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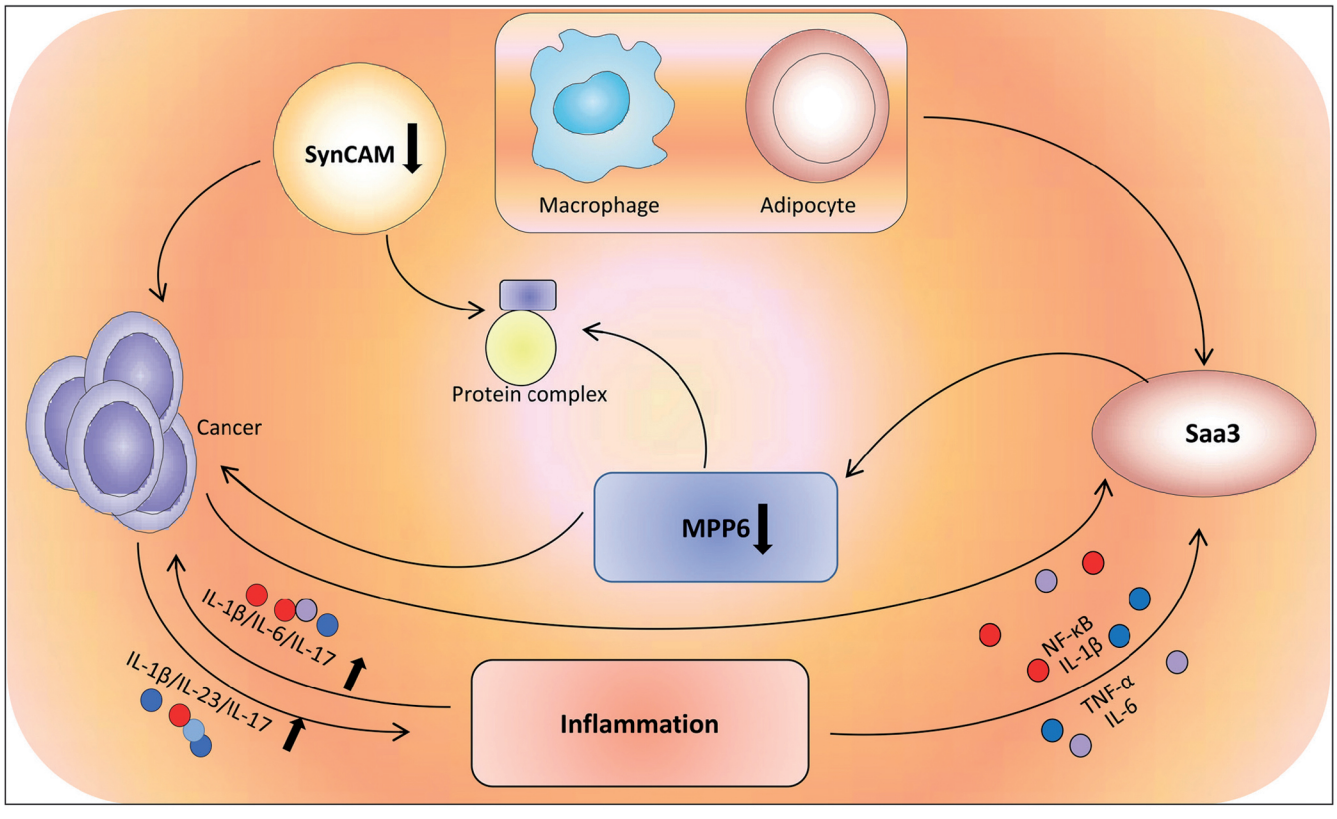

Multicomponent nutritional supplement Oncoxin and its influence on quality of life and therapy toxicity in patients receiving adjuvant chemotherapy

