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The Administration of Ocoxin Increases the Quality of Life of Patients with Advanced Epithelial or Metastatic Ovarian Cancer Undergoing Neoadjuvant Chemotherapy

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Abstract

Background: 70% of ovarian cancer cases are diagnosed at an advanced stage (III or IV) of the disease and, in turn, with a high prevalence of peritoneal carcinosis and ascites, which leads to progressive malnutrition in patients, with the consequent deterioration of their general condition. There is a very important relationship between nutritional status, quality of life, survival, and the ability to tolerate multidisciplinary treatment of peritoneal carcinosis. **Methods:** A phase II, open-label, single-center, non-randomised clinical trial was conducted that included 36 patients with advanced disease who were administered the nutritional supplement Ocoxin, 30 ml twice a day, beginning one week before chemotherapy (CT) based on carboplatin/paclitaxel, of which

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they receive three cycles with neoadjuvant intent. Ocoxin treatment was continued during chemotherapy and for three weeks after completion of the last cycle, as well as during any periods for which this treatment was discontinued due to toxicity. The effect of Ocoxin on the quality of life was assessed through the QLQ C30 and QLQ OV28 questionnaires from the start of treatment until the end of the follow-up period. In addition, the Karnofsky Index and nutritional parameters were assessed. **Results:** There were no significant differences between adverse events versus baseline values, except in leukocytes, lymphocytes, neutrophils, ALT, and AST. There was no deterioration of the QoL scales, except for those related to the effects of chemotherapy and alopecia. **Conclusions:** Ocoxin as an adjuvant to chemotherapy appears to improve better tolerance to chemotherapy, showed a good safety profile, and improved quality of life. For further information on Ocoxin neoadjuvant therapy benefits, a phase III clinical trial will be needed.

Keywords

Chemotherapy, Radiotherapy, Ovarian Cancer, Oncology, Quality of Life, Adjuvant Therapy, Supportive Care

1. Introduction

Epithelial ovarian cancer (EOC) is diagnosed at locally advanced or metastatic stages in more than 75% of women, as symptoms are often vague and short-lasting and no effective screening programs are currently available [1].

In advanced stages, the disease frequently presents with ascites and peritoneal carcinosis, leading to progressive malnutrition in patients, with the consequent deterioration of their general condition. There is a very important relationship between nutritional status, quality of life, survival, and the ability to tolerate multidisciplinary treatment for peritoneal carcinosis. In these cases, cytoreductive surgery is one of the most viable options, although only 33% of patients survive for more than five years as a result. The treatment of choice for epithelial ovarian cancer is surgical debulking followed by chemotherapy with platinum-derived agents (carboplatin or cisplatin) in combination with taxanes (paclitaxel or docetaxel), and it is suggested to start neoadjuvant chemotherapy in advanced stages. Most ovarian carcinomas are sensitive to this therapeutic regimen, but 20% - 30% are resistant [2] [3] [4] [5].

Oxidative stress has been associated with several diseases and particularly cancer, causing an imbalance in the levels of pro- and antioxidant agents. The most active pro-oxidant agents are free radicals, which constitute a threat to cellular balance. Several studies have been conducted to evaluate the efficacy of cancer-specific treatments with nutritional and antioxidant supplements to reduce adverse events and treatment interruptions and increase overall survival [6] [7].

Ocoxin (OOS), a nutritional supplement developed by Catalysis S.A., has been

evaluated in preclinical and clinical studies on different cancer sites, with and without associated malnutrition. It has demonstrated antitumor effects, as it limits angiogenic processes, inhibits cell proliferation, blocks metastasis, inhibits urokinase, an enzyme found in some malignant tumours, and induces apoptosis. It works in synergy with CT, increasing the antitumor effect, as well as acting as a radiosensitizer and tissue protector, reducing toxicities from cancer treatments [8] [9] [10] [11] [12]. It is a well-tolerated product with low toxicity, and it has been used in Cuba before with no adverse effects reported [13].

Based on the evidence from the previous studies, the present clinical trial was conducted to evaluate the effect of the Ocoxin nutritional supplement on the quality of life of patients with advanced or metastatic epithelial ovarian cancer undergoing neoadjuvant chemotherapy.

2. Material and Methods

A phase II, open-label, single-center, non-randomised clinical trial was conducted. The study included thirty-six patients diagnosed with advanced, unresectable, or metastatic epithelial ovarian cancer seen at the Institute of Oncology and Radiobiology (INOR) in Cuba between November 2018 and September 2021, with organ function determined by clinical laboratory ranges, general health status ≥70 according to the Karnofsky Index and ventricular ejection fraction ≥ 55% measured by echocardiography, who were not receiving another investigational product and required neoadjuvant chemotherapy based on platinum salts and taxanes. All participants gave their informed consent.

Patients took the nutritional supplement Ocoxin (Table 1) at a dose of 30 ml twice a day, after breakfast and lunch. Treatment was initiated one week before starting a chemotherapy (CT) regimen consisting of carboplatin and paclitaxel every three weeks, of which they received three cycles with neoadjuvant intent. Treatment with Ocoxin was continued during CT and for three weeks after completion of the last cycle, as well as during any periods when CT was suspended due to toxicity. The final evaluation took place 3 weeks after the last CT cycle. The study lasted for approximately 10 weeks.

This research was approved by the Research Ethics Committee of the INOR and the regulatory agency CECMED and was included in the Cuban public registry of clinical trials and ClinicalTrials.gov Identifier NCT03562897.

