10.5433/1679-0367.2019v40n2p185

Can fish oil supplementation in breast cancer patients with neoadjuvant chemotherapy alter nutritional, biochemical and immunological parameters?

Suplementação de óleo de peixe em pacientes com câncer de mama com quimioterapia neoadjuvante pode alterar parâmetros nutricionais, bioquímicos e imunológicos?

Ana Julia Lieber Rosset[1]; Mariana Abe Vicente Cavagnari[2]; Angélica Rocha de Freitas Melhem[3]; Gabriela Datsch Bennemann[4]; Diogo Dequech Gavarrete[5]; Dalton Luiz Schiessel[6]

Abstract

The aim of this study was to evaluate the n-3 fatty acid supplementation effects in breast cancer patients. Methods: it was a prospective longitudinal study performed in breast cancer patients supplemented with fish oil during 8 weeks in neoadjuvant AC-T regimen. Anthropometric, Bioelectrical impedance (BIA) ((Lean Body Mass (LBM), and Phase Angle (PA)), food consumption, nutritional impact symptoms (NIS), metabolic and inflammatory profile were evaluated for 2 months. Results: supplemented patients presented weight gain of 1.4 kg, representing 1.8% of body weight. LBM was 42.3 Kg and PA 6.1º. Nausea, diarrhea and anorexia were the main NIS with reduction in incidence with the supplementation, but xerostomia and heartburn had increase. There was significant drop in hemoglobin values to 12.3 mg/dL, metabolic parameters and nutritional prognosis (CRP/albumin ratio) were not altered. Cytokines levels of TNF-α and interleukin-6 did not change, however interleukin-2 have shown significant increasing. Conclusion: Body weight gain was noticed in breast cancer patients, independent of food consumption. Fish oil supplementation during neoadjuvant chemotherapy was able to reduce NIS incidence, but not avoiding the decrease of hemoglobin levels, but it keeps the maintenance of pro-inflammatory parameters, except for increased the cytokine IL-2.

Key words: Nutritional assessment. Breast cancer. Fish oil. Chemotherapy. Cytokines.

Resumo

O objetivo foi avaliar os efeitos da suplementação de ácidos graxos n-3 em pacientes com câncer de mama. Metodologia: estudo prospectivo longitudinal realizado em pacientes suplementados com óleo de peixe durante 8 semanas em quimioterapia neoadjuvante com regime AC-T. Antropometria e impedância bioelétrica (massa corporal magra (massa magra) - ângulo de fase (AP)), consumo alimentar, sintomas de impacto nutricional (SIN) e perfil metabólico e inflamatório foram avaliados. Resultados:

[1] Graduated in Nutrition
[2] PhD in Sciences from the Universidade Federal de São Paulo. Professor of Nutrition Course at UNICENTRO
[3] PhD in Gastroenterology from the Universidade Federal de São Paulo. Professor of Nutrition Course at UNICENTRO
[4] PhD from the Universidade Estadual do Centro-Oeste. Professor at the Universidade Estadual do Centro-Oeste - UNICENTRO.
[5] Oncologist physician - Clinic of Oncology - Hospital de Caridade São Vicente de Paulo - Guarapuava - PR
[6] PhD in Cell and Molecular Biology from the Universidade Federal do Paraná. Postdoctoral degree at the University of Alberta - Cross Cancer Institute. Adjunct Professor at the Universidade Estadual do Centro-Oeste - UNICENTRO.

Os pacientes apresentaram ganho de peso de 1,4 kg, representando 1,8% do peso corporal. LBM foi 42,3 kg e AP 6,1º. Náusea, diarreia e anorexia foram o SIN com redução na incidência com a suplementação, mas a xerostomia e a azia aumentaram. Houve uma queda significativa nos valores de hemoglobina para 12,3 mg/dL, parâmetros metabólicos e prognóstico nutricional (relação PCR/albumina) não foram alterados. Os níveis de citocinas de TNF-α e interleucina-6 não mudaram, entretanto a interleucina-2 mostrou um aumento significativo. Conclusão: O ganho de peso corporal foi observado nas pacientes com câncer de mama, independente do consumo alimentar. Durante a quimioterapia neoadjuvante com suplementação de óleo de peixe houve redução da presença de SIN, diminuição dos níveis de hemoglobina e manutenção de parâmetros bioquímicos e inflamatórios, exceto pelo aumento da citocina IL-2.

Palavras-chave: Avaliação nutricional. Câncer de mama. Óleo de peixe. Quimioterapia. Citocinas.

Introduction

Breast cancer is responsible for the second highest incidence of malignant neoplasms in the world. The Globocan/IARC is a set of worldwide estimates analysis of cancer incidence and mortality produced by the International Agency for Research on Cancer (IARC). IARC estimated that, more than 1.7 million cases of breast cancer occurred worldwide in 2012, which made breast cancer the most common between women. In Brazil, the National Institute for Cancer Jose Alencar Gomes da Silva (INCA) estimate to 2018-2019, which will present the occurrence with an expectation to 600 thousand of cancer new cases and 59.7 thousand for each year at the biennium to breast cancer.[1]

There are many aspects related to increased breast cancer incidence, been the main relevant such as; physiological factors such as reproductive (long menstrual history and late menopause, nulliparity or advanced age at first calving and menopause after 55 years old), hormonal (recent use of postmenopausal hormone therapy or oral contraceptives) and, genetic factors such as family history of breast cancer.[2] The most important factor is lifestyle. Environmental factors such as, smoking, alcohol beverages consumption and sedentary lifestyle and, nutritional factors as, weight gain, obesity and hypercaloric diet composition, overweight and obesity can influence the development of breast cancer.[3,4]

