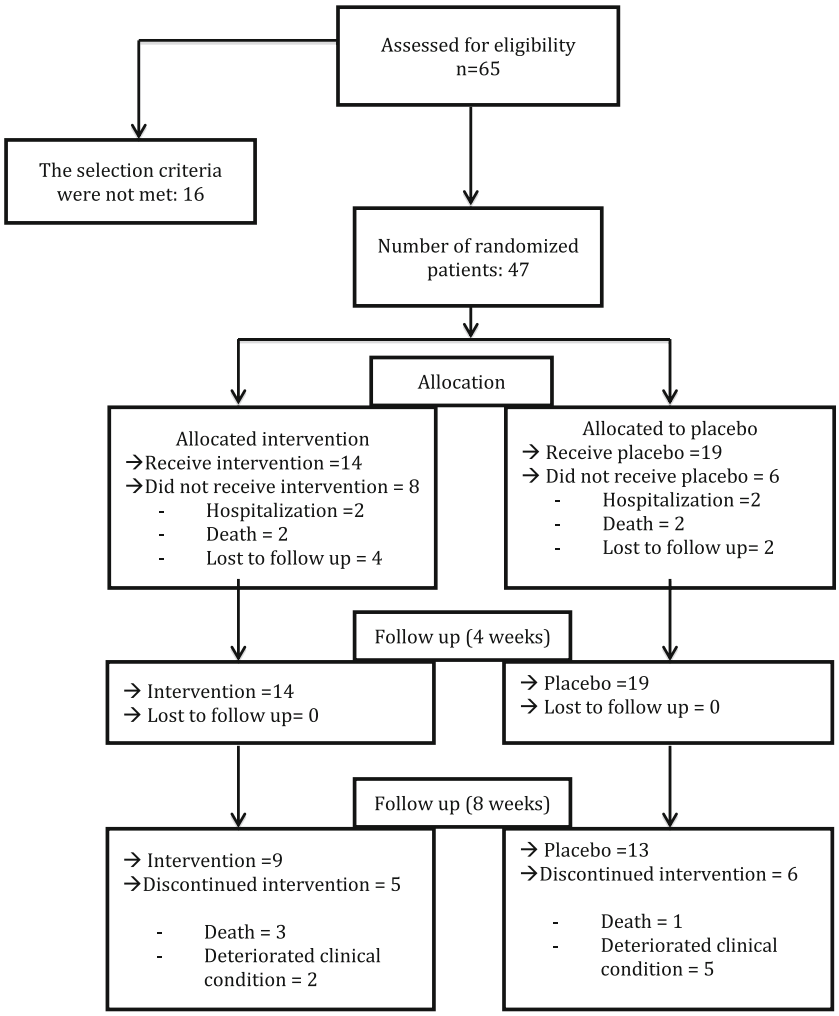
Participants

A total of 65 patients were evaluated at the National Cancer Institute of Mexico to be included in this study, from December 2013 to December 2015. Sixteen patients did not meet the inclusion criteria, and 47 patients were randomized to the experimental and control groups (Fig. 1). From the already randomized patients, four never started treatments because of an event of hospitalization after randomization, four died, and six did not return for the complete evaluation (Fig. 1). Sixty-four percent ($n = 13$) of patients in the placebo group and 68% ($n = 9$) of patients in the experimental group completed the 8 weeks of follow-up. The loss of follow-up in the experimental and control groups was due to death (3 and 1, respectively) and to deterioration in their medical condition (2 and 5, respectively), both related to cancer (Fig. 1). Baseline differences among groups included a worse performance status ($p = 0.010$), older age ($p = 0.042$), and greater weight loss in the last 6 months ($p = 0.032$) for patients in the experimental arm of the trial (Table 1).

At the 4-week evaluation, no statistically significant differences were found between the control and experimental groups in regard to appetite and anthropometric and biochemical variables (Supplementary Table 1).