2.1. Assessments of Clinical Laboratory Parameters and Quality of Life

Control variables such as age, clinical stage, histological type, comorbidities, oligometastatic disease, and presence of ascites were assessed.

Treatment safety was assessed through the reporting of adverse events, which were identified by laboratory tests (complete blood count and blood chemistry), physical examination, and patient questioning from the start of treatment until the final evaluation.

Table 1. The chemical composition of Ocoxin nutritional supplement oral solution (30 ml bottles) is shown in the following table.

Ingredient	Value (mg/30ml)
Glucosamine sulfate potassium chloride	600 mg
L-Glycine	600 mg
Malic acid	360 mg
L-Arginine	192 mg
L-Cysteine	61.2 mg
Monoammonium glycyrrhizinate	60 mg
Ascorbic acid	36 mg
Sodium benzoate	30 mg
Zinc sulfate	30 mg
Green tea extract	7.5 mg
Calcium pantothenate	3.6 mg
Manganese sulfate	1.2 mg
Pyridoxine hydrochloride	1.2 mg
Cinnamon extract	0.9 mg
Folic acid	120 μg
Cyanocobalamin	0.6 μg
Water q.s.p.	30 ml

Health-related Quality of Life was assessed through the QLQ C30 [14] and QLQ OV28 [15] questionnaires. In addition, the Karnofsky Index and nutritional parameters were assessed.

2.2. Statistical Analysis

Planned number of subjects: To obtain the sample size for the phase II design and given that this is a dietary supplement with extensive information on its safety, A Hern's single-stage design [16] is used, with no early termination rules. The investigational product would be declared ineffective if the success rate (P)—where P is the proportion of subjects in the trial suffering a deterioration of their quality of life (at least for some of the scales or dimensions), measured at the end of treatment in comparison with the baseline measurement—is less than or equal to 25% (p_0). That is, this number is the maximum level of success below which the product shows no signs of efficacy (the study does not warrant further investigation). If there is a p_1 value of 45%—where p_1 is the minimum level of efficacy required above which the product would be declared as effective, then the results warrant continuation to a phase III study. Assuming a 5% α error rate (probability of rejecting the null hypothesis when it is true) and a 20% β error rate (probability of rejecting the alternative hypothesis when it is true) (power of

the test: $1 - \beta = 80\%$), we decided to recruit a maximum of 36 subjects. Allowing for a 10% loss to follow-up, a total of 40 patients would be required. The trial tested the null hypothesis H_0: $P \leq p_0$ against the alternative hypothesis: H_1: $P \geq p_1$.

The number of responses (a) is set at 13 (cut-off point), so the product will be declared ineffective if the responses do not exceed this number (H_0 is acceptable). And $r = a + 1 = 14$; that is, the number of responses where the generated efficacy level warrants continuation to a phase III study.

Quality of life was the main response variable, as determined by the Karnofsky index and by the general EORTC QLQ-C30 and specific EORTC QLQ-OV28 quality of life questionnaires. Nutritional status, adherence to the planned chemotherapy regimen, and the occurrence and type of any AEs were assessed as secondary variables. The non-parametric Wilcoxon signed-rank test was used to statistically compare the change in the primary response variables. For secondary variables, the response rate (improvement if value D_{final} > value D_0) was estimated and the exact 95% CI was calculated.

3. Results

3.1. Patient Characteristics

Data were analysed for all included patients with data recorded in the Case Report Form (CRF), for N = 36. This sample corresponded to the expected sample size (without losses). All patients remained in the study for at least 7 days and received at least 14 doses of investigational product and also the first cycle of CT (Table 2).

The mean age was 55.2 years, ranging from 31 to 73. Papillary serous adenocarcinoma was the most frequent histological type (N = 23; 63.9%). Most patients were diagnosed at stage IIIC (N = 28; 77.8%), with a Karnofsky index indicating a good general condition (N = 25; 69.4%). Ascites was present in all patients (N = 36; 100.0%) and only three had the oligometastatic disease (8%). Twenty-eight patients reported concurrent diseases (77.8%), the most frequent of which was HTN (N = 15; 41.7%).

Four treatment discontinuations occurred, three due to death caused by cancer progression and one case due to a serious adverse event (cerebral infarction), none of which were related to the product under evaluation. The rest of the patients remained until the end of the study. Patients were considered to have been assessed on schedule if they were evaluated within seven days of the study schedule. In cycles 2 (day 28) and 3 (day 49), three patients were evaluated outside the planned schedule (patients deferred due to adverse events); in the final evaluation, five patients were evaluated more than seven days behind schedule (Table 3).

Cycle deferral was due to G2 anaemia (N = 3), G1 neutropenia (N = 2). None of these adverse events interrupted the experimental treatment and they had re-

solved by the final evaluation.

3.2. Results of Clinical Laboratory Parameters

There was a decrease in haemoglobin (p = 0.017), leukocytes (p = 0.000), absolute neutrophil count (p = 0.000), eosinophils (p = 0.000) and platelets (p = 0.000), while monocyte (p = 0.002), lymphocyte (p = 0.000) and basophil (p = 0.034) values increased (Table 4).

Table 2. Patient characteristics.