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Abstract. Treatment of cancer often requires the use of adjuvant chemotherapy (ACT). In real clinical practice, numerous patients suffer from severe toxicity and reduced quality of life (QoL). Hence, there is a need to maintain QoL and to reduce therapy toxicity to comply with recommended chemotherapy (CT) regimens. The present study focused on the effects of the multi-component nutritional supplement Oncoxin (ONCX) on QoL and CT-induced toxicity in patients undergoing ACT. A total of 133 patients aged 50-70 years with gastric cancer IIB-IIIC or non-small cell lung cancer IIB-IIIA were enrolled in the present study: 84 received ONCX, and 49 were included in the control arm and received CT only. It was identified that after 2 weeks of treatment the patients receiving ONCX exhibited clinically meaningful improvement of QoL (measured by Edmonton Symptom Assessment System Questionnaire) compared with those in the control group (odds ratio, 2.07; 95% CI, 1.00-4.29). By the end of a 3 week-period, the albumin level was higher in patients of the ONCX group compared with those in the control group (mean, 38.1; 95% CI, 37.1-39.1 g/l; vs. mean, 35.5; 95% CI, 33.9-37.0; P=0.03; respectively). Furthermore, the use of ONCX substantively reduced the hepatic toxicity of ACT. The present prospective real clinical setting study revealed positive effects of ONCX on QoL and ACT toxicity. The present study was retrospectively registered under the study registration number NCT03550482 at ClinicalTrials.gov (June 8, 2018).

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Abbreviations: ACT, adjuvant chemotherapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CT, chemotherapy; EGCG, epigallocatechin gallate; ESAS, Edmonton Symptom Assessment System; FOLFOX, folinic acid (leucovorin), fluorouracil, oxaliplatin; MCID, minimal clinically important difference; NSCLC, non-small cell lung cancer; ONCX, Oncoxin; OR, odds ratio; QoL, quality of life; SDS, symptom distress score; XELOX, oxaliplatin, capecitabine

Key words: Oncoxin, adjuvant chemotherapy, quality of life, therapy toxicity

Introduction

The treatment of cancer often requires chemotherapy (CT). Adjuvant chemotherapy (ACT) is often prescribed after surgery and required to eradicate residual tumour cells. The appropriate doses and regimens of CT depend on the type of cancer, stage, performance status of patient, and several other factors. The dose intensity is known to be critically important to increase the disease-free and overall survival in patients with potentially curable tumours, such as diffuse B-cell lymphoma or germ cell tumours. However, for ACT used in early breast cancer, colorectal cancer, non-small cell lung cancer (NSCLC) and pancreatic tumours, the decision to commence cytotoxic therapy is not an easy one since, for some patients, ACT may be unnecessary and accompanied by significant, even fatal adverse effects (1).

Despite the use of guideline recommended doses, in real clinical practice, the rate of patients with serious manifestations of treatment-associated toxicity can be significantly higher compared to the data published in randomised trials. For example, in a retrospective study by Lakhanpal (2) (real practice) the febrile neutropenia rate in patients with breast cancer, who had received docetaxel/cyclophosphamide ACT, accounted for 25% of cases. Likewise, the Jones *et al* (3) clinical trial showed that only 2.4% of patients had this severe adverse event. Poor tolerability of anticancer drugs often requires dose decrease or treatment discontinuation. A study of oxaliplatin in patients with colorectal cancer showed that the rate of patients who discontinued participation early in the study rose up to 31%, and the rate of those who required dose reduction accounted for 62% of cases (4,5). Reduction of doses and even treatment cessation may be caused by several undesirable effects: Haematological toxicity, hepatic toxicity, renal toxicity, severe mucositis, poor nutritional status, progressive weakness. Therapy toxicity and side effects are associated with poor quality of life (QoL) that in turn may negatively affect patients' mood, appetite, compliance and decision-making regarding CT continuation (6).

To maintain QoL and effective CT dosages, the use of all available supportive therapy options needs to be explored. In this regard, the development of new approaches to maintain QoL and comply with recommended CT regimens is an important task to increase the survival of patients with ACT.

Recent studies showed that a number of amino acids, micronutrients, vitamins and biologically active substances can reduce the severity of CT's side effects, enhance appetite and may reduce infectious complications. For example, the use of glycyrrhizin as a supplement to FOLFOX and XELOX CT regimens was accompanied by significant liver function improvement and fewer cases of liver dysfunction (cases of hepatic dysfunction reduced by more than twice compared to control group) (7). Due to its antioxidant and anti-inflammatory properties, epigallocatechin gallate (EGCG), a natural polyphenol, is highly effective in relieving acute esophagitis induced by radiation therapy or CT (8,9). The present prospective study was performed to evaluate the impact of the multicomponent nutritional supplement Oncoxin on QoL and tolerability of anticancer drugs in patients receiving ACT. Oncoxin is a solution containing amino acids, vitamins, micronutrients and biologically active substances. Previous studies showed that ONCX was able to increase life expectancy, improve QoL and appetite in patients with end-stage hepatocellular carcinoma (10) and effectively reduce the severity of oral mucositis symptoms in patients receiving CT, radiation therapy or their combination (11).