Studies have reported that during chemotherapy treatment, patients with breast cancer frequently had body weight gain between 1 and 6 kg, regardless of caloric consumption and have been considered an independent prognostic factor to progression and/or recurrence and, shorter survival.[5]

Cancer and its treatment, such as neoadjuvant chemotherapy, is related to increase chronic inflammation, which is correlated with worst prognostic. Some proinflammatory cytokines (i.e. tumor necrosis factor (TNF)-α, Interleukin (IL) 6 and IL-2),[6] inducing cancer-associated sarcopenia by lean body mass (LBM) atrophy[7] or obesity sarcopenia.[8] Bioelectrical impedance (BIA) is an inexpensive and noninvasive tool to measure lean body mass (LBM) and it have shown that low LBM is associated with more severe toxicity[9] and a shorter time to tumor progression[10]. Phase Angle is described as a predictive tool in several clinical diseases outcomes and mortality, and typically healthy subjects phase angle has between 5º to 7.[11]

Among the nutritional factors, omega-3 polyunsaturated fatty acids are distinguished by their beneficial effect on human health, since they have effects on the immune and inflammatory response, having a suppressive effects, such as inhibition of proliferation, on immune system cells there are an increase in cellular activity and reduction in the production of pro-inflammatory cytokines.[12]

Evidences on nutritional impact of omega-3 fatty acid consumption on risk of breast cancer has shown that a diet rich in fish oil has been effective in mammary tumor and can suppress tumor growth by inhibiting its proliferation and the appearance of metastases.[13] Also, omega-3 fatty acids reduced the

synthesis of catabolic pro-inflammatory cytokines (TNF-α, IL-6) that induce muscle loss.[14]

Therapies proposed for cancer treatment, such as surgery, chemotherapy and radiotherapy, incite the presence of nutritional impact symptoms (NIS) that are signs who's limit or prevent the patient from feeding and thus reduce the patient's dietary intake in quantity and quality of diet and in some cases, determine diseases deficiencies due to lower consumption of vitamins and minerals and weight loss. NISs in patients that occur with great frequency are alteration of taste and smell, mucositis, nausea and constipation.[15]

Thus, the objective of this study was to evaluate the nutritional status, NIS, biochemical and inflammatory plasma parameters in women diagnosed with breast cancer during neoadjuvant chemotherapy before and after 8 weeks of fish oil supplementation.

Materials And Methods

It was performed a longitudinal prospective study. Fifteen patients diagnosed with breast cancer receiving neoadjuvant chemotherapy treatment (AC-T regimen: doxorubicin - 60 mg/m^2, cyclophosphamide 600 mg/m^2 and paclitaxel 175 mg/m^2) were enrolled at the study until the third sessions in an oncology clinic linked to the Unified Health System (SUS) in Guarapuava – PR – Brazil. This study was approved by the Research Ethics Committee (COMEP) of UNICENTRO (nº 840,180). Patients enrolled to the study received 4 capsules/day (4g/day) of fish oil (FO) (Herbarium®) (total consumption/day of eicosapentaenoic acid (EPA) ≅ 1.2g and docosahexaenoic acid (DHA) ≅ 1.0 g),[16] during 8 weeks and were instructed to take two capsules before lunch and two before dinner **(Figure 1)**. Anthropometric evaluations were performed at two times, and weights were done on an anthropometric scale and height using the stadiometer (Toledo® - Toledo do Brasil, São Bernardo do Campo, SP, Brazil). Stage of disease was based on the American Joint Committee on Cancer (AJCC), stage groupings, I, II, III, and IV, which in turn are based on the Tumor, Nodes, and Metastasis (TNM) staging system.

