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Nutritional Supplement Ocoxin® Combined with Gemcitabine-Based Chemotherapy in Patients with Advanced Pancreatic Adenocarcinoma

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Abstract

Background: the quality of life (QoL) of patients with pancreatic ductal adenocarcinoma (PDAC), with its limited survival, can be affected by chemotherapy-induced toxicity. The main objective was to evaluate the effect of introducing ocoxin oral solution (OOS) in combination with standard therapy on quality of life. **Methods**: Thirty patients were enrolled in an exploratory, prospective, single-centre clinical trial in the oncology department of "Hermanos Ameijeiras" University Hospital in Havana, Cuba. Quality of life was measured using the EORTC QLQ-C30 questionnaire and toxicity was assessed using the NCI-CTC-AE classification version 5.0. **Results**: There was stability in the scores over time for overall QoL and the functional scale criteria, while in terms of symptoms, fatigue, pain and loss of appetite were reduced. No grade 3 - 4 adverse events (AEs) were recorded, and only 14.9% of toxicities were classified as grade 2, and these were considered to be unrelated to OOS. Biochemical and nutritional parameters were normalised at 12 months compared to the baseline values. **Conclusions**: This clinical study is the first report of the use of OOS in patients with advanced pancreatic cancer, and demonstrates that it is able to maintain optimal quality of life with reduced severity of toxicity during and after combination treatment with gemcitabine-based chemotherapy.

Keywords

EORTC QLQ-C30, Ocoxin, Chemotherapy, Pancreatic Cancer, Quality of Life

1. Introduction

Globally, pancreatic cancer (PC) ranks twelfth in terms of incidence, but seventh in terms of overall mortality, and is one of the neoplastic diseases with the highest trend for both parameters [1]. In Cuba, malignant gastrointestinal tumours account for 16% of cancers and just over a quarter of the mortality, while pancreatic cancer specifically accounts for 11% and 14% of the incidence and mortality from cancer of the digestive system, respectively [2].

Because most cases are in advanced and/or metastatic stages at diagnosis, chemotherapy is the cornerstone of treatment for these patients [3]. Despite therapeutic advances in recent decades, few cytostatic drugs have been shown to act on this malignancy, and gemcitabine-based chemotherapy has been the most widely used, albeit with modest survival benefits. The introduction of chemotherapy doublets or triplets has significantly improved survival, but has also increased adverse events [4] [5]. The toxic effect of chemotherapy combined with the deterioration of the general condition of these patients as a result of their disease means that one of the main problems during treatment is the occurrence of adverse events, which impact patients' quality of life and compromise treatment outcomes, and in many cases lead to treatment discontinuation [5]. Thus, the effect of chemotherapy depends not only on the treatment plan but also on the patient's health status, such as individual physiological status and laboratory tests.

Oxidative stress is a biochemical and pathophysiological imbalance between free radicals (pro-oxidants) and antioxidant defence mechanisms. Cancer is inherently an oxidative stress-inducing disease [6]. Metabolic alterations of neoplastic cells, tumour infiltration by inflammatory cells, malnutrition and specific cancer treatments such as chemotherapy and ionising radiation contribute to elevated levels of oxidative stress in cancer patients [6] [7]. Although controversial, the use of antioxidants may counteract or at least minimise the toxic effects of oxidative stress on normal cells [8]

OOS is a nutritional supplement with recognised antioxidant, anti-inflammatory and immunomodulatory capacity. It is composed of plant extracts, amino acids, vitamins and minerals that have been subjected to an internal manufacturing process of molecular activation, which increases and enhances its antioxidant capacity and the biological actions of its ingredients, as is the case of itsanti-tumour effectsconfirmedin several preclinical studies. In animal models, adecrease in anti-tumour cell proliferation has been observed due to its synergy with chemotherapy and targeted therapies [9] [10]. Moreover, in clinical trials, mainly in pa-

tients in advanced stages, OOS significantly improved their quality of life, with better tolerability to conventional therapies and reduced adverse effects [11].

Taking into account the previous evidence, the aim of the present study is to evaluate the effect of OOS combined with standard therapy on quality of life in patients with advanced pancreatic adenocarcinoma.

2. Methods

2.1. Study Design

This is an exploratory, prospective, single-centre clinical trial that enrolled 30 patients. The primary objective was to evaluate the effect of OOS in combination with standard therapy on quality of life in patients with advanced pancreatic adenocarcinoma. The secondary objective was to evaluate changes in clinical parameters, nutritional status, and toxicity in the patients.

2.2. Study Population

Patients had to be ≥18 years old with a new cytological or histological diagnosis of pancreatic adenocarcinoma; advanced and unresectable stages; general health status according to Karnofsky score ≥70%; life expectancy greater than or equal to 3 months; eligible for specific cancer treatments; haematological parameters that do not contraindicate the administration of chemotherapy; total bilirubin values ≤1.5 times and ALAT/ASAT ≤2.5 times the upper limit of the normal range established in the institution and creatinine values within the normal limits of the institution; and who have signed the informed consent.