Materials and methods

Study population. The eligibility criteria for inclusion in the study were as follows: Male and female patients who had signed an informed consent, aged 50-70 years, with gastric cancer IIB-IIIC, NSCLC IIB-IIIA; R0 surgery, ACT required, 2nd and further course of ACT, XELOX regimen of ACT for gastric cancer and paclitaxel+carboplatin regimen for NSCLC, body mass index (BMI) >15, serum albumin ≥25 g/l, Easter n Cooperative Oncology Group performance status ≤2. The exclusion criteria were as follows: Severe concomitant diseases or conditions that may complicate or make the patient's participation in the study impossible, or make it difficult to explain clinical findings (including mental disorders, severe infectious and parasitic diseases, and an intolerability to any of the ONCX components), the patient's family or official relations with a member of staff of the clinical site, the patient's failure to assess his/her physical and/or emotional condition, the patient's failure to comply with the study requirements, the patient's refusal to participate in the study, as well as pregnancy or breastfeeding.

The present study was approved by the Ethics Committee of the Loginov Moscow Clinical Scientific Centre, protocol 3/2017, April 17, 2017. All patients were enrolled between November 2017 and March 2019. In accordance with the Declaration of Helsinki, all patients provided written informed consent to participate in the study and to publish the results. The study was retrospectively registered under the study registration number NCT03550482 at ClinicalTrials.gov resource, June 8, 2018.

Study design and treatment. The present study was multicentre, open-label, non-randomised clinical trial in two parallel groups with a 20-day treatment period. No follow-up period was intended. The following visits were scheduled: Visit 1-the first day of 2nd or further course of ACT; Visit 2-7±1 days before the next course of ACT; Visit 3-the first day of the next course of ACT (before administration of drugs) (21±3 days after Visit 1). The following primary endpoint was used: The percentage of patients who had an improvement in QoL corresponding to the minimal clinically important difference (MCID) that any patient felt at Visits 2 in total symptom distress score of the Edmonton Symptom Assessment System questionnaire (SDS ESAS) (12). This MCID corresponds to 6 points of improvement within-patient change for improvement (12). ESAS is a validated set of questions that assesses the average intensity of 10 symptoms (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, feelings of well-being and sleep) over the past 24 h, each with an 11-point numerical rating scale that ranges from 0 (no symptom) to 10 (worst intensity). Secondary endpoints included total SDS ESAS, emotional SDS ESAS, physical SDS ESAS scores, separate symptoms of ESAS, body mass, serum albumin level, and the Common Toxicity Criteria (ver. 2) of the

National Cancer Institute (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf) using the blood and hepatic scales.

The study was conducted in 10 clinical sites in Russia and Kazakhstan. Patients were grouped in ONCX and control groups as 2:1. A total of 133 patients were enrolled in the study; 84 in the ONCX group and 49 in the control group.

In addition to ACT treatment (XELOX or paclitaxel+carboplatin), patients in the ONCX group received 25 ml of ONCX (Catalysis S.L., 28016 Madrid, Spain) twice daily for 20 days. ONCX's composition is shown in Table I. In case of nausea/vomiting after ONCX use, patients were advised to dilute it in water, juice or milk. Patients with BMI <20 and serum albumin levels <30 g/l received nutritional support. Nutritional support was provided through nutritionally complete, high energy, high protein, ready to drink supplement enriched with n-3 fatty acids and fibre.

Because of Glycyrrhizin may increase blood pressure (BP), the information regarding possible BP increase was added to Study protocol and Informed consent form. Thus, both investigators and patients were informed of possible BP increase. Patients' BP was monitored as a part of routine practice and corrected if needed.

To decrease therapy toxicity, the following drugs/methods were available and used if needed: filgrastim, epoetin alfa, blood transfusions, corticosteroids, 5H3 antagonists, ademetionine, polyunsaturated phosphatidyl choline and nutritional supplements containing vitamins and minerals.

Statistical analysis. Statistical analysis was performed using StatSoft Statistica 10.0 software (http://statsoft.ru/). For odds ratios' (OR) 95% confidence interval (CI) VassarStats online service (vassarstats.net) was used.

Sample size was calculated based on the following conditions:

1. It was expected that the proportion of patients with MCID improvement in total SDS ESAS is 50% in ONCX group and 20% in control group (with 30-point baseline total SDS ESAS).
2. Patients' allocation as 2:1 in comparison groups for the ONCX and control groups, respectively.
3. Alpha 0.05 and power not less than 0.9.