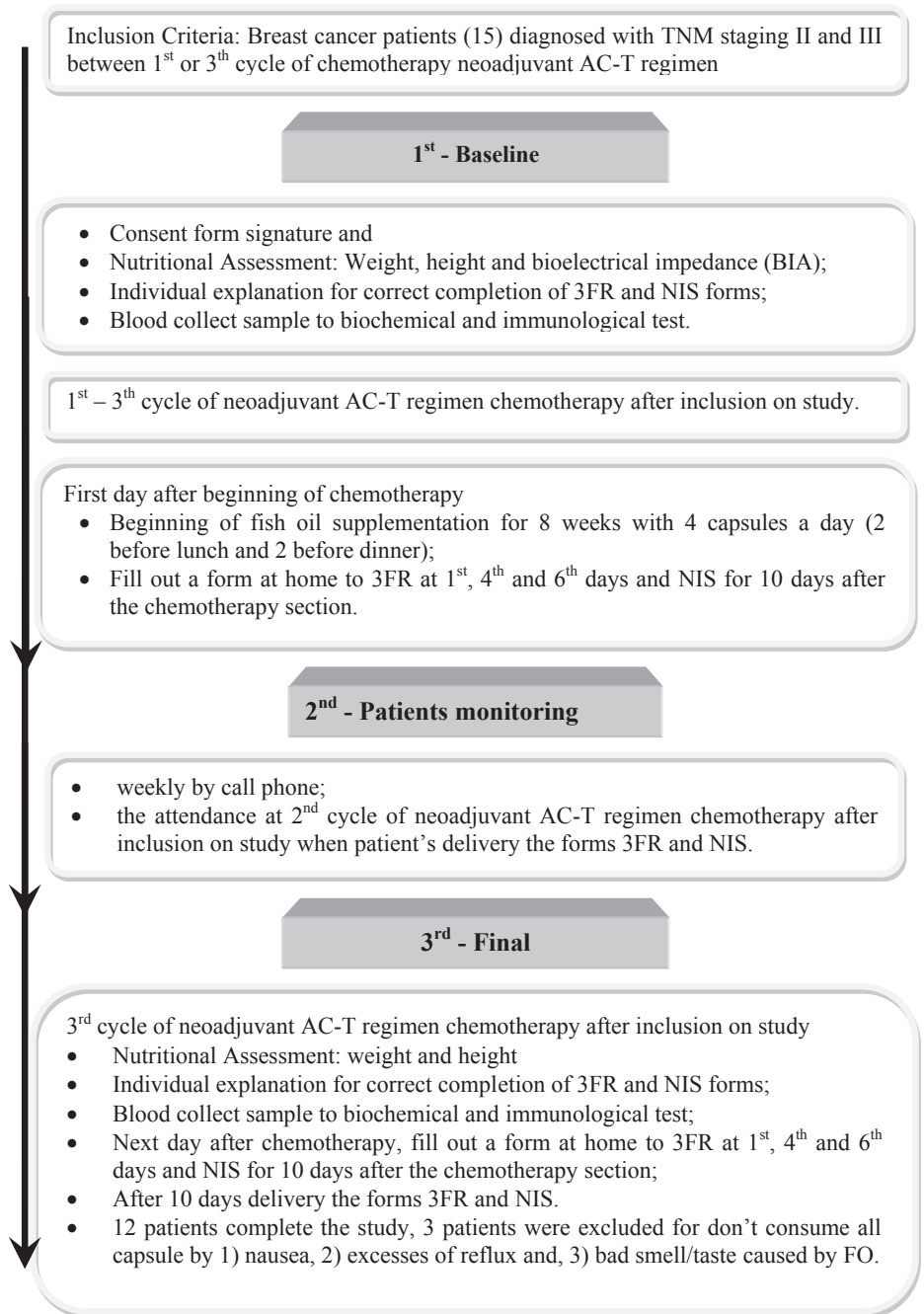
Body Mass Index (BMI) was calculated according to the ratio between body weight (kg) and square height (m^2), classified according to the World Health Organization (WHO).[17] The weight change (WC) (final weight - initial weight), weight change percentage (% WC) (final weight/initial weight) x100/ final weight were calculated. Tetrapolar bioelectrical impedance (BIA) (Biodynamics® model 450) was performed by according[18] to the baseline for body composition analysis, to evaluate Lean Body Mass (LBM), Fat mass (FM) and Phase Angle (PA).

Evaluation of dietary intake was obtained using a 3-days food record (3FR) answered by the patient at home reporting mealtime, type of meal, food consumed and quantity. The data obtained from the records were converted from home measurements to grams, with the aim of obtaining ingested values of macro nutrients (total calories), with the aid of Nutwin® software (UNIFESP). Nutritional Impact Symptoms (NIS) were reported by patients in a specific form for 10 consecutive days base at the Patient-Generated Subjective Global Assessment (PG-SGA).

A blood sample from patients (10 mL in EDTA tubes – centrifuged 1200rpm/10min) was collected on baseline day and after 8 weeks of FO supplementation at the clinical laboratory analyzes agreed with the oncology clinic and checked for hemogram (erythrocytes and hemoglobin), plasma albumin, triglycerides, urea, C reactive protein (CRP) and serum lactate. The sample was centrifuged at 1200 rpm for 6 minutes at 4°C. Plasma was collected and frozen at -80° C for the subsequent performance of the experimental procedures for TNF-α, IL-6, IL-2 and IL-10 (ELISA Development Kit - Catalog #: 900-K16, Human IL-6 ELISA Development Kit - Catalog #: 900-K16, Human IL-2 ELISA Development Kit - Catalog #: 900-K12 - PeproTech Inc. Rocky Hill, New Jersey - USA).

Descriptive statistics were performed to characterize the data presented in the form of frequencies, means and standard deviation. Shapiro-Wilk normality test was performed, and the continuous variables were compared using the Student's T-test of paired samples and the nonparametric Wilcoxon test. The categorical variables were compared using the Pearson's or McNemar's Chi-square test. The analyzes were performed using SPSS version 22.0, with a significance level of 5% ($p < 0.05$).

Figure 1 - Flowchart of Study design



3FR - 3-days food record; NIS - Nutritional Impact Symptoms; FO- Fish oil

Results

Twelve patients with breast cancer reported to consume all capsules during the 8 weeks, and 3 patients was excluded for not completely consumption of fish oil capsules and they self-report the reason (e.g. bad taste and smell, nausea). The average age was 49.7±9.9 years, ranging between 33.0 to 65.0 years. After eight weeks of fish oil supplementation, all patients presented weight gain, at 1.4 kg ($p< 0.05$) representing an increasing in 1.8% of the body weight. Nine patients have had weight gain (2.1 kg) and three patients have had weight loss (-0,7 Kg). There was a noteworthy increase at BMI ($p< 0.05$), but without variation on nutritional status. Analysis at the body composition by bioelectrical impedance have shown 42.3 Kg of LBM and Phase angle 6.1º. (Table 1)

Table 1 - Anthropometric characteristics of patients with breast cancer on neoadjuvant chemotherapy supplemented with fish oil, Guarapuava, 2017.

