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Potential usefulness of an EPA-enriched nutritional supplement on chemotherapy tolerability in cancer patients without overt malnutrition

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Abstract

**Objectives:** To assess the effect of an intervention with an Eicosapentaenoic Acid-enriched oral nutritional supplement on chemotherapy tolerability in patients with advanced colorectal cancer.

**Methods:** Thirteen patients diagnosed with stage IV colorectal cancer were included. Patients in the experimental group received 2 packs of supplement per day during 12 weeks plus dietary counseling. The control group only received dietary counseling. Patients were assessed for nutritional status, dietary intake, health related quality of life (HRQOL) and chemotherapy compliance.

**Results:** Only patients in the supplemented group significantly increased their weight after the intervention. They also had better scores in important domains of HRQOL, compared to controls. Although not statistically significant, the supplemented group did not experience interruptions in their chemotherapy treatment compared to the control group, with more interruptions due to toxicity.

**Conclusions:** The present study, although limited by sample size, points out towards a positive effect of the intervention on chemotherapy tolerability.


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Key words: Colorectal Neoplasms. Eicosapentaenoic Acid. Nutritional Status. Antineoplastic Agents. Quality of Life.

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USO POTENCIAL DE UN SUPLEMENTO NUTRICIONAL ENRIQUECIDO EN EPA EN LA TOLERABILIDAD A LA QUIMIOTERAPIA EN PACIENTES CON CÁNCER SIN DESNUTRICIÓN MANIFIESTA

Resumen

**Objetivos:** Valorar el efecto de una intervención con un suplemento nutricional oral enriquecido en Ácido Eicosapentaenoico sobre la tolerabilidad a la quimioterapia en pacientes con cáncer colorectal avanzado.

**Métodos:** Se incluyeron 13 pacientes diagnosticados con cáncer colorectal en estadio IV. Los pacientes en el grupo experimental recibieron 2 briks de suplemento al día durante 12 semanas junto a consejo dietético. El grupo control solo recibió consejo dietético. Se valoró el estado nutricional, ingesta dietética, calidad de vida relacionada con la salud (CVRS) y el cumplimiento de la quimioterapia de los pacientes.

**Resultados:** Solo los pacientes en el grupo suplementado incrementaron su peso significativamente tras la intervención. También obtuvieron mejores puntuaciones en importantes dominios de la CVRS, comparado con los controles. Aunque no de forma estadísticamente significativa, la mayor parte de los pacientes en el grupo suplementado no experimentaron interrupciones en el tratamiento de quimioterapia comparado con el grupo control, con más interrupciones debidas a toxicidad.

**Conclusiones:** El presente estudio, aunque limitado por el tamaño muestral, apunta hacia un efecto positivo de la intervención sobre la tolerabilidad a la quimioterapia.


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Abreviaturas

HRQOL: Health related quality of life.
EPA: Eicosapentaenoic Acid.
DHA: Docosahexaenoic Acid.
EPA-ONS: EPA-enriched oral nutritional supplement.
CRC: Colorectal cancer.
SGA: Subjective Global Assessment.
GHS/QoL: Global health status/quality of life.

Introduction

In cancer, there is a narrow relationship between malnutrition and the pathology itself. Undernourished individuals are likely to report decreased health related quality of life (HRQOL), decreased levels of physical performance, and to present increased risks of treatment failure and side-effects, in addition to a higher mortality rate. Nowadays, we know about the potential benefits of a good nutritional status on some of these outcomes. However, less is known about the effect of nutritional support on chemotherapy tolerability. It has been documented that patients with weight loss receive lower doses of chemotherapy; nevertheless, they can develop even more toxicity to the treatment, which translates into poorer outcomes. It is assumed that a good nutritional status improves chemotherapy tolerability, but there is only scarce experimental evidence showing how feeding can modify, in some way, the toxicity and response to chemotherapy.

The ω-3 polyunsaturated fatty acids, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have shown to interfere with the action of proinflammatory cytokines, suppressing proteolysis and lipolysis, and improving appetite, leading to an attenuation of weight loss. The lack of solid evidence in this field raises the question whether seeking the maximum effect of nutritional support with an EPA-enriched oral nutritional supplement (EPA-ONS) would help chemotherapy tolerability in non-malnourished cancer patients.

Therefore, the aim of the present study was to assess the effect of an intervention with an EPA-ONS on chemotherapy tolerability in patients with advanced colorectal cancer (CRC).

Methods

Patients

In this prospective, randomized, controlled, open-label pilot study, we enrolled patients over 18 years of age with diagnosis of stage IV CRC that were going to receive first line chemotherapy treatment in the oncology outpatient clinic. Patients were excluded if they had severe malnutrition according to the classification of the Subjective Global Assessment (SGA); Body Mass Index below 16.5 or over 30; antecedents of other malignant tumors with the exception of basocellular epithelioma; or taking drugs that affected the metabolism (e.g., anabolic steroids, orexigenics), among other criteria.