Based on the above conditions, data from 120 patients had to be analysed. With a dropout of 25%, 150 patients had to be included in the study (100 ONCX/50 controls).

Baseline characteristics (quantitative and semiquantitative) are presented as mean and (standard deviation), unless otherwise stated; when comparisons between groups or within a group were made, the data are presented as mean and [95% CI]. Categorical variables are expressed as absolute numbers and percentages. The differences of quantitative and semiquantitative variables between the ONCX and control groups were compared using the Mann-Whitney U test and the differences within each group were compared using the sign test. For tables 2x2, OR and OR's [95% CI] were calculated. The differences of categorical variables were compared using the Yates corrected Chi-square or two-sided exact Fisher test. P<0.05 was considered to indicate a statistically significant difference.

Table I. Composition of ONCX per 100 ml.

Component	Mass
Glycine	2,000 mg
Glucosamine	2,000 mg
Malic acid	1,200 mg
Arginine	640 mg
Cysteine	204 mg
Mono-ammonium glycyrrhizinate	200 mg
Ascorbic acid	200 mg
Sodium methylparaben	120 mg
Zinc sulphate	100 mg
Green tea extract	80 mg
Calcium pantothenate	25 mg
Pyridoxine	12 mg
Manganese sulphate	4 mg
Cinnamon extract	3 mg
Folic acid	400 μg
Cyanocobalamin	2 μg

ONCX, Oncoxin.

Results

One hundred thirty-three patients were enrolled in the study; of which 84 received ONCX and 49 were included in the control group. Patient disposition is shown in Fig. 1. The initial clinical characteristics of the subjects are provided in Table II. No significant differences were found between the compared groups at baseline.

Improvement in QoL corresponding to the MCID that any patient felt at Visits 2 and 3 was assessed. At Visit 2, the number of such patients in the ONCX group accounted for 52% vs. 35% in the control group, at Visit 3-59% and 43%, respectively. At Visit 2, the chance of ONCX-treated patients having MCID improvement in total SDS ESAS was twice as high compared to the control group: OR=2.07 [1.00-4.29], P=0.005. The difference was insignificant by Visit 3: OR=1.89 [0.91-3.93].

Total SDS ESAS declined significantly in each group by Visit 2. However, there were no significant differences noted between the groups. By Visit 3, the QoL in patients receiving ONCX was significantly better, including the total SDS ESAS and physical SDS ESAS (see Table III).

A few symptoms within the ESAS questionnaire improved in ONXC patients by Visit 2. Those values included QoL aspects such as appetite and well-being. Furthermore, at Visit 3, differences in the fatigue severity were detected (Table III). Changes in body weight and serum albumin levels were insignificant by Visit 2, with no differences found between groups or within groups. By Visit 3, albumin levels were significantly higher in the ONCX group compared to the control group [38.1 (37.1-39.1) g/l vs. 35.5 (33.9-37.0), P=0.03, respectively]. Weight loss in the ONCX group was less pronounced by Visit 2, and patients regained their body weight by Visit 3 (Fig. 2A). Similar results were obtained for serum albumin levels at Visits 2 and 3 (Fig. 2B).

Table II. Patient baseline characteristics for each group.

Characteristic	ONCX	Controls	P-value
Number of patients, n	84	49	
Non-small cell lung cancer, abs (%)	53 (63.1)	31 (63.3)	0.9
Males, abs (%)	50 (59.5)	33 (67.3)	0.5
Age, years	59.0 (6.1)	57.2 (5.2)	0.1
Height, cm	167.5 (6.9)	170.1 (6.5)	0.1
Body mass, kg	63.7 (10.7)	67.5 (11.3)	0.1
BMI (min-max)	22.7 (15.9-32.4)	23.2 (17.9-31.7)	0.2
Serum albumin, g/l	34.5 (3.9)	35.6 (5.0)	0.2
ESAS			
Emotional SDS ESAS	3.1 (3.6)	3.0 (3.5)	0.9
Physical SDS ESAS	16.6 (9.1)	15.0 (7.4)	0.2
Total SDS ESAS	22.9 (12.5)	21.2 (11.0)	0.4
Mean toxicity grades			
Leukocytes	0.03 (0.17)	0.15 (0.37)	0.3
Platelets	0	0.05 (0.22)	0.7
Haemoglobin	0.78 (0.71)	1.00 (0.76)	0.2
Lymphocytes	0.12 (0.44)	0.31 (0.61)	0.2
Alkaline phosphatase	0.27 (0.54)	0.18 (0.56)	0.4
ALT	0.09 (0.29)	0.08 (0.27)	0.9
AST	0	0.05 (0.22)	0.7
Total bilirubin	0	0	

Data are presented as the mean (standard deviation), unless otherwise specified. ONCX, Oncoxin; BMI, body mass index; SDS, symptom distress score; ESAS, Edmonton Symptom Assessment System; ALT, alanine aminotransferase; AST, aspartate aminotransferase; abs, absolute number.