	Anthropometric data					Nutritional Status - n (%)			Bioelectrical impedance (BIA)		
	Height (m)	Weight (Kg)	BMI (kg/m²)	WC (Kg)	% WC (%)	Normal weight	Over Weight	Obese	LBM (kg)	FM (Kg)	PA (º)
Baseline	1.62±0.04	75.4±18.1	28.6±5.9			3 (25.0)	4 (33.3)	5 (41.7)	42.3±3.5	25.3±4.9	6.1±0.9
Final		76.8±18.8	29.1±6.2	1.4±2.2	1.8±3.3%	3 (25.0)	4 (33.3)	5 (41.7)			
p-value		0.044*	0.047*				**1.000				

BMI – Body mass index, WC - Weight Change; % WC – percentual of Weight Change; LBM - Lean body mass; FM – Fat mass; PA - Phase angle. Shapiro-Wilk normality test, * t-test of paired samples, ** Pearson's chi-square test

According the TMN classification, 75% of patients were in stage II and 25% stage III, eight patients (66.7%) reported family history of cancer with a first-degree relative. Tobacco and alcohol consumption use have been described by 2 (16.7%) and 1 (8.3%) respectively and, physical activity 83.3% of the women reported did not practice regularly.

The 3-days food recall was evaluated in two moments starting after the chemotherapy; at the beginning, an average of 1421.7 Kcal was consumed and, in the final moment after 8 weeks of fish oil supplementation with, an average of food consumption of 1286.0 Kcal (Table 2). It was observed a significant statistical tendency with a reduction of 25.2% in calories ingested at the 1st day between the beginning to the final period.

Table 2 – 3-days food recall (Kcal/day) of patients with breast cancer in neoadjuvant chemotherapy supplemented with fish oil, Guarapuava, 2017.

	1° day	4° day	6° day	Median 3 days
Baseline	1417.8±416.5	1423.1±451.7	1424.2±337.9	1421.7±249.0
Final	1060.5±373.0	1425.7±354.6	1371.8±500.1	1286.0±327.8
p-value	0.053*	0.587*	0.953**	0.121*

Shapiro-Wilk normality test, * t-test of paired samples, ** non-parametric Wilcoxon.

The main nutritional impact symptoms (NIS) reported by patients at the beginning of FO supplementation were nausea 41.7% (n = 5), followed by taste alteration 33.3% (n = 4) and xerostomia 33.3% (n = 4). At the final moment there was an increase in incidence of xerostomia in 50.0% (n = 6) and heartburn 33.3% (n = 4), but there was a reduction of nausea, taste alterations and anorexia after FO supplementation in patients (Table 3).

Table 3 - Incidence of Nutritional Impact Symptoms (NIS) of patients with breast cancer in neoadjuvant chemotherapy supplemented with fish oil, Guarapuava, 2017.

	Baseline		Final		
	yes	no	yes	no	***p-value***
Nausea	**5 (41.7)**	7 (58.3)	1 (8.3)	11 (91.7)	0.125
Xerostomia	**4 (33.3)**	8 (66.7)	**6 (50.0)**	6 (50.0)	0.625
Taste alteration	**4 (33.3)**	8 (66.7)	2 (16.7)	10 (83.3)	0.500
Heartburn	3 (25.0)	9 (75.0)	**4 (33.3)**	8 (66.7)	1
Anorexia	3 (25.0)	9 (75.0)	1 (8.3)	11 (91.7)	0.5
Diarrhea	3 (25.0)	9 (75.0)	-	12 (100.0)	*
Flatulence	2 (16.7)	10 (83.3)	1 (8.3)	11 (91.7)	1
Constipation	1 (8.3)	11 (91.7)	2 (16.7)	10 (83.3)	1
Dysphagia	1 (8.3)	11 (91.7)	-	12 (100.0)	*
Vomiting	1 (8.3)	11 (91.7)	-	12 (100.0)	*
Mucosite	-	12 (100.0)	-	12 (100.0)	*
Odynophagia	-	12 (100.0)	1 (8.3)	11 (91.7)	*

* It does not apply due to lack of prevalence. McNemar chi-square test.

Regarding the hematological parameters (Table 4) evaluated, there were a statistical reduction to erythrocytes and hemoglobin. TG, Urea and Lactate parameters evaluated were not changed, ranging inside the reference values. Albumin and CRP ranging among the normal values and did not change. Cytokines TNF-α and IL-2 have increased and small reduction to IL-6 at the beginning to the end of supplementation with w-3 fatty acids and neoadjuvant chemotherapy, there was only a significant increase for the IL-2 cytokine.

Table 4 - Biochemical and inflammatory data of patients with breast cancer in neoadjuvant chemotherapy supplemented with fish oil, Guarapuava, 2017.

	Baseline	Final	***p-value***
Erythrocytes (millions/mL)	4.6 ± 0.4	4.1 ± 0.4	<0.001*
Hemoglobin (g/dL)	13.5 ± 1.4	12.3 ± 1.2	<0.001*
Triglycerides (TG) (mg/dL)	189.3 ± 87.3	170.2 ±53.1	0.572*
Urea (mg/dL)	23.3 ± 6.8	28.8 ± 7.8	0.144**
Lactate (mg/dL)	13.1 ± 3,2	14.9 ± 2.3	0.365*
Albumin (g/dL)	3.85 ± 0.26	3.95 ± 0.26	0.296*
CRP (mg/dL)	3.64± 2.94	3.55 ± 1.34	0.881*
Ratio CRP/Albumin	0.97±0.69	0.91±0.38	0.715**
TNF-α (pg/mL)	164.1 ± 55.4	175.4 ± 40.1	0.913
IL-2 (pg/mL)	112.0 ± 41.7	133.7 ± 40.5	0.025*
IL-6 (pg/mL)	96.0 ± 52.5	84.2 ± 47.2	0.130

Shapiro-Wilk normality test, * t-test of paired samples,
** non-parametric Wilcoxon.