Variables		*N*	*% of N*
Age	Mean (SD)	55.2 (10.4)	
	Median (IQR)	56 (49 - 62)	
	Min, Max	(31; 73)	
Histological type (recoded)	Papillary serous adenocarcinoma	23	63.9
	Adenocarcinoma of unknown primary	6	16.7
	Poorly differentiated carcinoma	5	13.9
	Peritoneal papillary serous carcinoma	2	5.6
Clinical stage classification (recoded)	IIIC	28	77.8%
	IVA	1	2.8%
	IVB	7	19.4%
Karnofsky index	100	8	22.2%
	90	25	69.4%
	80	3	8.3%
Metastatic site	None	28	77.8%
	Mediastinal lymphadenopathy	2	5.6%
	Liver	4	11.1%
	Pleura	1	2.8%
	Lung	1	2.8%
Ascites	Yes	36	100%
Oligometastatic disease	Yes	3	8%
	No	33	92%
Concurrent disease	Yes	28	77.8%
	No	8	22.2%
Hypertension	Yes	15	41.7%
	No	21	58.3%
Diabetes Mellitus	Yes	6	16.7%
	No	30	83.3%

Table 3. Discontinuation and adherence to planned treatment and evaluation.

		N (%)
Discontinuation	Definitive	4 (11.1%)
	Ocoxin treatment	4 (11.1%)
	CT treatment	4 (11.1%)
Reasons for discontinuation	Death	3 (%)
	Serious adverse event	1 (%)
Compliance with scheduled treatment	Chemotherapy	32 (88.9%)
	Ocoxin	32 (88.9%)
OV vials consumed	Mean (95% CI)	130 (118; 143)
	Median (IQR)	143 (137; 145)
	Min, Max	(14; 211)
CT administration	Received all CT cycles	32 (88.9%)
	Delayed administration of CT cycles (≥7 days)	4 (11.1%)
CT cycles on time	1st cycle	36 (100%)
	2nd cycle	32 (88.9%)
	3rd cycle	32 (88.9%)
Regimen used	Carboplatin/paclitaxel	36 (100%)
	Cisplatin/paclitaxel	0
Compliance with the evaluation time	Cycle	Median (IQR); (Min, Max)
	Initial	0 (0); (0;3)
	Cycle 1 (day 7)	7 (2); (7; 12)
	Cycle 2 (day 28)	28 (3); (28; 53)
	Cycle 3 (day 49)	49 (3); (49; 77)
	Final (day 63)	72.5 (6); (69; 105)

In blood biochemistry parameters, there were only an increase in total bilirubin ($p = 0.009$), cholesterol ($p = 0.000$), and triglycerides ($p = 0.004$). Interestingly, creatinine did not show a statistically significant increase ($p = 0.389$) (Table 5).

3.3. Adverse Events

At least one adverse event was reported in all subjects, with a total of 290 adverse events reported (Table 6).

Alopecia was reported in all 36 subjects included and was associated with chemotherapy. The other most frequent adverse events were anaemia, abdominal pain, headache, diarrhoea, and nausea (Table 7).

According to the intensity classification, the majority of adverse events were

Table 4. Description of haematological parameters by time and evaluation of final change vs initial value.

Laboratory parameter	Initial evaluation	Cycle 2	Cycle 3	End	Paired Initial-Final variances (Var 95% CI) p
Haemoglobin (g/l)	36 115 (106 - 125.5)	33 112 (106 - 119)	32 111.5 (96 - 119)	32 110.5 (100.5 - 117.5)	6.9 (1.4 - 12.5) 0.017
Leukocytes ($\times 10^9$/l)	36 8.61 (7.72 - 0.42)	34 6.12 (4.74 - 8)	32 5.37 (4.71 - 6.6)	32 5.28 (4.41 - 6.6)	3.6 (2.8 - 4.3) 0.000
Neutrophils (%)	36 72.6 (66.4 - 76.9)	34 58.5 (50.1 - 65.5)	32 54.8 (45.1 - 58.8)	32 51 (45.6 - 60.9)	20 (16 - 24.1) 0.000
Monocytes (%)	36 8.35 (7 - 10.1)	32 10.2 (7.5 - 12.4)	30 9.9 (8.6 - 11.6)	32 10.0 (8.4 - 13)	−2.3 (−3.7 - 0.9) 0.002
Lymphocytes (%)	36 16.5 (12.6 - 22.9)	34 28.8 (20.7 - 35.8)	31 34.6 (28.2 - 42.2)	32 37.05 (32.6 - 43.4)	−18.9 (−22.4 - 15.4) 0.000
Eosinophils (%)	36 1.4 (0.7 - 2.1)	27 0.8 (0.4 - 1.5)	26 0.65 (0.3 - 1.3)	28 0.45 (0.25 - 0.95)	1.2 (0.5 - 1.8) 0.000
Basophils (%)	33 0.3 (0.2 - 0.5)	26 0.45 (0.2 - 0.6)	26 0.4 (0.3 - 0.6)	27 0.5 (0.3 - 0.7)	−0.2 (−0.4 - 0) 0.034
Platelets ($\times 10^9$/l)	36 453 (407.5 - 541.5)	34 320 (250 - 386)	32 267 (218.5 - 348)	32 243 (191 - 324.5)	232.5 (169.5 - 295.5) 0.000
ANC ($\times 10^9$/l)	36 6.41 (5.28 - 7.77)	34 3.135 (2.54 - 4.92)	31 2.82 (2.06 - 3.84)	32 2.44 (2.01 - 3.325)	3.7 (3.1 - 4.3) 0.000

Table 5. Description of blood chemistry parameters by the time of evaluation and differences between the final value and initial value.