Patients were excluded in the following situations: if they were receiving another investigational product; with known hypersensitivity to any of the active ingredients of the treatments used; chronic or decompensated intercurrent diseases, or any other special condition that in the physician's opinion could put their health and life at risk during the study or their participation in the trial; pregnant or breastfeeding; mental disorders that could limit adherence to the requirements of the clinical trial and could hinder the collection of information, treatment or follow-up; patients with brain metastases.

2.3. Diagnostic and Clinical Extension Procedures

Extension, staging and confirmatory diagnostic tests were carried out in accordance with the hospital's approved protocol for this neoplastic disease. Clinical examinations, haematological and blood chemistry tests, abdominal/pelvic ultrasound, chest x-ray and thoracic, abdominal and pelvic computed axial tomography (CT) (simple and contrasted) were performed in all patients. Laparoscopy was performed to detect small peritoneal and hepatic nodules and to identify patients with unresectable disease. Endoscopic retrograde cholangiography was only performed in cases of complete obstruction or stenosis of the pancreatic duct (with jaundice) for stent placement. Cyto- or histopathological confirmation, whether or not guided by ultrasound and CT, was performed in

all cases.

2.4. Treatment Plan

After staging, patients were evaluated in the multidisciplinary consultation of the Functional Digestive Tumour Unit of the HHA. When the joint discussion concluded that the patient was unresectable and not a candidate for localised treatment (surgery and/or radiotherapy) with curative intent, it was decided to administer chemotherapy. This was determined on the basis of the following factors: general condition, vital organ function, associated diseases, potential adherence to the proposed treatment, patient preferences and patient tolerability.

The chemotherapy regimen was GEMOX consisting of intravenous infusion of gemcitabine (1,000 mg/m^2) on days 1 and 8 and infusion of oxaliplatin (85 mg/m^2) on day 1, every 3 weeks, for eight cycles, and the anti-Her1 monoclonal antibody Nimotuzumab (200 mg) was administered intravenously, every 14 days for the duration of chemotherapy administration.

The nutritional supplement OOS was administered at a rate of 60 mL daily (1 vial of 30 mL twice daily), preferably administered after breakfast and lunch, for twelve months. Continuation beyond 12 months was decided based on tolerability, as long as the patient's condition allowed, in the judgement of the treating physician. The composition of OOS per 30 mL vial is glucosamine sulphate potassium chloride 600 mg, L-glycine 600 mg, malic acid 360 mg, L-arginine 192 mg, L-cysteine 61.2 mg, Liquorice extract (*Glycyrrhiza glabra* L.) 60 mg, vitamin C (L-ascorbic acid) 36 mg, sodium benzoate 30 mg, potassium sorbate 30 mg, zinc sulphate 24 mg, passion fruit flavouring 15 mg, green tea extract (*Camellia sinensis* (L.) Kuntze) 7.5 mg, sucralose 7.2 mg, pantothenic acid (D-calcium pantothenate) 3.6 mg, manganese sulphate 1.2 mg, vitamin B6 (pyridoxine hydrochloride) 1.2 mg, cinnamon extract (*Cinnamomum verum* J. Presl.) 0.9 mg, folic acid (pteroylmonoglutamic acid) 120 μg, vitamin B12 (cyanocobalamin) 0.6 μg, and water q.s.p.30 mL.

2.5. Evaluated Parameters

For the measurement of health-related quality of life (HRQoL), we used the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) [12]. This 30-item instrument, validated for Spanish, measures overall QoL and 5 functional areas (physical function, autonomy, emotional well-being, cognitive function, and social function) and 9 symptoms (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation, diarrhoea and economic impact) on a scale from 0 to 100, where higher scores for overall health status and the functional scales suggest better QoL and functioning, while higher scores for symptoms represent more symptoms and therefore worse QoL. To assess the strength of clinically meaningful differences, we used the evidence-based guidelines for interpreting EORTC QLQ-C30 probability scores developed by Cocks *et al* [13].

Toxicity was assessed using the NCI-CTC-AE classification version 5.0 [US

Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0]. For the assessment of toxicity, the highest degree of toxicity and complication recorded by each patient was obtained, and the duration, intensity (mild, moderate, severe, life-threatening, death related to the adverse event (AE)), severity (severe/serious, not severe/not serious), attitude to study treatment (unchanged, dose modification, temporary discontinuation, definitive discontinuation), the outcome of AE (recovered, improved, persists, sequelae), causality (very likely/certain, likely, possible, unlikely, unrelated, not evaluable/unclassifiable) were considered.