At the 8-week evaluation, we did not find a statistically significant difference when comparing the experimental and control group in regard to appetite and anthropometric and biochemical variables (Table 2). The appetite increase for each group was close in magnitude, and the final change in the AC/S score was similar between both arms of the trial (AC/S Δ 8 vs. 8.4; $p = 0.929$). However, there was a statistically significant improvement in VAS for the experimental group ($p = 0.006$), with the higher difference towards improvement between groups (Δ −1.1 control vs. −2.8 experimental, $p = 0.219$). The experimental group had a higher weight loss compared to the control group (300 g); however, this difference was not statistically significant when comparing both groups ($p = 0.724$) (Table 3).

Fig. 1 CONSORT diagram



In regard to biochemical parameters, patients in the experimental group experienced a statistically significant decrease in PLR when comparing baseline vs. 8-week value (Table 2). Interestingly, patients with lower PLR (≤ 150 vs. > 150) had better OS (12.6 vs. 20.6 months in patients with PLR > 150 vs. PLR ≤ 150; $p = 0.034$) (Fig. 2).

In terms of nutritional consumption, patients in the experimental group had a statistically significant difference in regard to carbohydrate consumption compared to the control group (Δ − 42.4 g vs. 21.8 g control and experimental groups respectively, $p = 0.040$) in the 8-week evaluation (Table 3). The control group had a statistically significant decrease in energy consumption ($p = 0.041$) and when comparing groups, we found a difference in energy consumption of 342 kcal (Δ − 280 kcal control vs. 61.4 kcal experimental; $p = 0.123$) (Table 3) (Supplementary Fig. 1). Other differences in terms of protein and fat intake can be consulted in Table 3. Previously, it has been determined that anorexia can dictate the types of foods preferred by patients, and therefore, its treatment may reverse alterations in dietary preferences [25, 26].

The evaluation of HRQL showed that the experimental group has an improvement in the functional scale ($p = 0.030$), emotional scale ($p = 0.018$), social scale ($p = 0.036$), pain ($p = 0.016$), and insomnia ($p = 0.020$) at 8 weeks, while the control group did not register any significant improvement in relation to these HRQL scales (Table 4). Nonetheless, the control group showed a significant reduction in appetite loss, whereas the experimental group also shows a difference, although this was only borderline significant ($p = 0.060$). In regard to nausea and vomiting, the control group also showed a significant improvement when comparing the baseline and 8-week evaluation ($p = 0.043$), but it is important to highlight that the experimental group did not record any events of grade 3 or higher nausea after treatment had been administered (4- and 8-week evaluation).

Discussion

This study compares nabilone and placebo in lung cancer-associated anorexia. Both groups improved appetite according