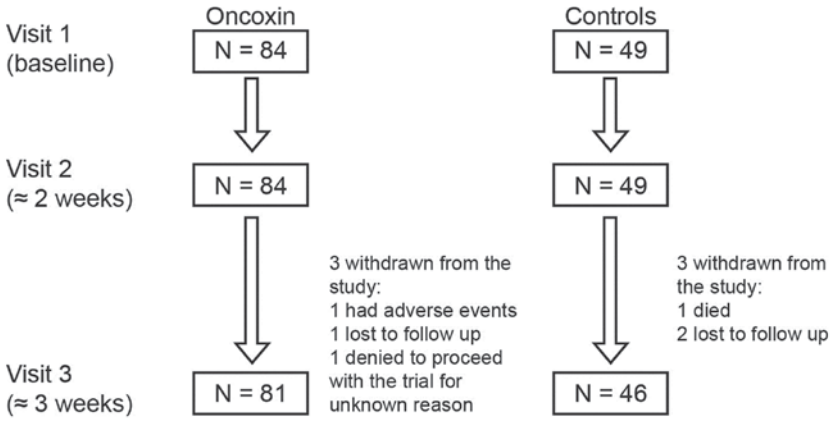

Figure 1. Disposition of patients.

During the study, the rate of patients whose body weight and serum albumin levels remained unchanged or increased was significantly higher in the ONCX group (Fig. 3; Table IV). Initially, 25% of patients among those received ONCX and 29% in the control group needed nutritional support. By the end of the study, the proportions of such patients were 19 and 30%, respectively. However, the difference was not significant (P=0.19).

Patients distribution across toxicity grades according to allocation group and study progress is presented in Table V. The therapy toxicity analysis showed that the use of ONCX reduced drops in haemoglobin and alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevation at Visit 2 and ALT/AST elevation at Visit 3 (Table VI). Special attention should be paid to the differences in the rate of patients in the ONCX and control groups, in which AST and ALT levels corresponded to a zero degree of toxicity at Visits 2 and 3 (Fig. 4).

ONCX was well tolerated except for nausea. Seven patients reported ONCX-related nausea immediately after swallowing

Table III. Alterations in emotional, physical and total SDS ESAS and separate ESAS symptoms during the present study.

Time point	Variable	ONCX, mean (95% CI)	Controls, mean (95% CI)	P-value
Baseline	Emotional SDS ESAS	3.11 (2.32-3.90)	2.98 (1.96-4.00)	0.887
	Physical SDS ESAS	16.6 (14.7-18.6)	15.0 (12.9-17.1)	0.173
	Total SDS ESAS	22.9 (20.2-25.6)	21.2 (18.0-24.4)	0.358
Week 2	Appetite	1.75 (1.18-2.32)	3.55 (2.56-4.54)	0.002
	Well-being	2.15 (1.62-2.69)	3.02 (2.52-3.52)	<0.001
	Emotional SDS ESAS	2.49 (1.81-3.16)	1.94 (0.90-2.98)	0.142
	Physical SDS ESAS	11.3 (9.8-12.8)	13.5 (11.4-15.5)	0.092
	Total SDS ESAS	16.0 (13.7-18.2)	18.5 (15.5-21.4)	0.112
Week 3	Appetite	1.20 (0.79-1.61)	2.76 (2.06-3.46)	<0.001
	Tiredness	1.56 (1.19-1.92)	2.85 (2.30-3.40)	<0.001
	Well-being	1.46 (1.05-1.87)	2.96 (2.45-3.46)	<0.001
	Emotional SDS ESAS	1.65 (1.15-2.16)	1.85 (0.95-2.75)	0.789
	Physical SDS ESAS	8.68 (7.49-9.87)	11.9 (10.2-13.8)	0.001
	Total SDS ESAS	11.8 (10.0-13.6)	16.8 (14.1-19.5)	<0.001

Only statistically significant differences in symptoms are shown. ONCX, Oncoxin; SDS, symptom distress score; ESAS, Edmonton Symptom Assessment System.