Nutritional status was assessed using body mass index, and the haematological parameters analysed were haemoglobin, platelets, neutrophils and lymphocytes. The blood chemistry parameters were albumin, glycaemia, ALAT/ASAT, total bilirubin, and creatinine. Two indices of systemic inflammation were calculated: neutrophil-lymphocyte ratio (NLR) and nutritional prognostic index (NPI). NLR was calculated as the ratio between the absolute neutrophil value and the absolute lymphocyte value from the complete blood count, while NPI was calculated using the formula:

$$NPI = \left(10 \times serum\ albumin\left[g/dL\right]\right) \times \left(0.005 \times Lymphocytes/\mu L\right)$$

For all parameters, measurements were performed at four time points: baseline, month 3, month 6 and month 12.

2.6. Statistical Analysis

The data analysis was descriptive. Qualitative variables were described using absolute and relative percentage frequencies. Pearson's chi-squared (X^2) statistical test was used as a method of analysis to assess the association between qualitative variables, and the non-parametric Wilcoxon test was used to compare quantitative variables. The probability of survival was estimated using the Kaplan-Meier method. A significance level of 0.05 with a 95% confidence interval (CI) was set for all tests. The data were analysed using SPSS statistical software, version 28.0.

2.7. Ethical Aspects

The protocol was reviewed and approved by the research ethics committee of "Hermanos Ameijeiras" University Hospital, Havana, Cuba, and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to the start of the study. National data protection legislation was applied. Documents containing patients' personal information were encrypted; only authorised staff had access to them.

Trial registration: in the Cuban Clinical Trials Register (RPC). Code: RPCEC00000281. ClinicalTrials.gov ID (NCT03717298).

3. Results

At patient enrolment, the most frequent symptoms and signs at disease diagno-

sis were abdominal pain, jaundice, weight loss, and diarrhoea in 63.3%, 16.7%, 16.7%, and 6.7% of patients, respectively. The most frequently reported associated comorbidities were hypertension (50.0%) and diabetes mellitus (36.7%). Of the patients studied, 20.0% of them presented both diseases. All patients had an ECOG classification between 0 and 1.

The median age of patients studied (Table 1) was 61.5 years (min.: 45; max.: 71), with a predominance of male patients aged ≥60 years. The majority of patients had body mass indexes classified as normal weight, with locally advanced tumours, with greater involvement of the pancreatic head, moderately differentiated, and with positive regional lymph nodes. Only two patients had normal carbohydrate antigen 19 - 9 (CA 19.9) levels, and just under half had CA levels over 20 times the upper limit of normal. At the time of treatment initiation, more than 80% of patients had normal serum albumin levels and absolute lymphocyte and platelet counts.

Table 2 shows the evolution of analytical parameters at different times during patient follow-up. A significant reduction in BMI, albumin, and haemoglobin was observed at 3 months compared to baseline ($p < 0.05$), although at the final assessment, there was a recovery of BMI, albumin, and haemoglobin to above baseline. The lowest absolute platelet count levels were found at 3 and 6 months but were statistically significant for 12 months. No reduction in absolute lymphocyte count was observed during treatment. Regarding the inflammatory and immuno-nutritional indices, only a significant decrease in NLR was observed after 6 months of treatment.PNI was higher than baseline at 12 months. The tumour marker (CA 19.9) was significantly reduced at 6 months, while glycaemia and creatinine remained unchanged throughout treatment.

Table 1. Patient characteristics.

Characteristic	n	%
Gender		
Male	16	53.3
Female	14	46.7
Age		
<60 years	12	40.0
≥60 years	18	60.0
Tumour Location*		
Head	20	66.7
Body	7	23.3
Tail	3	10.0
Histological differentiation		
Well-differentiated	3	10.0
Moderately differentiated	24	80.0
Poorly differentiated	3	10.0
Tumour Classification (T)		
≤T3	8	26.7
T4	22	73.3
Lymph node involvement		

Continued

≤N1	22	73.3
N2	8	26.7
Tumour extension		
Locally advanced	18	60.0
Metastatic	12	40.0
Body Mass Index (BMI) (kg/m^2)		
<18.5	1	3.3
18.5 - 24.9	21	70.0
≥25	8	26.7
Tumour marker CA19-9**		
≤740 u/mL	16	53.3
>740 u/mL	14	46.7
Serum albumin		
≤35 g/L	4	13.3
>35 g/L	26	86.7
Absolute leukocyte count ***		
≤4.0 × 10^9	13	43.3
>4.0 × 10^9	17	56.7
Absolute lymphocyte count		
≤1.0 × 10^9	5	16.7
>1.0 × 10^9	25	83.3
Absolute platelet count ******		
≤150 × 10^9	3	10.0
150 - 400 × 10^9	24	80.0
>400 × 10^9	3	10.0

*Predominant tumour location (>50%); **CA 19.9 (range: 0 - 37 U/mL) × 20 upper limit of normal (ULN); ***Absolute leukocyte count (range: 4.0 - 10.0 × 10^9) **** Absolute platelet count (range: 150 - 400 × 10^9).

Table 2. Analytical parameters.