Table 1 Baseline characteristics among nabilone and control group patients

		Control $n = 19$ Mean ± SD	Experimental $n = 14$ Mean ± SD	p value
Sex	Male	4 (21.1)	3 (21.4)	1
	Female	15 (78.9)	11 (78.6)	
Stage	III	4 (21.1)	9 (64.2)	0.625
	IV	15 (78.9)	4 (28.6)	
	Not available	0 (0)	1 (7.2)	
Chemotherapy line	1	6 (31.6)	4 (28.6)	0.841
	2	3 (15.8)	3 (21.4)	
	≥ 3	10 (52.6)	6 (42.8)	
	Not available	0 (0)	1 (7.2)	
ECOG	0	0 (0)	0 (0)	0.010
	1	19 (100)	9 (64.3)	
	2	0 (0)	5 (35.7)	
SGA	A	0 (0)	0 (0)	0.506
	B	6 (31.6)	6 (42.9)	
	C	13 (68.4)	8 (57.1)	
Anorexia (CTCAE)		19 (100)	14 (100)	
Age	years	52.6 ± 11.8	61.1 ± 10.6	0.042
Weight	kg	49.5 ± 9.7	50.7 ± 9.9	0.720
BMI	kg/m^2	21.1 ± 2.6	20.9 ± 3.5	0.852
Weight loss past6-months	%	10 ± 4.6	14.8 ± 7.3	0.032
AC/S (FAACT)		16.8 ± 6.7	21.4 ± 6.3	0.060
VAS appetite loss	cm	7.1 ± 2.1	8.1 ± 2.1	0.191
Appetite (QLQ-C30)		80 ± 24.5	90.4 ± 4.2	0.258
Energy intake	Kcal/day	1216 ± 310.4	1126 ± 393	0.475
Proteins	gr/day	37.9 ± 14	35.2 ± 12.3	0.577
Carbohydrates	gr/day	179.5 ± 48	164.8 ± 60.8	0.448
Fats	gr/day	43.3 ± 16	39.9 ± 16.2	0.559
Iron	mg/day	6.7 ± 1.9	6.8 ± 2.4	0.914
HRQL global status		41.1 ± 30.5	52.3 ± 28.9	0.312
VAS pain		4.8 ± 3	5 ± 3.5	0.891
Albumin	mg/dl	3.6 ± 0.4	3.5 ± 0.7	0.634
Hemoglobin	g/dl	11.7 ± 2.3	12.5 ± 1.7	0.323
Platelets	$\times 10^3/\mu L$	332.3 ± 143.4	321.08 ± 124.4	0.825
Leucocytes	$\times 10^3/\mu L$	6.6 ± 4.2	7.7 ± 4.2	0.515
Lymphocytes	$\times 10^3/\mu L$	1.2 ± 1	1.3 ± 0.4	0.805
Neutrophils	$\times 10^3/\mu L$	5.1 ± 3.8	5.7 ± 4	0.681
NLR		5.4 ± 3.9	4.7 ± 3.6	0.611
PLR		335.1 ± 192.5	263.2 ± 113.4	0.255

SGA subjective global assessment, *BMI* body mass index, *AC/S* anorexia cachexia scale from the functional assessment of anorexia cachexia therapy (FAACT) tool, *VAS* visual analogue scale, *NLR* neutrophils lymphocytes ratio, *PLR* platelet lymphocyte ratio, *CTCAE* common terminology criteria for adverse event

to the AC/S and VAS tools; however, the nutrimental consumption and quality of life was considerably different when taking into consideration the experimental and control groups of our study. It is important to highlight that all participants were initially screened for depression, and results between groups showed no statistically significant difference; therefore, this important confounding factor in terms of appetite is not present in our study [27].

Our findings support that treatment with nabilone in patients diagnosed with anorexia increases energy consumption, specifically carbohydrates, and improves functional scales of quality of life, pain, and insomnia.

Patients with CACS frequently report reduced appetite and food intake [5]. However, there is an important proportion of patients with anorexia who have not yet fully developed CACS. It remains unclear up to this day what proportion of

Table 2 Differences in appetite and anthropometric and biochemical variables after 8 weeks of treatment