Laboratory parameter	Initial evaluation	Cycle 2	Cycle 3	End	Paired Initial-Final variances (Var 95% CI) p
ALT/GPT (U/l)	36 17 (11.825 - 28.5)	34 24.5 (15.7 - 41)	30 19.5 (13 - 32)	30 23.5 (18 - 43.2)	−12.2 (−22.9 - 1.5) 0.072
AST/GOT (U/l)	13 19 (16 - 30.6)	11 40 (19 - 44)	11 25 (18.9 - 48)	17 21 (18 - 30)	2 (−5.5 - 9.5) 0.500

Continued

Direct bilirubin (µmol/l)	35 3.2 (2.6 - 4.3)	30 3.55 (2.9 - 4.7)	27 3.8 (2.7 - 4.9)	30 3.8 (2.5 - 4.7)	−1.3 (−2.7 - 0.2) 0.096
Total bilirubin (µmol/l)	35 9.7 (5.6 - 11)	30 12 (9.6 - 15.2)	25 11.6 (7.9 - 13.9)	30 12.1 (8.3 - 13.7)	−5.3 (−11.6 - 1) 0.009
Glycaemia (mmol/l)	36 5.15 (4.6 - 5.5)	34 4.9 (4.5 - 5.4)	30 5.2 (4.6 - 5.9)	32 5.1 (4.55 - 5.7)	−0.2 (−0.5 - 0.2) 0.492
Creatinine (µmol/l)	36 57 (49.5 - 66.5)	34 55.5 (48 - 72)	31 59 (48 - 71)	32 60.5 (51 - 70.5)	−0.4 (−5.3 - 4.5) 0.389
Uric acid (µmol/l)	35 282 (224 - 365)	32 276 (222 - 331)	31 288 (245 - 349)	30 304 (268 - 366)	−22 (−75.9 - 31.9) 0.262
Total proteins (g/l)	36 71.5 (65.3 - 77.5)	34 74.1 (69.2 - 79)	30 75.2 (70.8 - 79)	31 73.1 (69.3 - 78.5)	−0.8 (−4.5 - 2.8) 0.643
Albumin (g/l)	36 37.0 (33.75 - 40.55)	34 37.7 (33.2 - 42.07)	30 38.05 (34.4 - 40.7)	31 38.1 (35.4 - 41.7)	−0.3 (−3 - 2.4) 0.825
Cholesterol (mmol/l)	35 4.03 (3.45 - 4.42)	34 4.22 (3.86 - 4.9)	28 4.8 (4.0 - 5.24)	30 4.6 (4.2 - 5.32)	−0.7 (−1.1 - −0.4) P < 0.0001
Triglycerides (mmol/l)	35 1.12 (0.9 - 1.4)	34 1.4 (1.1 - 1.7)	28 1.5 (1.09 - 1.7)	29 1.3 (1.2 - 1.8)	−0.4 (−0.7 - −0.1) 0.004
Alkaline phosphatase (U/l)	34 122 (103 - 161)	34 133.5 (104.5 - 173.7)	29 110 (98 - 140)	29 115 (88 - 124)	−11.7 (−61.6 - 38.2) 0.554

Table 6. Frequency of adverse events in the study.

Adverse events	**N = 36**
Patients presenting at least one AE, n % 95% CI (exact)	36 (100%) (90.3%; 100.0%)
The total number of AEs reported in the study	290
Days between the start of the trial and adverse events	
Mean (SD)	30 (20.8)
Median (IQR)	28 (11.7-46.3)
Min, Max	0; 103

Table 7. Description of the type of adverse event.

types of adverse events	n = 290	
	n	%
Alopecia	36	12.4
Anaemia	25	8.6
Abdominal pain	24	8.3
Headache	16	5.5
Diarrhoea	16	5.5
Nausea	16	5.5
Arthralgia	11	3.8
Asthenia	11	3.8
Hypoalbuminemia	9	3.1
Vomiting	8	2.8
Colic	6	2.1
Myalgia	6	2.1
Itching	6	2.1
Epigastric pain	5	1.7
Thrombocytopenia	5	1.7
Infections (cellulitis, dehiscence, pneumoperitoneum, dental abscess)	4	1.4
Heartburn	4	1.4
Constipation	4	1.4
Dehydration	4	1.4
Elevated direct bilirubin	4	1.4
Neutropenia	4	1.4
Other	63	21.7

mild (N = 192; 66.2%) and moderate (N = 74; 25.5%) (Table 8).

Fifteen adverse events (5.2%) were classified as Serious, including three deaths and an equal number of serious adverse events with life-threatening or incapacitating effects. None of the AEs classified as serious were related to the investigational product (Table 9).

There were 250 non-serious adverse events (86.2%) that were not related to the investigational product. One, eight, and four of these adverse events were classified in terms of causality as very likely, possible, and likely, respectively (Table A1).

Regarding the investigational product, there were 12 (4.1%) definitive discontinuations and 7 temporary discontinuations (2.4%). In a total of 162 cases, the patient recovered from the adverse events (resolved); one patient experienced sequelae and 96 patients had adverse events that persisted until the final evalua-

tion date.

3.4. Adverse Events Affecting Clinical Laboratory Results

The haematological parameters that appeared to be linked to the time of evaluation were leukocytes, which increased in grade 1 adverse events (p = 0.0001), and lymphocytes, which decreased in grade 1 adverse events (p = 0.040) (Table A2).

Adverse events related to increased liver enzymes ALT and AST were associated with a decrease at the end of the evaluation, with statistically significant differences (p = 0.034 and p = 0.048, respectively). Adverse events for the remaining blood chemistry parameters assessed were not associated with the time of assessment (Table A3).