Parameters	Baseline (±SD)	3 months (±SD)	p*	6 months (± SD)	p**	12 months (± SD)	p***
BMI (kg/m^2)	23.5(±3.1)	22.8(±3.4)	0.043	23.2(±3.8)	0.142	24.1(±1.5)	0.960
Neutrophil count (x 106)	4409.8(±1861.3)	3659.5(±1284.1)	0.052	3114.5(±1215.6)	0.003	4343.6(±2055.9)	0.590
Lymphocyte count (x 106)	1502.4(±449.2)	1633.0(±633.2)	0.217	1684.7(±481.3)	0.107	1660.1(±485.8)	0.488
Platelet count (x 109)	281.3(±17.5)	182.2(±13.6)	0.001	178.3(±14.8)	0.001	228.1(±20.3)	0.017
Albumin (g/L)	43.3(±5.7)	39.8(±5.4)	0.013	40.8(±5.1)	0.127	45.3(±5.0)	0.941
Haemoglobin (g/L)	12.2(±1.5)	11.0(±1.5)	0.001	11.2(±1.4)	0.008	12.5(±1.5)	0.818
CA 19.9 **** (U/mL)	564.4(±79.1)	NE	-	260.3(±64.3)	0.001	370.61(±91.8)	0.067
Glycaemia**** (mmol/L)	6.2(±1.5)	NE	-	5.8(±1.4)	0.364	5.9(±1.6)	0.416
Creatinine ****(mmol/L)	72.1(±4.8)	NE	-	68.8(±4.5)	0.147	70.3(±3.9)	0.254
PNI	51.2(±7.2)	48.1(±7.2)	0.050	48.5(±7.4)	0.212	53.6(±5.0)	0.791
NLR	3.2(±1.5)	2.5(±1.3)	0.050	2.2(±1.0)	0.015	2.8(±1.4)	0.230

SD: standard deviation; p < 0.05 *3 months versus baseline; *6 months versus baseline; *** 12 months versus baseline; **** only performed 3 times (baseline, end of chemotherapy, and final evaluation); PNI: prognostic nutritional index; NLR: neutrophil-lymphocyte ratio; NE: not evaluated.

The most frequently observed toxicities were neuropathy and thrombocytopenia in 50% of patients, while anaemia and anorexia occurred in 36.7% and 30.0%, respectively. Only 14.9% of the toxicities were classified as grade 2, while the remaining 85.1% were classified as grade 1. No grade 3 - 4 adverse events were recorded. The AEs were considered as not related to the investigational product (Table 3).

The EORTC QLQ-C 30 questionnaires (Table 4) were administered to patients at baseline, 3, 6 and 12 months after enrolment in the study to assess QoL. The overall mean HRQoL was 79.4 out of a maximum of 100 points prior to treatment and 81.4 and 81.1 points at the end of treatment and at the final assessment, respectively. There was stability in the overall QoL criteria over time. In terms of the symptom scale, fatigue was reduced by 22.9% at 6 months and 12% at 12 months, while pain and loss of appetite decreased earlier (at 3 months) by 34% and 41%, respectively, which was statistically significant. Loss of appetite was reduced by 75% at 12 months compared to baseline. However, the economic impact of the disease on the patient increased by 38% at 6 months, and by 53.4% at 12 months.

The variation observed in the overall QoL criteria can be considered trivial in terms of impact. Autonomy and emotional function were similarly classified in terms of the functional scales. The greatest deterioration occurred in physical functioning (79.3 to 74.5) (low according to Cocks), while cognitive function (+4.6) and social function (+11.5) at 12 months showed a low and medium increase, respectively. In terms of the symptom scale, the greatest impact (medium according to Cocks) was on patients' perception of loss of appetite (−18.3) and financial difficulties (+9.5), with the former being positive and the latter negative at 6 and 12 months. Both pain and fatigue decreased by more than 5 points at 6 months and were considered low impact. This benefit was maintained at 12 months in the perception of fatigue. In all other areas, the differences in symptoms were trivial or non-existent (Table 5).

Table 3. Adverse events according to NCI-CTC-AE (National Cancer Institute—Common Terminology Criteria for Adverse Events) by severity.

Adverse events	Grade 1	Grade 2	Grade 3 - 4	Total
Asthenia	7	1	0	8
Anorexia	9	0	0	9
Mucositis	3	0	0	3
Diarrhoea	6	1	0	7
Neuropathy	11	4	0	15
Neutropenia	4	2	0	6
Thrombocytopenia	12	3	0	15
Anaemia	10	1	0	11
Vomiting	7	1	0	8
Nausea	5	0	0	5

Table 4. QLQ-C30 quality of life (QoL) scales.