		Control $n = 19$	Experimental $n = 14$	p
AC/S	Baseline	19 ± 6.6	18 ± 3.9	0.929
	8 weeks	27 ± 7.6	26 ± 8.4	
	Δ	8.07 ± 9.4	8.4 ± 9.4	
	p	0.009	0.028	
VAS (visual analogue scale)	Baseline	6.5 ± 2.08	9 ± 1.6	0.219
	8 weeks	5.3 ± 3.04	6.1 ± 3.1	
	Δ	− 1.1 ± 3.7	− 2.8 ± 2.3	
	p	0.300	0.006	
Weight (kg)	Baseline	51.1 ± 9.4	51.6 ± 11.37	0.724
	8 weeks	50.06 ± 9.1	50.2 ± 11.6	
	Δ	− 1.09 ± 2.6	− 1.4 ± 1.6	
	p	0.119	0.032	
BMI (body mass index)	Baseline	21.3 ± 2.8	21.2 ± 4.3	0.854
	8 weeks	20.8 ± 2.8	20.6 ± 4.3	
	Δ	− 0.5 ± 1.2	− 0.6 ± 0.7	
	p	0.111	0.029	
Hemoglobin (mg/dl)	Baseline	11.9 ± 2.2	13.3 ± 1.7	0.638
	8 weeks	11.6 ± 1.6	13.4 ± 1.9	
	Δ	− 0.3 ± 2.1	0.1 ± 1.3	
	p	0.559	0.847	
Platelets ($\times 10^3/\mu L$)	Baseline	342.6 ± 151.9	364.1 ± 145.7	0.720
	8 weeks	284.3 ± 114.9	283.2 ± 55.7	
	Δ	− 58.2 ± 140.6	− 80.8 ± 123.7	
	p	0.131	0.135	
Leucocytes ($\times 10^3/\mu L$)	Baseline	6.4 ± 4.1	5.8 ± 2.7	0.737
	8 weeks	7.08 ± 2.4	7 ± 2.9	
	Δ	0.6 ± 3.5	1.1 ± 3.7	
	p	0.506	0.434	
Lymphocytes ($\times 10^3/\mu L$)	Baseline	1.2 ± 1	1.3 ± 0.4	0.381
	8 weeks	1.2 ± 0.7	1.6 ± 0.3	
	Δ	0.0 ± 0.9	0.3 ± 0.5	
	p	0.979	0.135	
Neutrophils ($\times 10^3/\mu L$)	Baseline	4.9 ± 3.9	4.04 ± 2.5	0.773
	8 weeks	5.2 ± 2.4	4.7 ± 3.03	
	Δ	0.2 ± 3.2	0.7 ± 3.6	
	p	0.752	0.618	
Albumin (mg/dl)	Baseline	3.6 ± 0.3	3.5 ± 0.6	0.209
	8 weeks	3.7 ± 0.4	3.8 ± 0.3	
	Δ	0.05 ± 0.2	0.2 ± 0.3	
	p	0.543	0.140	
NLR (neutrophils/lymphocytes ratio)	Baseline	5.3 ± 4.3	3.1 ± 1.9	0.709
	8 weeks	6.1 ± 6.2	3.1 ± 2.5	
	Δ	0.7 ± 4.8	− 0.0 ± 2.9	
	p	0.564	0.988	
PLR (platelets/lymphocytes Ratio)	Baseline	315.5 ± 135.3	295.9 ± 125.9	0.361
	8 weeks	304.2 ± 318.5	177.6 ± 51.1	
	Δ	− 11.2 ± 289.3	− 118.3 ± 117.8	
	p	0.882	0.038	

p differences between groups

lung cancer-associated anorexia can be successfully treated, and therefore the onset of CACS averted in these patients. Studies such as the one we present build on the already existing body of evidence in terms of the treatment options available for cancer patients who experience anorexia. Existing therapies aim to improve patient's appetite and increase food intake but must also have a specific safety profile in order to be safely administered to population whose health is deteriorated and who are receiving many different drugs.

In our study, patient self-perception of loss of appetite was 1.5 times better in patients receiving the experimental therapy vs. the placebo group at the 4-week evaluation, although this difference did not reach statistical significance, probably due to a limited sample size. Another important observation relates

Table 3 Energy intake evaluation in control and experimental groups, differences in 8 weeks