Discussion

At the present study analyzed the effects of FO supplementation during 8 weeks in breast cancer women court during the neoadjuvant chemotherapy with AC-T regimen. The foremost aim was investigating the nutritional status by body composition, food consumption and nutritional impact symptoms, as well as the hematological parameters and immune parameters during this period.

Breast cancer is the main cancer that affects women the in the world,[19] with age and obesity have being the chief risk factor, where incidence rates increase rapidly until age 50, but in younger women have an additional aggressive.[20] In this study, mean age of breast cancer patients on neoadjuvant chemotherapy was 49.7 years and 7 patients (58%) were younger than 50 years old.

Obesity prevalence has increased substantially in all countries in the world, is the major factor, additionally, westernized lifestyle and diet, reduced physical activity, are increasing the risks of breast cancer in young women. Body fatness increases relative risk in all age groups to breast cancer development and it is 12% higher in overweight women, 16% higher in obese, compared with women with normal BMI.[21]

Studies have reported a significant increase in weight gain in patients with breast cancer[3,4], also adjuvant chemotherapy has been shown to be an independent prognosis for weight gain, independently of the total caloric intake reported by the patient.[22]

During 8 weeks of fish oil supplementation, it was observed weight gain of 1.4 kg representing 1.8% of body weight. This have caused a significant increase in body mass and BMI, but it has not changed the BMI classification in the nutritional status in the group.

Despite of the weight gain, the final food intake did not present differences when supplementing with fish oil, however, a reduction was observed comparing day 1 after chemotherapy between the beginning and the end period. Yaw et al.[22], in a study with 368 women with breast cancer, showed that total energy consumption was 1,350 kcal/day (95% CI: 1307.5 - 1391.8), and after one year of the diagnosis, 63.3% women experienced weight gain.

Other possibly responsible mechanisms by weight gain include reduced physical activity.[5] Women who practice physical activity during the neoadjuvant treatment contribute to weight loss, lean body mass (LBM) gain, and fat mass reduction while those who do not practice physical activity have seen the opposite.[23]

In this study, it was observed that more than 80% of the women do not practice physical activity. Patients who practice physical activity regularly presented a higher food intake, but maintenance of the body weight or weight loss of 0.1 kg compared to the women who do not practice activity have presented a greater weight gain of 2.3 kg (data not shown).

Reduced LBM is predictor of high toxicity prevalence during the chemotherapy treatment.[24] Prado et al.[10] evaluating a cohort of breast cancer patients using computerized tomographic and measuring muscle cross-sectional area (cm^2) to calculate LBM (kg) (40.3±5.8 (26.3-55.8)) have shown that 25.5% of those patients had sarcopenia (reduced LBM) also presented a higher toxicity prevalence in 50% patients.

In the present study the patients presented 42.3 kg of LBM and phase angle (PA) 6.1º and estimated by the BIA. The Phase angle (PA) that represents a very sensitive nutritional marker and also is related to functional status, thus, low PA (<5º) is associated with a decrease in physical function, nutritional status, and predicted mortality in patients with cancer.[25]

NISs during chemotherapy may interfere with the patients' ability to feed, and the most observed in oncology patients are xerostomia,

anorexia, dysphagia, taste and smell alteration, constipation, abdominal pain and epigastric pain. [4] During the neoadjuvant treatment of cancer with AC-T regimen supplemented with fish oil rich in w-3 polyunsaturated fatty acids a reduction in the incidence of NIS was observed.

Anemia is a frequent finding in cancer patients, occurring in more than 40% of cases. In patients treated with chemotherapy the anemia incidence can up to 90% of patients, being an unfavorable prognostic factor and exerting a negative influence on quality of life. Anemia is clinically characterized as a hemoglobin level of <14 g/dL in men and < 12g/dL in women.[26] Prevalence of anemia vary depending on many factors, including type of cancer, chemotherapy, stage of disease, and anemia is defined as hemoglobin at <11 g/dL, reduced nutrition causes a nutritional deficiency of folic acid, vitamin B12 and iron.[27]

In 2008, a consensus defined parameters to classify anemia in cancer cachexia patients and for this classification hemoglobin values lower than 12 g/dL was determined.[28] In this study, patients during the neoadjuvant chemotherapeutic treatment had a significant reduction in erythrocyte and hemoglobin values indicating toxicity, and anemia it is induced and increased by cancer, chemotherapy treatment and proinflammatory cytokines, particularly TNF-α and IL-6 reducing erythropoiesis.[29]

It has been established that there is an interplay between cancer and chemotherapy to regulate patient immune system by activated immune cells to increase expression of proinflammatory cytokines. Also, many studies support the role of obesity and weight gain in breast cancer progression, thus, accumulation of body fat during neoadjuvant treatment increases circulating levels of proinflammatory markers and cytokines.[23] Increased expression of CRP, Tumor Necrosis Factor (TNF-α), interleukin-6 (IL-6) blood levels, have been associated to reduction of LBM[23], carcinogenesis, proliferation, angiogenesis and tumor metastasis.[30-31]

CRP is an acute-phase serum protein produced mainly by hepatocytes and is regulated at the transcriptional level by IL-6. CRP plasma concentration have reduced in naïve breast cancer patient supplemented with FO without chemotherapy treatment and increased in placebo patients.[32] TNF-α, has been reported to be associated with breast cancer development as indicated by their presence within tumor microenvironment and metastatic sites, also TNF-α regulates IL-6 synthesis.[33]

In this study, inflammatory markers CRP, TNF-α and IL-6 values not changed. However, we rationale that w-3 fatty acid present in FO have modulated the immune system keeping these cytokines in the same values during the supplemented period and thus collaborating to reduce cancer complications reported in paragraph above.