	Baseline (±SD)	3 months (±SD)	p*	6 months (±SD)	p**	12 months (±SD)	p***
Overall Quality of life (QoL)							
QoL	79.4(±2.8)	81.4(±2.0)	0.91	81.4(±3.4)	0.12	81.1(±3.3)	0.31
Functional scale							
Physical function	79.3(±3.8)	75.6(±3.7)	0.24	77.9(±5.0)	0.75	74.5(±6.2)	0.45
Daily activity	81.0(±4.2)	77.2(±4.6)	0.25	80.7(±6.4)	0.71	77.3(±5.6)	0.44
Emotional well-being	69.4(±4.3)	73.1(±4.2)	0.33	75.0(±5.6)	0.54	70.5(±7.3)	0.71
Cognitive function	93.9(±3.1)	95.0(±3.0)	0.75	94.7(±2.6)	0.5	98.5(±1.5)	0.38
Social function	79.4(±4.4)	82.2(±4.2)	0.52	80.7(±5.9)	0.69	90.9(±5.2)	0.38
Symptoms							
Fatigue	34.1(±4.6)	34.8(±4.4)	0.58	26.3(±5.1)	0.05	30.0(±6.9)	0.31
Nausea	7.8(±3.2)	4.6(±2.0)	0.4	6.1(±2.9)	0.38	3.0(±2.0)	1.00
Pain	23.6(±4.3)	15.6(±3.2)	0.02	18.4(±4.4)	0.013	21.2(±6.8)	0.18
Insomnia	19.5(±5.6)	25.6(±5.9)	0.59	22.8(±7.2)	0.53	21.2(±8.1)	0.75
Anorexia	24.4(±5.7)	14.4(±5.0)	0.08	10.5(±6.3)	0.027	6.1(±3.1)	0.03
Constipation	6.7(±4.0)	6.9(±3.8)	1.00	5.3(±3.8)	0.75	6.1(±3.1)	1.00
Diarrhoea	11.1(±5.4)	12.2(±4.7)	0.78	17.5(±5.9)	1.00	3.0(±3.0)	1.00
Economic impact	17.8(±5.2)	22.2(±6.5)	0.25	24.6(±8.0)	0.25	27.3(±9.9)	0.31

*$p < 0.05$; SD: standard deviation.

Table 5. Analysis of the quality-of-life questionnaire (QLQ-C30), at baseline, 6 months and final evaluations.

	Baseline	**6 months**	**Variation 1***	**CC**	**12 months**	**Variation 2****	**CC**
Overall Quality of life (QoL)							
QoL	79.4	81.4	2.0	●	81.1	1.7	●
Functional scale							
Physical function	79.3	77.9	−1.4	▲	74.5	−4.8	▲
Daily activity	81.0	80.7	−0.3	●	77.3	−3.7	●
Emotional well-being	69.4	75.0	5.6	●	70.5	1.1	●
Cognitive function	93.9	94.7	0.8	●	98.5	4.6	▲
Social function	79.4	80.7	1.3	●	90.9	11.5	■
Symptoms							
Fatigue	34.1	26.3	−7.8	▲	30.0	−4.1	▲
Nausea	7.8	6.1	−1.7	●	3.0	−4.8	●
Pain	23.6	18.4	−5.2	●	21.2	−2.4	●
Insomnia	19.5	22.8	3.3	●	21.2	1.7	●
Anorexia	24.4	10.5	−13.9	■	6.1	−18.3	■
Constipation	6.7	5.3	−1.4	●	6.1	−0.6	●
Diarrhoea	11.1	17.5	6.4	▲	3.0	−8.1	▲
Economic impact	17.8	24.6	6.8	■	27.3	9.5	■

*Variation 1: (6 months vs. baseline); Variation 2: (12 months vs. baseline); CC: Cocks' Classification (▲Small, ■ Medium, ● No difference or trivial)

Median survival was 13.2 months (95% CI: 9.3 - 16.8), and 7 of the 30 patients (23.3%) achieved survival of more than 18 months.

4. Discussion

The patient population presented here corresponds to the usual presentation of patients with advanced pancreatic cancer who are candidates for chemotherapy treatment and reported by other authors, where there is a predominance of male patients, presentation in the sixth decade of life, and the primary tumour is located in the pancreatic head [14]. Arterial hypertension and diabetes mellitus were the most commonly observed associated diseases in the population. Both diseases are very common and associated with each other. Cardiovascular diseases overlap (concordant diseases) with diabetes mellitus (DM) in their pathophysiology and treatment [15].

The clinical features of pancreatic cancer are determined by the retroperitoneal location of the pancreas, which makes the initial growth of the cancer silent; therefore, symptoms are usually a sign of advanced disease [16]. The clinical features most frequently reported by patients were abdominal pain and jaundice, which is closely related to the predominance of the tumour being located in the pancreatic head in this population, while weight loss was mostly associated with non-pancreatic head tumour locations. The symptoms reported by patients at diagnosis were in line with those reported by other authors [16] [17].

The differences in general patient characteristics found between the general pancreatic cancer patient population and those of the sample presented in this research are explained by the inclusion criteria used for chemotherapy treatment. This introduced selection bias, although they are less strict criteria than those that might exist in clinical trials with any biological or targeted therapy or combination of these.