		Control $n = 19$	Δ	Experimental n = 14	Δ	p
Energy intake Kcal/day	Baseline	1246.1 ± 316.5	− 280.8 ± 420	1120 ± 310.5	61.4 ± 553	0.123
	8 weeks	965.3 ± 294		1181.5 ± 471		
	p	0.041		0.748		
Proteins (gr/day)	Baseline	38 ± 14.4	− 7.6 ± 20.6	35.4 ± 11.7	− 2.3 ± 18.1	0.551
	8 weeks	30.3 ± 15.7		33.1 ± 10.5		
	p	0.226		0.705		
Carbohydrates (gr/day)	Baseline	192.8 ± 40.5	− 42.4 ± 63.7	166.4 ± 46.4	21.8 ± 68.9	0.040
	8 weeks	150.3 ± 49.5		188.2 ± 69.6		
	p	0.041		0.370		
Fats (gr/day)	Baseline	41.5 ± 16.9	− 12.07 ± 19	38.9 ± 15.8	1.9 ± 28.5	0.193
	8 weeks	29.4 ± 12.6		40.8 ± 19.5		
	p	0.051		0.844		
Iron (mg/day)	Baseline	7.1 ± 1.6	− 1.1 ± 3.3	7.1 ± 1.9	0.3 ± 2.9	0.319
	8 weeks	5.9 ± 2.6		7.4 ± 2.7		
	p	0.288		0.747		

p differences between control and experimental group 8 weeks post-randomization

to the fact that at 4 weeks post-treatment start, the mean AC/S score for the experimental group was 26.4, while the diagnostic cutoff for anorexia in this scale is 24, which would show that on average, patients receiving nabilone averted an anorexia diagnosis 4 weeks post-treatment, compared to the control group who had an average AC/S score at 4 weeks of 23.6.

We identified several important issues throughout the course of this study, specifically regarding the diagnostic cutoff score for anorexia while using the AC/S tool. The European Society for Clinical Nutrition and Metabolism (ESPEN) has suggested that a score ≤ 24 when using the AC/S is diagnostic of anorexia; however, in our practice, many patients reported loss of appetite with a score > 24 using the AC/S. As the proposed score of ≤ 24 was set as an arbitrary cutoff point, and lacked clinical validation, we set out to validate a specific cutoff point to diagnose anorexia in lung cancer patients. In a previous study, we had validated the Spanish version of the FAACT tool [28] and following this validation, we additionally report that a cutoff point of AC/S ≤ 32.5 for anorexia diagnosis has a sensibility of 80.3% and a specificity of 85%, and therefore is able to screen and identify patients who are already experiencing anorexia, but in early stages, and it is perhaps these early patients who would most benefit from receiving a timely pharmacological intervention [29]. When taking into consideration that when using the AC/S score a lower score represents higher-grade anorexia, the patients included in this pilot study are considered to have severe anorexia (cutoff AC/S ≤ 24), and nonetheless, they still showed a reversible effect when treated with nabilone. Patients in the experimental arm of this trial consumed 300 more kcal compared to the placebo group, and importantly, many of these calories came from a higher carbohydrate intake in these patients; in this case, it is important to highlight that 342 cal represent an important proportion of the calories included in the daily intake of cancer patients.

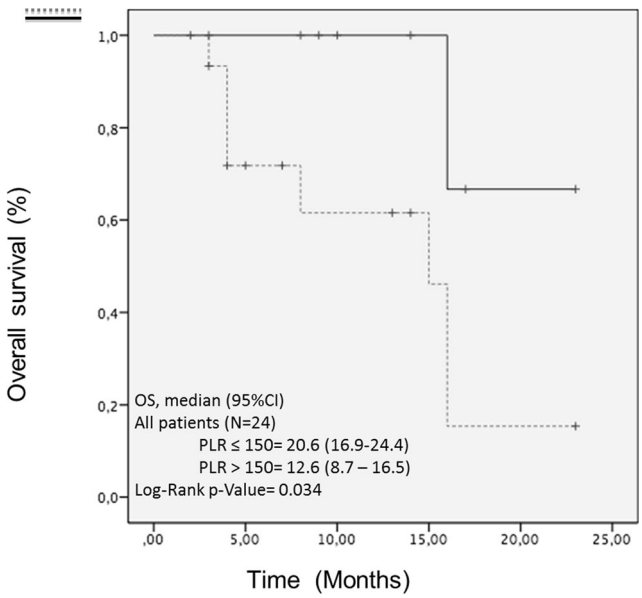


Fig. 2 Overall survival according to PLR

Patients in the experimental group not only avoided a reduction in energy, carbohydrates, and fat consumption but increased intake in all the previously mentioned parameters. It is likely that because of the small sample size included, the differences between groups in terms of energy, proteins, fats, and iron did not reach statistical significance. Although, we do observe energy and fats were significantly reduced in the control group, compared to the experimental group, which showed improvement. It is important to mention that any pharmacological therapy prescribed must be granted along