Nevertheless, for IL-2, significant increase was observed in this study. IL-2 is expressed by B cells and able to mediating tumor regression, playing a pivotal role in anticancer immune response[29], controlling in humans by activating T cells that promote $CD8^+$ T-cell and NK cell cytotoxicity and activity produce it to facilitate and direct the innate and adaptive immune cell responses.[34] In a breast cancer mice model (HER-2/neu FVB transgenic mice) supplemented fish oil, tumor infiltrated T-helper cells produced significantly more IL-2. Therefore, it is suggested that w-3 PUFAs exert a protective effect by altering an effector function in T-helper cells against cancer cells.[35]

C-reactive protein (CRP)/albumin (Alb) ratio is used as an inflammatory and nutritional risk for complications[36] and is prognostic indicator for survival in multiple types of tumor.[37-38] The classification adopted for patients is: No risk: 0.4; Low risk: 0.4 - 1.2; Moderate risk: 1.2 - 2.0 and High risk:> 2.0.[39] In patients undergoing chemotherapy, the supplementation of 0.6 g/d of EPA þ DHA orally during 9 week reduces CRP/albumin ratio.[39] Silva et al.,[40] supplementing 4 fish oil capsules per day in

patients with colorectal cancer found a significant increase in the CRP/albumin ratio.

At the present study supplemented breast cancer patients have presented values mean of CRP/albumin ratio 0.97 at the baseline and decreased to 0.91 after 8 weeks receiving FO supplementation setting a low risk in this prognostic according the Classification applied for Mocellin et al.[36] This result has shown that w-3 fatty acids can modulate inflammatory profile holding these parameters in breast cancer patients reviving neoadjuvant chemotherapy AC-T regimen.

Studies have found that maintenance of body weight, modulation in the diet and regular physical activity are associated with a reduction in the risk of breast cancer.[2] Epidemiological evidence demonstrated effects of w-3 polyunsaturated fatty acids in cancer prevention and treatment , in addition with physical activity, thus contributing to the immune system modulation and also during neoadjuvant treatment it was observed that diets enriched with these fatty acids improved the efficiency of doxorubicin by inhibiting tumor growth.[41]

Conclusion

The main aim of this study was to compare the effects of w-3 PUFAS during the 8 weeks of neoadjuvant chemotherapy. For this reason, a control group without supplementation is not shown. Limitations of this study is the number of patients enrolled in the research by limited amount of FO capsules gently donated and the lack of BIA to LBM, FM and PA. However, we observed that in a short period of time receiving neoadjuvant treatment the patients presented weight gain, this being commonly observed in women with breast cancer, even without verifying variations in food consumption. Supplementation with fish oil has reduced the incidence of symptoms of nutritional impact which may limit food intake. It was also observed that the neoadjuvant treatment with doxorubicin caused a reduction in hemoglobin values, which can lead to anemia. It was observed that most patients do not practice regular physical activity and that its practice contributes to the control of body weight and, also assists in the modulation of the immune system, triggering an anti-inflammatory profile. Supplementation with fish oil has reduced the incidence of symptoms of nutritional impact, which may limit food intake. It was also observed that the neoadjuvant treatment with doxorubicin caused a reduction in hemoglobin values, which may lead to anemia in the patients. Both weight gain and metabolic stress induced by chemotherapy may increase the production of inflammatory cytokines, however, we observed that supplemented fish oil has kept CRP, TNF-α, and IL-6 production in breast cancer patients maintaining the inflammatory state commonly soaring during cancer chemotherapy treatment. In this way, we believe that nutritional guidelines that modify nutrient quality and quantity and practice of physical activity may be beneficial for breast cancer patients.

Acknowledgment

We thank to Vickie E. Baracos for her expertise at the manuscript in corrections of English writing, data analysis and interpretation.

This study was supported by Grant Support of Fundação Araucária-PR/SESA-PR/MS-Decit/CNPq. Programa Pesquisa para o SUS: Gestão Compartilhada em Saúde (PPSUS) - Chamada 04/2013 - Convênio n°:978/2013. Fish oil capsules were kindly donated by *Fundação Herbarium de Saúde e Pesquisa* – Colombo - PR, Brasil

References

1 Instituto Nacional do Cancer (BR). Estimativa 2018: Incidência de câncer no Brasil. Rio Janeiro: INCA; 2017.

2 Assi HA, Khoury KE, Dbouk H, Khalil LE, Mouhieddine TH, El Saghir NS. Epidemiology and prognosis of breast cancer in young women. J Thorac

Dis [Internet]. 2013 [cited 2018, May 8]; 5 Suppl 1:S2-8. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3695538&tool=pmcentrez&rendertype=abstract

3 Lotici T, Antunes LBB, Melhem AR de F, Bennemann GD, Schiessel DL, Bianca L, et al. Prevalência De perda de peso, caquexia e desnutrição, em pacientes oncológicos. Rev Uniabeu. 2014;17(17):107-24.