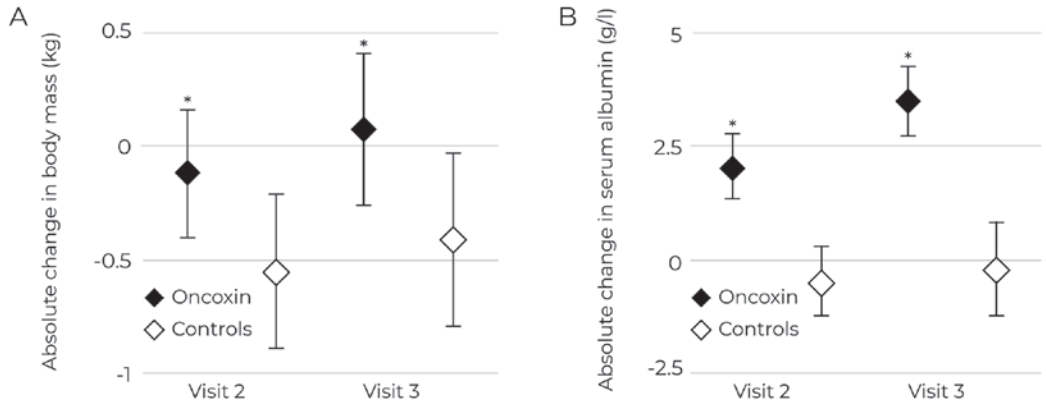

Figure 2. Absolute changes from baseline (Visit 1) in (A) body mass and (B) serum albumin level. Visits 2 and 3 correspond to 2 and 3 weeks after the chemotherapy started, respectively. Rhombus are mean values and bars are lower and upper limits of 95% CI. *P<0.05 vs. controls.

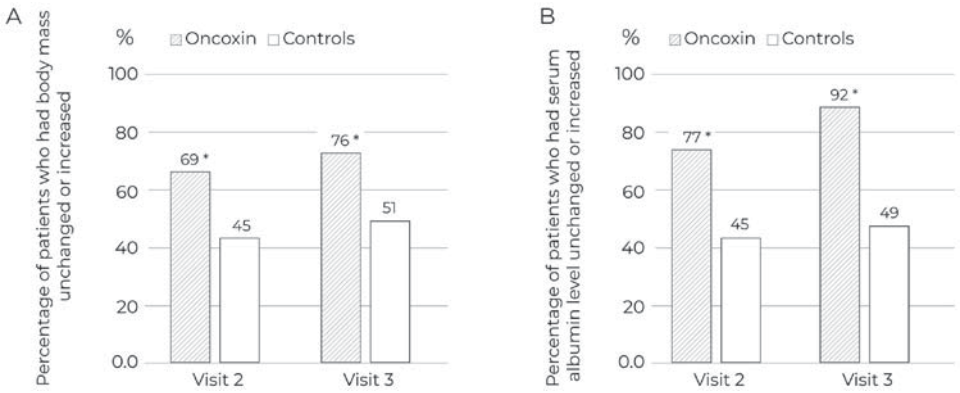

Figure 3. Percentages of patients whose (A) body mass and (B) serum albumin level remained unchanged or increased. Visits 2 and 3 correspond to 2 and 3 weeks after the chemotherapy started, respectively. *P<0.05 vs. controls.

with or without vomiting; one of them refused to participate in Visit 2 of the study and the rest of the subjects were able to continue participation once ONCX was diluted, as they were advised at Visit 1.

Discussion

This is the first study to show that the Oncoxin nutritional supplement containing amino acids, vitamins, micronutrient elements and naturally-occurring biologically-active macromolecules is able to improve the patients' QoL, prevent the loss of body weight and reduction of albumin, and equally as important, reduce ACT hepatic toxicity as it is evident by the proportions of patient with ALT and AST levels within normal limits. An important feature of this study was that it was conducted in the context of real clinical practice. The only exception was the requirement to fill out the ESAS patient questionnaire. There were no other special requirements for the centres that participated in the study.

The cancer patients' QoL is one of the key influencing factors for patient compliance and determines the possibility of implementation or continuation of treatment. QoL is what a person feels independently, without considering the objective state, findings of instrumental/laboratory tests and knowledge of the essence of the disease. Thus, QoL is vitally important in assessing the therapy's effects; it shows how patients feel about their condition, and how this attitude changes during the disease progression or medical intervention (6).