Table 4 HRQL differences between control and experimental group 8 weeks post-treatment

		Control $n = 19$	Experimental $n = 14$
Global health status/QoL	Baseline	47.4 ± 28	50 ± 32.2
	4 weeks	58.3 ± 15.7	61.1 ± 13.8
	8 weeks	60.8 ± 25.7	52.7 ± 31.4
	p	0.307	0.755
Physical functioning	Baseline	55.3 ± 27.2	52.5 ± 16.4
	4 weeks	60.6 ± 24.6	51.8 ± 27.4
	8 weeks	62 ± 28.4	56.2 ± 26.8
	p	0.490	0.296
Role functioning	Baseline	46.6 ± 39.9	24 ± 25.1
	4 weeks	41.6 ± 29.6	61.1 ± 36.3
	8 weeks	53.3 ± 36.6	55.5 ± 39.9
	p	0.325	0.030
Emotional functioning	Baseline	64.9 ± 20.7	62 ± 19.1
	4 weeks	78.3 ± 21.9	78.7 ± 9.4
	8 weeks	76.6 ± 17.4	72.2 ± 21.2
	p	0.227	0.018
Cognitive functioning	Baseline	79.9 ± 28.1	61.1 ± 25
	4 weeks	83.3 ± 20.7	62.9 ± 32
	8 weeks	85 ± 14.5	62.9 ± 20
	p	0.593	1
Social functioning	Baseline	58.3 ± 41.7	35.1 ± 30.5
	4 weeks	65 ± 32.8	59.2 ± 37.3
	8 weeks	56.6 ± 33.5	70.3 ± 28.5
	p	0.428	0.036
Fatigue	Baseline	65.5 ± 25.3	56.7 ± 33
	4 weeks	45.5 ± 27.9	44.44 ± 31.4
	8 weeks	49.9 ± 26.3	49.3 ± 28.9
	p	0.149	0.695
Nausea and vomiting	Baseline	31.6 ± 18.3	33.3 ± 38.1
	4 weeks	16.6 ± 15.7	16.6 ± 14.4
	8 weeks	20 ± 31	27.7 ± 25
	p	0.043	0.756
Pain	Baseline	54.9 ± 33.3	50 ± 38.1
	4 weeks	41.6 ± 34.4	11.1 ± 11.7
	8 weeks	48.3 ± 35.5	37 ± 29.7
	p	0.356	0.016
Appetite loss	Baseline	76.6 ± 22.4	92.5 ± 22.2
	4 weeks	46.6 ± 28.1	51.8 ± 44.44
	8 weeks	49.9 ± 45.1	62.9 ± 30.9
	p	0.014	0.060
Insomnia	Baseline	43.2 ± 35.3	70.3 ± 30.9
	4 weeks	43.3 ± 35.3	33.3 ± 40.8
	8 weeks	33.3 ± 15.7	29.6 ± 35.1
	p	0.764	0.020

p differences between groups

with the appropriate nutritional care; in fact, it is likely that many of the improved parameters in the control group of our study might be related to the constant nutritional follow-up and guidance to which they were subjected, identical to the experimental group. The target of anorexia treatment must therefore be viewed as a complementary strategy in which the increase of food intake must be balanced, with an adequate proportion of carbohydrates, proteins, and fats.