Chemotherapy has established itself as the standard treatment for patients with advanced pancreatic cancer and achieves a modest benefit in both survival and symptom control when compared to best supportive care [18]. Gemcitabine has demonstrated activity in this type of patient and is a useful palliative agent, either in monotherapy or in combination with other drugs such as oxaliplatin, increasing survival [5]. Other chemotherapy regimens such as Nab-paclitaxel or the combination of fluorouracil with oxaliplatin (FOLFIRINOX) obtain longer survival periods and are considered standard treatments for patients in advanced stages, but their maximum efficacy is fundamentally limited to patients with excellent general condition (ECOG 0) [5] [19] [20]. In view of the evidence provided by the meta-analysis study by Hu *et al.* [21], and a real-world clinical study conducted in this department, combining nimotuzumab with the GEMOX regimen (gemcitabine and oxaliplatin) shows that similar results are obtained in terms of survival, adverse effects and more rational administration schedules, with reduced costs for the public health system [22].

As a result of the late-stage diagnosis of this cancer, malnutrition is one of the main problems in these patients, which is associated with lack of efficacy of treatments, increased toxicity and deterioration of QoL [23]. More than 80% of

PC patients report weight loss at diagnosis and during treatment, and approximately 70% of patients develop some degree of malnutrition [24].

The combination of nutritional supplements and chemotherapy has been established as a new therapeutic approach, targeting not only the tumour but also the components of its associated desmoplastic stroma, which represents a major obstacle for current pancreatic cancer treatments [25]. In a preclinical study conducted at the University of the Basque Country, OOS has been shown to slow tumour progression, decrease tumour cell proliferative activity, and increase cell apoptosis, in addition to affecting tumour-associated fibroblast infiltration and reducing the level of inflammatory cytokines in mouse serum, thereby reversing the chemo-resistance produced by stromal cells and the expression of pancreatic cancer-related genes [26].

In the patient population studied, the majority of cases were within the normal weight range at the start of chemotherapy treatment (70%) with a mean BMI of 23.5 kg/m^2. During chemotherapy treatment associated with OOS, although there was a significant reduction in BMI at 3 months, on average it always remained above 18.5 kg/m^2 (only one case had a low BMI from the start of treatment). It is noteworthy that the weight loss trend in the patients enrolled in the study was lower than expected for this type of patient, the advanced clinical stage of presentation, and based on observations from the department's historical database. Wong *et al* demonstrated that maintaining a stable body weight, and thus BMI, leads to better patient response to treatment [27]. The exact mechanism of the poor prognosis of weight loss in pancreatic cancer patients is multifactorial and is part of the cachexia phase in a very aggressive malignant disease. This is associated with loss of appetite and muscle mass, as well as a reduction in immune, cardiopulmonary and autoregulatory functions as part of the systemic inflammatory process [28].

Systemic inflammation is considered to be an important indicator of poor prognosis in pancreatic cancer patients. Inflammatory cells contribute substantially to tumour development and progression, promoting the processes of angiogenesis, cell survival and metastasis [28] [29]. In addition, increased inflammatory mediators such as the cytokines interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) can have various effects related to anorexia and cachexia, such as depletion of fat stores, increased protein degradation in skeletal muscle and synthesis of acute-phase proteins such as C-reactive protein [30]. Inflammation and cancer progression are closely related. In the previously cited work, OOS reduced the level of these pro-inflammatory cytokines in the serum of mice with pancreatic tumours and increased anti-inflammatory cytokines such as IL-10 [26]. Similar results have been reported with the use of OOS in animal models of liver metastasis from colorectal cancer [31].

Several studies have demonstrated the role of immuno-inflammatory and immuno-nutritional factors in the prognosis of patients with pancreatic cancer

[32]. In the patient population studied, the variations in NLR, NPI and albumin during treatment were measured, as in previous studies they have been shown to have a relevant relationship with survival in this type of patient [33]. A significant reduction in albumin levels was observed after 3 months of treatment, which may be related to the direct effect of chemotherapy. However, when analysing the trends in PNI, which reflects the patient's immuno-nutritional status through the albumin and lymphocyte values, and despite a noted reduction, this indicator was restored in the treatment and follow-up of patients due to the recovery of the lymphocyte count. Similarly, the NLR, which reflects the inflammatory state through the ratio of neutrophils to lymphocytes, decreased over time with respect to its baseline value, reaching its lowest value at 6 months, coinciding with the end of the first line of chemotherapy treatment and lymphocyte recovery.