ONCX was previously found to improve the QoL and life expectancy, as well as appetite in patients with end-stage hepatocellular carcinoma (10). The authors assumed that ONCX acted as a nutrient and expanded the food allowance, eliminating the possible shortage of its individual components. Indeed, various ONCX components can have such effect. Zinc has the capacity to correct taste disorders, including those associated with cancer, as well as stimulate food consumption, which is extremely important in the development of anorexia-cachexia syndrome (13). Up to 35% of elderly people in developed countries have deficiency of this nutrient element (14), and such deficiency is typical to lung and ovarian cancer (15), opioid use (16) and cisplatin CT (15). Vitamins can also affect the well-being of patients, e.g. vitamin B12 (17). Some amino acids, namely, arginine and glycine, can prevent muscle loss in cancer diseases (18,19). As demonstrated, a significant number of ONCX components suppress the severity of systemic inflammation, and this suppression seems to be a key mechanism to improve the QoL when using ONCX. Suppression of systemic inflammation has been found with glycine (20), glucosamine (21), EGCG (22), glycyrrhizin (23), zinc (24).

The ability of ONCX to reduce therapy toxicity is an important aspect of its use demonstrated in the study. The previous studies showed the role of several of its components in reducing the xenobiotics toxicity. Cysteine participates in remethylation of methionine, whose level is closely related to chemical toxicity manifestation threshold due to amino acid involvement in a series of antioxidant systems, including glutathione (25). Glycine is capable of reducing nephro- and hepatotoxicity of drugs and a number of toxic compounds (26), e.g. cyclosporine A nephrotoxicity (27). It is assumed that due to suppression of prostaglandin E2 release from Kupffer cells, glycine blocks the liver damage caused by this drug (28). The hepatoprotective properties of glycyrrhizin are well known and may be important in toxic liver damage caused by CT. This feature has been reported in patients with gastric cancer. It was established that the use of glycyrrhizin with FOLFOX and XELOX CT regimens was accompanied by a significantly smaller number of liver function abnormalities (more than twice as compared to the control group) (7). EGCG is another component with a clinically proven ability to affect the antitumor therapy's toxicity. EGCG is a basic green tea extract polyphenol that possesses radioprotective and chemoprotective effects. Due to its antioxidant and anti-inflammatory effects, EGCG was highly effective in relieving acute esophagitis induced by radiotherapy or chemoradiotherapy (8,9).

Table IV. Odds ratios of unchanged or increased body mass and serum albumin level in the Oncoxin group compared with in the control group.

Variable	Week of the study	OR (95% CI)
Body mass	Week 2	2.74 (1.32-5.67)
	Week 3	3.07 (1.45-6.52)
Serum albumin	Week 2	4.20 (1.96-8.98)
	Week 3	11.46 (4.41-29.8)

ONCX, Oncoxin; OR, odds ratio.

The antioxidant and anti-inflammatory properties of ONCX components are likely to be the basis of its ability to reduce ACT toxicity. The antioxidant activity was also found in other components of ONCX, including zinc (14,24) and manganese (29).

Being a real clinical setting study, it was planned to be as simple and non-burdening as possible for investigators. Therefore, it has several disadvantages. Except for the ESAS questionnaire, outcome measures were limited by current clinical practice. Another disadvantage of this study was the short observation period of patients between successive courses of ACT, i.e. about three weeks. It was not possible to assess the delayed effects of ONCX and to identify any details related to the effect of this nutritional supplement on the relative ACT dose intensity, as well as other measures that characterise the condition of patients during administration of anticancer agents.

The study showed that the use of the nutritional supplement ONCX, when administered concurrently with ACT, increased the proportions of patients with clinically meaningful improvement of QoL by 16% as early as after 2 weeks of use and who have not experienced a loss in body weight and a decrease in albumin levels, by 25 and 43%, respectively. In addition, ONCX reduced the severity of appetite disturbance and hepatic toxicity of anticancer therapy.

In conclusion, it should be noted that it was the first study carried out within the real clinical setting that showed the high efficacy of ONCX in improving the ACT patients' QoL and reducing the therapy's toxicity. Even though the obtained results look promising, further studies of multicomponent nutritional supplements, such as ONCX, are required to explore opportunities to improve patients' QoL and to achieve the best ACT efficacy with minimal toxicity.

Table V. Patient distribution across toxicity grades according to group and study progress.