Another aspect evaluated in this study is the pro-inflammatory factors produced by the tumor cells, which likely impact the onset and history of cachexia. Some relevant and easily accessible parameters to measure, as they are routinely tested in cancer patients, include the NLR, PLR, and C-reactive protein. NLR ≥ 5, PLR ≥ 150, and CPR above 3.9 mg/dl have been considered indicators of the SIR, which may contribute to the progressive decline in nutritional and functional status associated with a poor prognosis and OS in patients with advanced-stage NSCLC [26]. The present study shows that PLR was significantly reduced in the experimental group of this trial, and moreover, all patients with a PLR ≤

150 at the 8-week evaluation have an OS which is 8 months longer compared to patients with a PLR > 150.

In terms of HRQL, relevant differences were observed between groups. The experimental group showed improvement in the role functioning scale, emotional functioning scale, and social functioning scale; all of them strongly related to eating behavior. Likewise, significant reduction in pain and insomnia was observed in the nabilone group vs. control group. The role of cannabinoids in terms of quality of life has been controversial. In a previous study for patients with head and neck cancers treated with radiotherapy, those receiving nabilone did not show a significant improvement compared to placebo in terms of relieving symptoms like pain ($p = 0.6048$), nausea ($p = 0.7105$), loss of appetite ($p = 0.3295$), weight ($p = 0.1454$), mood ($p = 0.3214$), and sleep ($p = 0.4438$) [30]. On the other hand, a retrospective study evaluated the effect of nabilone treatment in 139 cancer patients in palliative care. Of these patients, 82 were prescribed nabilone and were compared to those who had not taken the drug. Nabilone-treated patients experienced significant reduction in pain ($p < 0.001$) and remained stable in terms of drowsiness, tiredness, appetite, and well-being ESAS scores, compared to the non-nabilone group [31]. Patients taking nabilone in the present study had a significant improvement in terms of pain at the administered dose of 1 mg/day for 8 weeks according with quality of life perception of patients, an important change achieved with a small dose. Nausea, one of the principal reasons for prescribing nabilone, did not show a significant improvement in our experimental group, although CTCAE grade 3 nausea was only observed in the placebo group, while the experimental group reported only grade 2 or less events at 8 weeks post-treatment. Nonetheless, it is important to mention that the maximum dose of nabilone prescribed for nausea is 6 mg/day, which is higher than our experimental dose.

This study exposes the potential improvement effect in quality of life in lung cancer patients undergoing either chemotherapy or targeted therapy, for which it is known that nutritional status greatly affects efficacy and toxicity profile [9, 32]. Moreover, the side effects of cannabis are generally tolerable and short lived [16]. One of the most expected side effects from nabilone is somnolence, which in the present study was significantly beneficial to balance the insomnia reported in the experimental group.

We are aware that the study findings are limited by several factors. One is the small sample size, which because of the nature of this study as a pilot did not allow for greater patient recruitment. On the other hand, there are some differences between the baseline characteristics of our patient population; however, it is important to observe that these changes favor the control group, who were slightly younger, had a better performance status, and had a lower weight loss in the last 6 months.

Future considerations should take into account the time since the start of anorexia, because of the adaptive behavior that can be crucial for cannabinoid effect and which might explain why the experimental group, which probably had anorexia for a longer period of time, did not avoid weight loss at 8 weeks post-treatment.

The current findings from this pilot study build on the existing body of evidence in regard to the use of pharmacologic therapy for the treatment of anorexia in cancer patients. It is the first trial to explore the effects of nabilone in lung cancer-related anorexia. Although the study presents several limitations, the results described warrant the future development of larger studies. In addition, an important conclusion supported by this study is the unequivocal need to provide cancer patients with timely and thorough nutritional evaluations and to follow their status throughout disease course. The future of the multidisciplinary approach to the management of cancer patients must therefore not overlook the important role of nutrition in the quality of life and outcomes of cancer patients.

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Compliance with ethical standards

Conflict of interest statement The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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