The global health status/QoL scale (based on Q29 and Q30 in QLQ-C30 [V3]), which can be considered as an overall summary measure, shows an increase in mean values. At 2.5 months after the start of treatment the difference was −11.5 points, 95% CI (−21.0; −1.9). Both confidence interval limits show a statistically significant increase (p = 0.027).

The scales that evaluate the symptoms (fatigue, loss of appetite and insomnia) show values that demonstrate a significant improvement after 2 months of treatment. It is also evident that for the fatigue and loss of appetite scales, the confidence interval limits have values outside the clinically relevant threshold of 5 points, which is a criterion for a clinically meaningful response. Overall, more than half of the patients improved in the different dimensions of the quality-of-life questionnaire two weeks after the end of treatment (Table 10).

Table 8. Frequency of adverse events by intensity.

Intensity	N	%
Serious, life-threatening or incapacitating	3	1.0
Death	3	1.0
Severe	18	6.2
Moderate	74	25.5
Mild	192	66.3
Total	290	100.0

Table 9. Frequency of intensity of serious adverse events.

	Intensity	N	%
Adverse events classified as Serious	Serious, life-threatening, or incapacitating	3	20.0
	Death	3	20.0
	Severe	7	46.7
	Moderate	2	13.3
	Total	15	100

Evaluations of the QLQ-OV28 questionnaire indicate that the Gastrointestinal Symptom Rating Scale (GSRS) shows significantly reduced values at the end of the study compared to baseline (mean 27.1, 95% CI 16: 38.1). The confidence interval limits have values outside the clinically relevant threshold of 5 points, which is a criterion for a clinically meaningful response.

Except for the items regarding attitude to treatment (N = 7, 47.2%, 95%CI 30.4, 64.5), peripheral neuropathy (N = 6, 44.4%, 95% CI 27.9, 61.9) and other chemotherapy-related effects, all other items were favourable in more than half of the patients (Table 11).

The Karnofsky index improved at the end of the study in 31 of the 36 patients included (86.1%); 95%CI (70.5, 95.3) (Table 12).

The evaluation of the secondary variables measuring nutritional status during the study shows that there was a statistically significant decrease in BMI (p = 0.0001) and body weight (p = 0.0001). There were no statistically significant changes in serum albumin and protein values (Table 13).

4. Discussion

The vast majority of patients with epithelial ovarian cancer are diagnosed at locally advanced and metastatic stages (stages III-IV) [17] [18], associated with malignant ascites and peritoneal carcinosis, which leads to protein-energy

Table 10. Comparison of the QLQ-C30 quality of life (QoL) scales (initial/final).

Scales	No. of signs −/0/+ (=Total)	Var (initial-final) 95% CI	Response	% 95% CI	P
Health/Overall QoL	10/4/18 = (32)	−11.5 (−21.0; −1.9)	22	61.1 (43.5; 76.9)	0.027
Functioning					
Physical Functioning	10/6/16 = (32)	−5.6 (−14.4; 3.2)	22	61.1 (43.5; 76.9)	0.232
Personal Functioning	10/7/15 = (32)	−8.9 −24.6; 6.9	22	61.1 (43.5; 76.9)	0.293
Emotional Functioning	11/5/16 = (32)	−2.3 (−13.5; 8.8)	21	58.3 (40.8; 74.5)	0.621
Cognitive Functioning	9/16/7 = (32)	0.0 (−10.0; 10.0)	23	63.9 (46.2; 79.2)	0.979
Social Functioning	8/12/12 = (32)	−7.3 (−17.6; 3.1)	24	66.7 (49.0; 81.4)	0.148
Symptoms					
Fatigue	17/10/5 = (32)	15.3 (5.1; 25.4)	27	75.0 (57.8; 87.9)	0.006
Nauseas-Vomiting	16/12/4 = (32)	9.9 (−1.0; 20.8)	28	77.8 (60.8; 89.9)	0.083
Pain	12/12/5 = (32)	10.9 (−4.1; 25.9)	24	66.7 (49.0; 81.4)	0.052
Dyspnoea	7/23/2 = (32)	8.3 (−1.8; 18.5)	30	83.3 (67.2; 93.6)	0.102
Insomnia	11/17/4 = (32)	19.8 (4.0; 35.6)	28	77.8 (60.8; 89.9)	0.014
Loss of Appetite	14/14/4 = (32)	26.0 (9.4; 42.7)	28	77.8 (60.8; 89.9)	0.004
Constipation	8/17/7 = (32)	4.2 (−12.8; 21.1)	25	69.4 (51.9; 83.7)	0.604
Diarrhoea	7/18/7 = (32)	3.1 (−11.3; 17.6)	25	69.4 (51.9; 83.7)	0.657
Financial Difficulties	5/18/9 = (32)	−7.3 (−20.12; 5.6)	23	63.9 (46.2; 79.2)	0.267

Table 11. Comparison of the QLQ-OV28 quality of life (QoL) scales (initial/final).