This observation may be related to the immunomodulatory actions of OOS described in animal models of both pancreatic and metastatic colon cancer [26] [31]. Decreased expression of the genes encoding these molecules and the polarisation of macrophages to a pro-inflammatory M2 phenotype through reduced free radical production have also been demonstrated. This alters the recruitment of stromal cells that produce a pro-inflammatory and pro-angiogenic microenvironment, thereby increasing the sensitivity of tumour cells to chemotherapy [26] [34]. Moreover, we presume that there is a synergistic effect with the type of chemo-immunotherapy used in the study, as both gemcitabine and oxaliplatin help tumour cells express damage-associated molecular patterns (DAMPs) that interact with the immune system and induce immunogenicity. Gemcitabine inhibits TGF-βsignalling and blocks the immune checkpoint, and its long-term administration leads to extensive reprogramming of the tumour microenvironment (TME), while oxaliplatin has the ability to stimulate immunological effects in response to DAMP presentation triggered by immunogenic cell death [35] [36]. Nimotuzumab is able to restore HLA-1 expression in tumour cells and reverses the immune escape mechanism by its effect on NK cells, induction of dendritic cell and CD8+ T cell maturation [37].

The addition of OOS to chemo-immunotherapy does not increase toxicity and the administration schedule is very well tolerated. The toxicity picture described in the sample corresponds to that expected for the type of chemotherapy received, and more closely resembles the spectrum of adverse events in the initial studies with the GEMOX regimen described by Louvet *et al* [38], and that previously obtained by our working group [22]. In this study, no grade 3-4 adverse events were reported, which differs considerably from the previously cited studies (17.2% - 52.0%) [22] [38]. Similarly, these same toxicities were lower than those reported by other authors in prospective observational or retrospective real-world clinical trials and studies using primarily FOLFIRINOX or nab-paclitaxel with gemcitabine [5] [19]-[21]. Similar results to the present research were obtained in a study by Chong *et al.* in patients with locally advanced squamous cell carcinoma of the head and neck who received concurrent radiotherapy and

chemotherapy, where no grade 3 toxicities were reported in the OOS arm and 43% were classified as grade 2, while 12% and 65% were reported in the placebo arm, respectively [39].

Neuropathy and thrombocytopenia were the most frequently observed toxicities in this study, and overall, they are higher in frequency than previously reported by our working group [22], but lower than reported in the original GEMOX regimen [38]. In this patient population, regardless of whether the effect of sample size (fewer patients) could have an amplified effect, the average chemotherapy exposure time was 21.1 weeks (data not shown), almost four weeks longer than in the reference studies [22] [38]. The incidence of neuropathy and thrombocytopenia is dose-dependent, and the longer the drug exposure over time, the higher the frequency of adverse events [40] [41]. However, it is striking that in all adverse events, there is a shift towards lower intensity or severity classifications, despite the fact that their incidence may be proportionally higher.

Neuropathy is a dose-limiting toxicity of oxaliplatin administration that causes deterioration of the patient's functionality, compromises the patient's QoL and often leads to suspension or reduction of treatment [40]. Grade 2 neuropathy was only 26.7%, which is much lower than reported in other studies in which grade 2 - 3 severity ranges from 65.3% to almost 95.0%, using the same cytotoxic drugs [22] [38]. Evidence has demonstrated the relationship between oxidative stress and oxaliplatin-induced neuropathy [42]. Increased drug exposure (doses greater than 540 mg/m^2) may increase nitro-oxidative stress due to mitochondrial dysfunction, as well as altered levels of some neurotransmitters [40] [42]. OOS has been shown to have strong anti-inflammatory, antioxidant and autophagy-regulating properties [9] [10]. OOS may provide neuroprotection or attenuation of toxicity on the nervous system by inhibition of some of the metabolic pathways involved, such as phosphoinositide 3-kinase/protein kinase B (PI3K/Akt2), which, in turn, inhibits cyclooxygenase-2 (COX-2), or by decreasing proinflammatory cytokines results in recovery of γ-aminobutyric acid (GABA) function and alleviation of both mechanical and cold hypersensitivity. A recent study has shown that glycyrrhizic acid, one of the ingredients of OOS, alleviated paclitaxel-induced neurotoxicity by inhibiting neuronal uptake mediated by organic anion-transporting polypeptides (OATP), which are the major neuronal transporters, without interfering with the anti-neoplastic properties [43].

With regard to haematological toxicities, the most reported was thrombocytopenia (50.0%) followed by anaemia (36.7%) and neutropenia (20.0%). These results differ from those found in the previous study of GEMOX use in Cuban patients with pancreatic cancer, where neutropenia was the most reported event (34.7%) and the percentage of cases with more severe haematological adverse events ranged from 34.8% to 63.4% (grades 2 - 4) [22]. Other clinical studies in gynaecological cancer, where OOS has been evaluated in combination with standard treatment, obtained similar results [44]. The recovery in the different

haematological parameters over time could be due to the inhibition of proinflammatory cytokines produced by OOS; mainly TNF-α and IL-1, which affect the activity of haematopoietic stem cells (HSC) [9]. On the one hand, these directly inhibit the ability to form erythroid progenitor colonies and suppress erythropoietin gene expression [45], and on the other hand, high concentrations of TNF-α show a significant inhibitory effect on megakaryopoiesis and thrombopoiesis [46].