Variable	Toxicity grades[a]	Baseline		Week 2		Week 3	
		ONCX, abs (%)	Control, abs (%)	ONCX, abs (%)	Control, abs (%)	ONCX, abs (%)	Control, abs (%)
Number of patients with assessed toxicity		67	39	67	39	64	36
Hemoglobin	0	26 (39)	11 (28)	44 (66)	9 (23)	51 (80)	21 (58)
	1	30 (45)	17 (44)	22 (33)	26 (67)	12 (19)	15 (42)
	2	11 (16)	11 (28)	1 (1)	4 (10)	1 (1)	0
ALT	0	61 (91)	36 (92)	59 (88)	15 (38)	59 (92)	18 (50)
	1	6 (9)	3 (8)	8 (12)	14 (36)	5 (8)	18 (50)
	2	0	0	0	10 (26)	0	0
AST	0	67 (100)	37 (95)	52 (78)	15 (38)	59 (92)	21 (58)
	1	0	2 (5)	15 (22)	22 (56)	5 (8)	15 (42)
	2	0	0	0	1 (3)	0	0
	3	0	0	0	1 (3)	0	0

[a]There were no patients with grade 4 across all toxicities and no patients with grade 3 ALT and hemoglobin toxicities. ONCX, Oncoxin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; abs, absolute number.

Table VI. Mean toxicity grades during the study visits.

Time point	Parameter	ONCX, mean (95% CI)	Controls, mean (95% CI)	P-value
Week 2	Haemoglobin	0.36 (0.23-0.48)	0.87 (0.69-1.06)	<0.001
	ALT	0.22 (0.12-0.33)	0.69 (0.48-0.90)	<0.001
	AST	0.12 (0.04-0.20)	0.87 (0.61-1.13)	<0.001
Week 3	ALT	0.08 (0.01-0.15)	0.42 (0.25-0.59)	0.005
	AST	0.08 (0.01-0.15)	0.50 (0.33-0.67)	<0.001

Only statistically significant differences are shown. ONCX, Oncoxin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

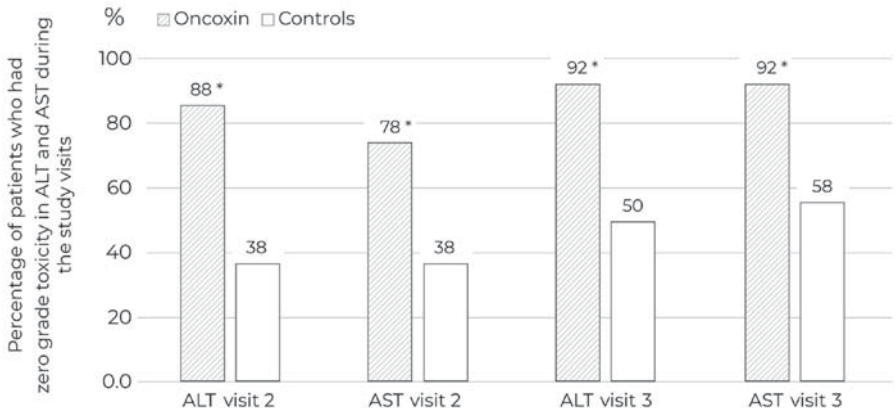

Figure 4. Percentages of patients who had zero grade hepatic toxicity in ALT and AST during the study visits. Visits 2 and 3 correspond to 2 and 3 weeks after the chemotherapy started, respectively. *P<0.05 vs. controls. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

DRK was involved in study design and interpretation of final results, patient selection and follow up. MVK was involved in study design, protocol and procedure development and interpretation of final results. VSP was involved in study design, protocol and procedure development, interpretation of final results, and patient selection and follow up. MD was involved in study design and interpretation of final results. EVB was responsible for patient selection and follow up, and involved in study design and interpretation of final results. ZMA, RZA, ENB, AVB, SNG, ASM, SSP, MVR and ASS were responsible for patient selection and follow up, and involved in study design and interpretation of final results. IAK was responsible for patient selection and treatment and involved in study design and interpretation of final results. ES was involved in study design, and protocol and procedures development. FIP performed statistical analysis and was a major contributor in writing the manuscript. All authors have read and approved the final version of this manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Loginov Moscow Clinical Scientific Centre (protocol 3/2017 April 17, 2017). In accordance with the Declaration of Helsinki, all patients provided written informed consent to participate in the present study.

Patient consent for publication

All patients provided written informed consent for publication of the results.

Competing interests

ES is a Scientific Department Managing Director of Catalysis S.L., the manufacturer and provider of Oncoxin for the purposes of the present study. All other authors declare that they have no competing interests.

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