Scales	No. of signs −/0/+ (=Total)	Var (initial-final) 95% CI	Response	% 95% CI	P
Functional scales					
Body image	14/12/6 (=32)	9.9 (−3.6; 23.4)	26	72.2 (54.8; 85.8)	0.148
Sexuality	6/20/6 (=32)	0.9 (−12.5; 10.7)	26	72.2 (54.8; 85.8)	0.937
Attitude to illness/treatment	14/3/15 (=32)	−0.3 (−13.6; 12.9)	17	47.2 (30.4; 64.5)	0.811
Symptom scales					
Gastrointestinal/abdominal symptoms	23/5/4 (=32)	**27.1 (16; 38.1)**	**28**	**77.8 (60.8; 89.9)**	0.0001
Peripheral neuropathy	7/16/9 (=32)	−9.4 (−22.3; 3.5)	16	44.4 (27.9; 61.9)	0.084
Menopausal/hormonal symptoms	10/12/10 (=32)	−3.1 (−18.8; 12.5)	22	61.1 (43.5; 76.9)	0.895
Other CT-related effects	8/7/17 (=32)	−2.7 (−12.1; 6.7)	15	41.7 (25.5; 59.2)	0.268
Hair loss	5/17/10 (=32)	−7.8 (−19.9; 4.3)	22	61.1 (43.5; 76.9)	0.240

Table 12. Karnofsky index at the beginning and end of the study.

	T_ini N = 32	T_final N = 32	Difference (fin-ini) N = 32	Improvement or Stability* (95CI)**
Karnofsky index				
Median (IQR)	90 (90; 97.5)	100 (90; 100)	10 (0; 10)	31/36* (70.5; 95.3)**
Min, Max	(80; 100)	(80; 100)	(−20; 20)	

Table 13. Secondary variables for measuring nutritional status.

Variables	T_ini N = 31	T_Cycle2 N = 31	T_final N = 31	Difference (fin-ini) N = 31	General (95%CI)
BMI					6/36 16.7 (6.4; 32.8)
Median (IQR)	25 (21.8; 30.4)	23.7 (20.2; 29.4)	23.3 (19.6; 27.7)	−1.3 (−2.2; −0.4)	
Wilcoxon signed-rank test (Two-sided, asymptotic significance) p = 0.0001					
Weight					5/36 13.9 (4.7; 29.5)
Median (IQR)	61 (55; 76.5)	61 (51; 72)	60 (50.5; 73)	−3.5 (−5.5; −1)	
Wilcoxon signed-rank test (Two-sided, asymptotic significance) p = 0.0001					
Total proteins					16/36 44.4 (27.9; 61.9)
Median (IQR)	72.2 (68.1; 77.5)	74.2 (69.2; 79)	73.1 (69.3; 78.5)	1.1 (−6.6; 8)	
Wilcoxon signed-rank test (Two-sided, asymptotic significance) p = 0.597					
Albumin					15/36 41.7 (25.5; 59.2)
Median (IQR)	37.2 (35.3; 41.9)	38 (33.3; 42.1)	38.1 (35.4; 41.7)	−0.2 (−5.8; 4.6)	
Wilcoxon signed-rank test (Two-sided, asymptotic significance) p = 0.914.					

malnutrition in patients. This profoundly alters their physical functions, psychological well-being, and social life, as it significantly impairs their health, increases complications, decreases tolerance to cancer treatment, and reduces the patient's quality of life. These patients need treatments based on chemotherapy and cytoreductive surgery as much as possible, which requires an adequate nutritional status.

Patients with epithelial ovarian cancer have an altered metabolism, marked by increased proteolysis and lipolysis, while muscle protein synthesis is decreased, ultimately leading to a loss of muscle mass and fat [19] [20]. In addition, carbohydrate metabolism is modified by tumour growth, with decreased hepatic glucose production and increased Cori cycle activity, while insulin sensitivity in peripheral tissues is reduced. All this leads to weight loss and reduced immune response to the tumour and the treatment received [21] [22].

The main variable that influences the development of malnutrition regardless of tumour histology is the cancer stage. In other words, it is more frequent in patients with disseminated disease, which characterises our study since there is a predominance of locally advanced and metastatic stages, where there is a deterioration in nutritional status caused by the tumour itself and ascites, in addition to the digestive symptoms typical of intra-abdominal dissemination, which lead to anorexia [23].

There are several factors regarding the origins of malnutrition in cancer patients, as the mechanisms involved depend on both the tumour and the treatment received. It is a clinical condition that includes an energy and nutrient imbalance affecting tissues and body composition [24].

The production of hormones and pro-inflammatory cytokines released during the pathological process of cancer, such as IL-6, IL-1, CRP, and PIF, reduce appetite, leading to anorexia. In turn, these mediators alter macronutrient metabolism, decreasing the body's muscle mass and increasing basal energy expenditure. Protein demands compromise protein reserves, meaning that if requirements are not met, visceral protein is depleted, leading to gastrointestinal malabsorption and reduced plasma protein production in the liver [25].

The prevalence of signs of malnutrition in ovarian cancer patients ranges from 28% to 67%, making this the type of cancer that is most associated with malnutrition [26]. There is also a very important relationship between nutritional status, quality of life, survival, and the ability to tolerate multidisciplinary treatment for peritoneal carcinosis [27] [28].

In the present study, the results obtained in terms of demographic data and clinical and pathological characteristics of epithelial ovarian cancer are in line with internationally reported epidemiological patterns, and stage IIIC was the most represented.

The adverse effects of CT treatment will depend on the type of regimen. In this series, the regimen administered was carboplatin/paclitaxel, which has an intermediate emetogenic potential and it is important to prescribe antiemetic protocols for adequate prophylaxis, which were complied with in the study subjects.

However, nausea and vomiting are among the most frequently encountered symptoms in ovarian cancer patients, caused by the tumour itself, ascites and peritoneal carcinosis. Once CT treatment is initiated, control of tumour-mediated symptoms and ascites begins, especially in high-grade papillary serous carcinomas, which are the most common and most chemo sensitive.