4 Rocha LA, Cavagnari MAV, Freitas Melhem AR, Bennemann GD, Antunes LBB, Gavarrete D, et al. Incidência de caquexia, anemia e sintomas de impacto nutricional em pacientes oncológicos. Mundo da Saude. 2016;40(3):353-61.

5 Trédan O, Bajard A, Meunier A, Roux P, Fiorletta I, Gargi T, et al. Body weight change in women receiving adjuvant chemotherapy for breast cancer: a French prospective study. Clin Nutr [Internet]. 2010 Apr [cited 2018 May 8];29(2):187–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19713014

6 Huang A, Cao S, Tang L. The tumor microenvironment and inflammatory breast cancer. J Cancer. 2017;8(10):1884–91.

7 Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Prim [Internet]. 2018 [cited 2018 May 8];4(17105):1-18. Available from: http://www.nature.com/articles/nrdp2017105

8 Cespedes Feliciano EM, Kroenke CH, Meyerhardt JA, Prado CM, Bradshaw PT, Kwan ML, et al. Association of systemic inflammation and sarcopenia with survival in nonmetastatic colorectal cancer. JAMA Oncol [Internet]. 2017 [cited 2018 May 8]; 94612(12):e172319. Available from: http://oncology.jamanetwork.com/article.aspx?doi=10.1001/jamaoncol.2017.2319

9 Prado CMM, Lima ISF, Baracos VE, Bies RR, McCargar LJ, Reiman T, et al. An exploratory study of body composition as a determinant of epirubicin pharmacokinetics and toxicity. Cancer Chemother Pharmacol. 2011;67(1):93–101.

10 Prado CMM, Baracos VE, Mccargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Cancer therapy: clinical sarcopenia as a determinant of chemotherapy toxicity and time to t umor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res. 2009;15(8):2920–6.

11 Norman K, Stobäus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis--clinical relevance and applicability of impedance parameters. Clin Nutr [Internet]. 2012 Dec [cited 2018 May 8]; 31(6):854–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22698802

12 Schiessel DL, Yamazaki RK, Kryczyk M, Coelho I, Yamaguchi AA, Pequito DCT, et al. α-Linolenic Fatty Acid Supplementation Decreases Tumor Growth and Cachexia Parameters in Walker 256 Tumor-Bearing Rats. Nutr Cancer [Internet]. 2015 [cited 2018 May 8]; 67(5):839-46. Available from: http://www.tandfonline.com/loi/hnuc20

13 Kim J, Lim S-Y, Shin A, Sung M-K, Ro J, Kang H-S, et al. Fatty fish and fish omega-3 fatty acid intakes decrease the breast cancer risk: a case-control study. BMC Cancer [Internet]. 2009 [cited 2018 May 7]; 9(216). Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2711973&tool=pmcentrez&rendertype=abstract

14 Liu Y, Chen F, Odle J, Lin X, Zhu H, Shi H, et al. Fish Oil Increases Muscle Protein Mass and Modulates Akt/FOXO , TLR4 , and NOD Signaling in Weanling Piglets After Lipopolysaccharide Challenge. J Nutr. 2013;143:1331-9.

15 Omlin A, Blum D, Wierecky J, Haile SR, Ottery FD, Strasser F. Nutrition impact symptoms in advanced cancer patients: Frequency and specific interventions, a case-control study. J Cachexia Sarcopenia Muscle. 2013;4(1):55-61.

16 Schiessel DL, Yamazaki RK, Kryczyk M, Coelho I, Castro D, Yamaguchi AA, et al. Does Oil Rich in Alpha-Linolenic Fatty Acid Cause the Same Immune Modulation as Fish Oil in Walker 256 Tumor-Bearing Rats ? Nutr Cancer [Internet]. 2016 [cited 2018 May 7]; 68(8):1369-80. Available from: http://dx.doi.org/10.1080/01635581.2016.1224364

17 WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Heal Organ - Tech Rep Ser [Internet]. 2000 [cited 2018 May 7]; 894:253. Available from: http://books.google.com/books?hl=en&lr=&id=AvnqOsqv9doC&oi=fnd&pg=PA1&dq=Obesity:+Preventing+and+managing+the+global+epidemic&ots=6UF0cjXY6M&sig=iA1h8eoKNhRTKDfXqIVZaivyyk4%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/11234459

18 Lohman TG. Advances in body composition assessment. Champaign, IL: Human Kinetics Publishers; 1992. 150 p.

19 Wiseman MJ. Nutrition and cancer : prevention and survival. Br J Nutr. 2018;1–7.

20 Instituto Nacional do Cancer (BR). Estimativa 2016: Incidência de câncer no Brasil. Rio Janeiro. 2015.

21 Heetun A, Cutress RI, Copson ER. Early breast cancer: why does obesity affect prognosis? Proc Nutr Soc. 2018;(December 2017):1–13.