There was a similar incidence of digestive toxicity to other studies, but with lower severity [22] [38]. The antioxidant and anti-inflammatory properties of epigallocatechin gallate [47] and glycyrrhizic acid [48] have been shown to be useful in reducing intestinal mucosal toxicity by reducing the production of pro-inflammatory cytokines, modifying the intestinal microbiome and/or directly or indirectly normalising liver function. Other components present in OOS, glucosamine and zinc, negatively regulate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), which, in turn, reduce inflammatory mediators such as IL-1B and TNF-α at the intestinal mucosal level [49] [50]. Other clinical studies with OOS reported a significant reduction in the severity of mucositis in combination treatments with chemotherapy and radiotherapy versus the placebo group [39] [51].

Due to the late detection, low survival rate and increasing number of new cases of pancreatic cancer, people with pancreatic cancer often have a lower QoL than other cancer patients [52]. The fundamental achievement of the present work is that (although it was not the objective), a survival time similar to other studies conducted both nationally and internationally was obtained [5] [18]-[22], with no deterioration in HRQoL and even achieving control of significant symptoms such as pain, loss of appetite and fatigue.OOS has been consistently shown to maintain or increase QoL in several clinical studies in cancers of the head and neck [39], endometrium and cervix [44], ovary [53] and prostate [54].

More than 50% of patients report chronic pain resulting from advanced pancreatic cancer [4]. Inadequate pain management is associated with eating disorders (reduced calorie intake), sleep disturbance and a reduced professional and social life, leading to poor patient tolerability to chemotherapy [55]. In addition to the psychological response to the diagnosis, some studies suggest a link between depression and the disease process itself, specifically with biomarkers of inflammation in the blood, including IL-6, which may mediate the depressive reaction through their influence on neurotransmitter metabolism and neuroendocrine function [56]. By reducing pro-inflammatory cytokines, OOS may contribute to lower early pain perception, as demonstrated by the responses to the EORTC QLQ-C30 questionnaire.

Social support does not directly affect QoL but modulates the effects of functional status and perceived health. Patients who receive high levels of social support have fewer emotional symptoms, such as depression and anxiety, and a reduction in physical symptoms [57]. Cuba's health care structure, and the ex-

isting interrelationship with the community, favours greater social and family support for the patient. However, the burden of financial hardship experienced by patients during and after chemotherapy treatment was a relevant factor, although not statistically significant. A study conducted in Greece, with similar results on this topic, highlights the so-called "financial toxicity", which can be caused by multiple factors that result in a need for increased care during treatments that is negatively associated with the economic burden of the disease [58].

For its part, Cuba is going through its worst economic crisis in 30 years, with its economy contracting by 2% in 2023 and inflation reaching 30% [59]. Therefore, "financial toxicity" could easily become an issue, especially in cancer patients, who often have limited capacity to work during and even after the end of treatments.

For the first time in OOS clinical studies assessing QoL, the method of Cocks *et al* [13] was introduced for the interpretation of the QLQ-C30 questionnaire, which showed a medium deterioration in economic impact (referred to in the previous paragraph) and low deterioration in physical functioning, which may be primarily associated with the underlying disease of pancreatic cancer. In another study, the greatest impact was on social functioning, perhaps biased by the COVID-19 pandemic [60]. It should be noted that, with this tool, except for the economic aspect, the symptom scales showed that OOS was able to improve each of the items listed, or at least did not worsen the indicators during the period of time the supplement was administered.

5. Limitations

The study was conducted at a single institution and with a homogenous patient population, who were candidates for chemotherapy treatment (selection bias), and therefore the results may not be generalisable to other patient populations with advanced cancer. However, this homogeneity of the population is also an advantage when developing future prognostic models, as it is based on standardised clinical practice. Another negative aspect to consider would be the limited number of patients (n = 30), and not having a placebo treatment arm to arrive at definitive conclusions, although this can be explained by the exploratory design of the search for a probable effect of OOS in this cancer site.

Assessment of the risk and nutritional status of cancer patients is essential for optimal comprehensive care, and clinical decisions, including enrolment in the clinical study, took place within the framework of a multidisciplinary team, but unfortunately measurements of biochemical and inflammatory markers were not performed, such as transferrin, C-reactive protein, tumour necrosis factor-α, and other cytokines related to the systemic inflammation process, as well as body composition assessment with computed tomography, bioelectrical impedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA) techniques [61]. These should be taken into account in the design of future clinical trials.

6. Conclusion

This clinical study is the first report of the use of OOS in patients with digestive system cancer, specifically advanced pancreatic cancer, and demonstrates that it is able to maintain optimal quality of life with reduced severity of toxicity during and after combination treatment with gemcitabine-based chemotherapy. OOS as a supplement to anti-tumour treatments is in line with the recommendations of clinical nutrition guidelines in oncology [62]. Further clinical research should be conducted to confirm the mechanisms of action postulated in preclinical studies and to corroborate the methodology of administering OOS only concurrent with or beyond chemotherapy treatment, as well as the effects of OOS reported here and its influence on patient survival.

Conflicts of Interest

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

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