Neijt *et al.* [29] showed in their research (N = 71) a higher number of grade 3 toxicities related to the carboplatin-paclitaxel regimen, namely grade 3 nausea/vomiting (16%), whereas in this trial, grade 1-2 nausea (5.5%) and grade 1 vomiting (2.8%) were reported. The ICON 4 study reported grade 2 - 4 nausea/vomiting (35%). These differences in the decrease in the intensity and frequency of these adverse events could be mediated by the investigational product. These results in turn show significantly reduced values at the end of the study compared to baseline (mean 27.1, 95% CI 16; 38.1), when applying the ovarian-specific quality of life questionnaires (QLQ-OV28), where the confidence interval limits show values outside the clinically relevant threshold of 5 points, which is a criterion for clinically significant response.

Traditionally used anti-cancer drugs induce apoptosis or cell death mechanisms by inhibiting cell growth or by damaging cellular deoxyribonucleic acid. However, this action does not specifically target tumour cells and may have a toxic effect on healthy tissues, limiting the dose to be administered. CT treatments have a severe impact on haemoglobin levels, causing varying degrees of anaemia [30]. Several antioxidants have shown a positive effect on haemoglobin levels during cancer treatment [31]. In groups receiving Ocoxin supplementation, anaemia decreased in 80% of patients compared to those receiving CT without the supplement. However, only 58% of patients receiving adjuvant CT without OV supplementation showed no toxicity [18].

Neutropenia is one of the adverse reactions of chemotherapy that most often makes it necessary to postpone administration or reduce the dose, which adversely affects patients' progress [32].

Similar results were reported by Ruiz-Lorente *et al.* [18] in cervical and endometrial cancer in patients receiving Ocoxin plus CT. They showed better haemoglobin levels compared to the group receiving CT/RT plus brachytherapy without OV supplementation. It was concluded that Ocoxin supplementation in the group receiving CT is more effective in mitigating the decrease in platelets and leukocytes compared to the group receiving CT without supplementation.

In this series, neutropenia accounted for 1.4% and was grade 1 - 2 and there was thrombocytopenia grade 1 - 2 in 1.7%, in contrast to Neijt *et al.*, who showed neutropenia grade 3 (31%) and grade 4 (45%), as well as thrombocytopenia grade 3 (4%). As for neurotoxicity, which is also dose-limiting, neurotoxicity (grade 3) occurred in 1% of the patients [13]. However, our series of 36 patients differs from those results, showing grade 1 - 2 peripheral neuropathy (N = 6, 44.4%), perhaps related to the protective effect on peripheral nerves of B-complex vitamins such as pyridoxine and cyanocobalamin, which are components of Ocoxin.

One of the organs that most suffers during CT treatments is the liver, as most cytostatic agents are metabolised in the liver, hence the need to monitor liver enzymes [33]. Liver damage is reflected in decreased albumin levels and increased ALT, AST, alkaline phosphatase and GGT. Previous clinical studies using Ocoxin coupled with CT in patients with gastric cancer revealed a significant increase in liver toxicity. The administration of Ocoxin together with CT led to an increase in serum albumin levels compared to the group receiving CT without the supplement [34]. In addition, Ocoxin counteracted hepatotoxicity related to increased ALT and AST in 92% of patients on the adjuvant CT treatment regimen after 3 weeks of treatment, while only 50% of patients in the non-supplemented CT group had unchanged AST and ALT levels. This reduction in hepatotoxicity was confirmed by Shumsky *et al.* (2019) in patients who received Ocoxin to decrease oral mucositis related to CT and RT [35]. They reported 4- and 7-fold lower ALT and AST levels in patients in the group receiving Ocoxin as a supplement compared to those receiving only CT and RT. The present investigation showed similar results, as adverse events related to increased levels of liver enzymes ALT and AST were associated with a decrease at the end of the evaluation period, with statistically significant differences ($p = 0.034$ and $p = 0.048$, respectively). Therefore, the antioxidant effect of Ocoxin may prevent liver tissue damage, as is the case with other antioxidants such as glucuronic acid, which is one of the components of OV [36] [37].

Other studies evaluated the effect of supplementation with essential amino acids such as arginine, glutamine, and the ketone body hydroxybutyrate [38]. The study by May [39], conducted in the United States with 33 patients, concluded that the administration of essential amino acids such as hydroxymethylbutyrate (3 g/day), L-arginine (14 g/day), L-glutamine (14 g/day) in cancer patients increased body weight secondary to fat synthesis and decreased proteolysis (average gain of 0.95 kg compared to the loss of 0.26 kg). In this study, the investigational product is composed of essential and non-essential amino acids, as well as B vitamins, among other chemicals, which could favour the increase in patients' body weight. To establish the mechanism of action of this supplement, it is necessary to design experimental studies with such objectives in mind.

The Karnofsky index is a scale that measures the functional capacity of cancer patients and is a predictor of patient prognosis. If the patient achieves a high Karnofsky score, his/her prognosis will be better. From previous studies, it is known that the administration of Ocoxin together with CT increases the Karnofsky index by 59.26%, compared to 30.38% in those receiving CT alone, which is the case in different epithelial tumours such as head and neck, cervical [40] and non-small cell lung carcinoma [41]. This effect may be mediated by the overall increase in health status observed in patients receiving daily doses of OV in conjunction with CT. Among the study subjects, this effect of the investigational product was positive as it shows that the Karnofsky index improved at the end of the study in 31 of the 36 patients included (86.1%), 95% CI (70.5, 95.3), bearing in mind that there were 4 definitive discontinuations due to disease progression.