22 Yaw YH, Shariff ZM, Kandiah M, Mun CY, Yusof RM, Othman Z, et al. Weight changes and lifestyle behaviors in women after breast cancer diagnosis: a cross-sectional study. BMC Public Health [Internet]. 2011 [cited 2018 May 7]; 11(1):309. Available from: http://www.biomedcentral.com/1471-2458/11/309

23 Dieli-Conwright CM, Parmentier J-H, Sami N, Lee K, Spicer D, Mack WJ, et al. Adipose tissue inflammation in breast cancer survivors: effects of a 16-week combined aerobic and resistance exercise training intervention. Breast Cancer Res Treat [Internet]. 2018 Feb [cited 2018 May7]; 168(1):147–57. Available from: http://link.springer.com/10.1007/s10549-017-4576-y

24 Shachar SS, Deal AM, Weinberg M, Williams GR, Nyrop KA, Popuri K, et al. Body Composition as a Predictor of Toxicity in Patients Receiving Anthracycline and Taxane Based Chemotherapy for Early Stage Breast Cancer. Clin Cancer Res. 2017;23(14):3537-43.

25 Pérez Camargo DA, Allende Pérez SR, Rivera Franco MM, Álvarez Licona NE, Urbalejo Ceniceros VI, Figueroa Baldenegro LE. Phase Angle of Bioelectrical Impedance Analysis as Prognostic Factor in Palliative Care Patients at the National Cancer Institute in Mexico. Nutr Cancer. 2017;69(4):601–6.

26 Dicato M, Plawny L, Diederich M. Anemia in cancer. Ann Oncol Off J Eur Soc Med Oncol / ESMO. 2010;21(Supplement 7):167-72.

27 Gilreath JA, Stenehjem DD, Rodgers GM. Diagnosis and treatment of cancer-related anemia. Am J Hematol. 2014;89(2):203-12.

28 Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clin Nutr [Internet]. 2008 Dec [cited 2018 Mar 7]; 27(6):793–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18718696

29 Madeddu C, Gramignano G, Astara G, Demontis R, Sanna E, Atzeni V, et al. Pathogenesis and treatment options of cancer related anemia: perspective for a targeted mechanism-based approach. Front Physiol. 2018;9(SEP):1–20.

30 Dieli-Conwright CM, Lee K, Kiwata JL. Reducing the Risk of Breast Cancer Recurrence: an Evaluation of the Effects and Mechanisms of Diet and Exercise. Curr Breast Cancer Rep. 2016;8(3):139–50.

31 Petekkaya I, Aksoy S, Roach EC, Okoh AK, Gecmez G, Gezgen G, et al. Impact of inflammatory markers on the prognosis of patients with operable breast cancer. J BUON. 2014;19(3):673–80.

32 Paixão EMDS, Oliveira ACDM, Pizato N, Muniz-Junqueira MI, Magalhães KG, Nakano EY, et al. The effects of EPA and DHA enriched fish oil on nutritional and immunological markers of treatment naïve breast cancer patients: A randomized double-blind controlled trial. Nutr J. 2017;16(1):1–11.

33 Khan S, Shukla S, Sinha S, Meeran SM. Role of adipokines and cytokines in obesity-associated breast cancer: Therapeutic targets. Cytokine Growth Factor Rev [Internet]. 2013 [cited 2018 May 7]; 24(6):503–13. Available from: http://dx.doi.org/10.1016/j.cytogfr.2013.10.001

34 Jiang T, Zhou C, Ren S. Role of IL-2 in cancer immunotherapy. Oncoimmunology [Internet]. 2016 [cited 2018 May7]; 5(6):1–10. Available from: http://dx.doi.org/10.1080/2162402X.2016.1163462

35 Turbitt WJ, Black AJ, Collins SD, Meng H, Xu H, Washington S, et al. Fish Oil Enhances T Cell Function and Tumor Infiltration and Is Correlated with a Cancer Prevention Effect in HER-2/neu but Not PyMT Transgenic Mice. Nutr Cancer. 2015;67(6):965–75.

36 Mocellin MC, Camargo CQ, Nunes EA, Fiates GMR, Trindade EBSM. A systematic review and meta-analysis of the n-3 polyunsaturated fatty acids effects on inflammatory markers in colorectal cancer. Clin Nutr. 2016;35(2):359–69.

37 Mao M, Wei X, Sheng H, Chi P, Liu Y, Huang X, et al. C-reactive protein/albumin and neutrophil/lymphocyte ratios and their combination predict overall survival in patients with gastric cancer. Oncol Lett. 2017;14(6):7417–24.

38 Xu H, Ma Y, Deng F, Ju W, Sun X, Wang H. The prognostic value of C-reactive protein / albumin ratio in human malignancies : an updated meta- analysis. Onco Targets Ther. 2017;10:3059-70.

39 Mocellin MC, Pastore e Silva JDA, Camargo CDQ, Fabre MEDS, Gevaerd S, Naliwaiko K, et al. Fish oil decreases C-reactive protein/albumin ratio improving nutritional prognosis and plasma fatty acid profile in colorectal cancer patients. Lipids. 2013;48(9):879–88.

40 Silva JDAP, Trindade EBSDM, Fabre MEDS, Menegotto VM, Gevaerd S, Buss ZDS, et al. Fish Oil Supplement Alters Markers of Inflammatory and Nutritional Status in Colorectal Cancer Patients. Nutr Cancer. 2012;64(2):267–73.

41 Abdelmagid SA, MacKinnon JL, Janssen SM, Ma DWL. Role of n-3 Polyunsaturated Fatty Acids and Exercise in Breast Cancer Prevention: Identifying Common Targets. Nutr Metab Insights [Internet]. 2016 [cited 2018 May 7]; 9:71–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27812288%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5089819

Recebido em: 28 fev. 2019

Aceito em: 27 maio 2019