According to statistical hypothesis assessment: From the results of the quality-of-life assessment based on the QLQ 30 scale and the Karnofsky index in this study, it can be observed that in all cases the number of patients responding exceeds the cut-off value (14) pre-specified by design in the study protocol. A minimal effect is evident, justifying further development of the product Ocoxin.

Based on the possibilities offered by the cancer treatment, patients receive treatment with curative or palliative intent. In both cases, treatment may be accompanied by appropriate specific nutritional interventions that primarily aim to improve the patient's general condition and quality of life (QoL) [42]. Nutritional supplementation accompanying curative treatment has additional and specific objectives, such as increasing the response to treatment, decreasing the rate of complications, and possibly reducing morbidity by maintaining the balance between energy expenditure and intake or minimising the imbalance between them [43] [44]. Nutritional treatment in palliative care aims to improve the QoL of patients, helping to manage the clinical symptoms associated with the natural course of neoplastic disease (nausea, vomiting, etc.) [45] [46].

Considering the safety profile of Ocoxin and its effect on improving the quality of life and health status of the patients included in this trial, we suggest that a phase III clinical trial should be conducted.

5. Conclusion

Cancer disrupts the balance of patients' physical functions, psychological well-being, and social life. During the acute phase of cancer treatment with curative intent, adequate support with the Ocoxin nutritional supplement has been shown to improve short-term outcomes in patients with advanced epithelial ovarian cancer by reducing the number of complications and reducing adverse events. This clinical improvement has had a positive impact on patients' quality of life.

Author Contributions

Study Concept: All authors. Study Design: Karen López Miguel, Juan Jesús Lence Anta, Eduardo Sanz. Statistical analysis: Mayté Robaina García, Ramón Ropero Toirac. Manuscript preparation: Karen López Miguel. Manuscript editing: Karen López Miguel, Ramón Ropero Toirac, Eduardo Sanz, and David Marquez. Manuscript review: All authors. All the authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Annexe

Table A1. The causal relationship of non-serious and serious adverse events.

Non-Serious Adverse Events		Causal Relationship					
		Unlikely	Very Likely	Not Assessable	Unrelated	Possible	Likely
Intensity	Mild	9	1	1	171	6	4
	Moderate	1	0	0	70	1	0
	Severe	1	0	0	9	1	0
Subtotal		11	1	1	250	8	4
Serious adverse events		**Unlikely**	**Very Likely**	**Not Assessable**	**Unrelated**	**Possible**	**Likely**
Intensity	Moderate	0	0	0	2	0	0
	Severe	0	0	0	7	0	0
	Serious, life-threatening	0	0	0	3	0	0
	Death	0	0	0	3	0	0
Subtotal		0	0	0	15	0	0

Table A2. Distribution of the intensity of haematological adverse events according to the time of evaluation.

Intensity	Initial	Cycle 2	Cycle 3	End	p
		Haemoglobin			
0	23	23	19	19	
1	7	4	4	6	0.759
2	6	7	9	6	
3	0	0	0	1	
	36	34	32	32	
		Leukocytes			
0	36	22	20	16	
1	0	12	12	16	0.0001
	36	34	32	32	
		Lymphocytes			
0	29	32	32	30	
1	6	1	0	0	
2	1	1	0	1	0.040
3	0	0	0	1	
	36	34	32	32	

Continued

		Platelets			
0	36	34	31	29	
1	0	0	1	3	0.083
	36	34	32	32	
		Absolute neutrophil count (ANC)			
0	36	29	29	26	
1	0	4	3	4	0.179
2	0	1	0	2	

Table A3. Distribution of adverse blood chemistry events by time of assessment.

Intensity	Initial	Cycle 2	Cycle 3	End	p
	36	34	32	32	
		ALT			
0	36	30	27	30	
1	0	4	4	0	0.034
	36	34	31	30	
		AST			
0	13	8	9	29	
1	0	3	2	1	0.048
	13	11	11	30	
		Direct bilirubin			
0	19	13	11	11	
1	10	13	11	13	
2	6	3	6	3	0.290
3	0	1	0	3	
	35	30	28	30	
		Total bilirubin			
0	35	27	26	29	
1	0	2	0	0	0.154
2	0	0	0	1	
	35	29	26	30	
		Creatinine			
0	34	33	32	32	
1	1	0	0	0	0.592
2	1	1	0	0	

Continued

	36	34	32	32	
		Uric acid			
0	26	27	26	21	
1	9	5	6	9	0.512
	35	32	32	30	
		Glucose			
0	28	26	24	27	
1	3	3	6	4	
G1 hypoglycaemia	5	5	1	1	0.340
	36	34	31	32	
		Total proteins			
0	33	27	28	29	1.00
	33	27	28	29	
		Albumin			
0	15	16	16	17	
1	21	18	15	14	0.724
	36	34	31	31	
		Cholesterol			
0	32	33	30	29	
1	0	0	0	1	0.363
	32	33	30	30	
		Triglycerides			
0	30	24	21	21	
1	5	9	8	8	0.489
	35	33	29	29	
		Alkaline phosphatase			
0	33	30	30	28	
1	1	2	1	0	
2	0	0	0	1	0.522
4	0	1	0	0	
	34	33	31	29	