Study design

Patients were randomized by blocks of 10 subjects; those allocated in the experimental group were asked to consume 2 packs per day of a commercially available formula enriched in fish oil for a 12 week period. Each 240 ml pack provided 295 Kcal, 16 g protein, 6.1 g fat with 1 g of EPA and was enriched in antioxidants (Prosure®, Abbott Laboratories). Supplement compliance was assessed based on the annotations of patients in a diary that were matched with computer records of delivered supplements. The minimum dosage considered acceptable was 28 packs each month. Besides the nutritional supplement, patients were given specific dietary counseling by a dietitian, aimed to treat food related chemotherapy side effects (e.g.: anorexia, mucositis…) and to improve dietary intake. Handouts with the same information were offered to patients and counseling was reinforced in each visit. Patients allocated in the control group were given the same dietary counseling and materials as the experimental group, but did not receive the supplement. Patients were withdrawn if they developed malnutrition, in order to receive the required nutritional support.

Nutritional, laboratory and dietary assessment

At baseline, height, pre-illness stable weight and weight loss were obtained. Patients were assessed for edema presence. All subjects underwent venous blood sampling for every visit to obtain routine biochemical and hematological parameters. There were monthly follow-up visits during the 12 weeks, where patients were weighed, blood samples were obtained, and SGA was performed. Dietary intake was assessed with food diaries 4 days previous to chemotherapy series, plus 4 days after the first day of chemotherapy. Patients were instructed by a dietitian on how to record food and beverage intake. Mean total energy and protein intakes were calculated using the software Dietsource 3.0 (Cath Soft, Spain). Total dietary intake was calculated by adding supplement consumption to spontaneous food intake.

Chemotherapy tolerability assessment

Chemotherapy tolerability, the primary endpoint, was assessed using the variation of changes in HRQOL, which was measured at baseline and week 12 using the 30-item questionnaire EORTC QLQ-C30 version 3.0. It is composed of five multi-item functional scales, one global health status/quality of life (GHS/QoL) scale, three multi-item symptom scales and six single items assessing different symptoms.
Higher scores on the functional scales indicate better functioning/quality of life, whereas higher scores on the symptom scales and single items denote more severe symptoms. Differences between HRQOL mean scores of groups over 10 points on the 0-100 range of the questionnaire scoring system, are considered as “clinically meaningful”\(^1\). Chemotherapy side effects in relation with food intake were also recorded. At the end of the study, information about reduction, delay or interruption of chemotherapy treatment, and its causes, were obtained from chemotherapy records.

**Statistical analysis**

The analysis was conducted using SPSS 14.0 (SPSS Inc., USA). Study groups were assessed for comparability. For continuous variables, changes were analyzed using Mann-Whitney U test or Wilcoxon signed-rank test, as appropriate. Categorical variables were analyzed using Fisher’s exact test. For all statistics, significance was accepted at the 5% probability level. This study was approved by the Ethical Committee of Clinical Research of the Hospital Clínic de Barcelona and informed written consent was obtained from all participants.

**Results**

**Patient characteristics**

From December 2005 to June 2007 a total of 24 patients were found fulfilling enrolment criteria, 13 (54.17%) agreed to participate in the study, and 5 in the experimental group and 6 in the control group completed the intervention period. All patients in the experimental group fulfilled the minimum requirements regarding supplementation compliance, with a mean dose of 1.6 packs per day (1.6 g EPA).

Tumor location was as follows: sigmoid colon 6 (46.2%) patients, rectum 5 (38.5%) patients and transverse colon 2 (15.4%) patients. Metastases were located in the following organs: liver 9 patients, liver and lung 2 patients, lung 1 patient, ovary and peritoneum 1 patient. Chemotherapy regimes administered were: 5-Fluorouracil + Oxaliplatin + Folinic acid in 8 (61.5%) patients and Capecitabine in 5 (38.5%) patients. Both groups were comparable at baseline as seen in table I.

<table>
<thead>
<tr>
<th>Table I</th>
<th>Baseline characteristics of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group</td>
</tr>
<tr>
<td>Sex (male: female)</td>
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</tr>
<tr>
<td>Age</td>
<td>61.5±15.8</td>
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<tr>
<td>Body weight (kg)</td>
<td>69.9±15.9</td>
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<tr>
<td>BMI</td>
<td>25.8±4.3</td>
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<tr>
<td>% weight loss</td>
<td>8.1±6.9</td>
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<tr>
<td>QLQ-C30 GHS/QoL</td>
<td>61</td>
</tr>
<tr>
<td>QLQ-C30 Physical</td>
<td>80</td>
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<tr>
<td>QLQ-C30 Role</td>
<td>61</td>
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<tr>
<td>QLQ-C30 Social</td>
<td>67</td>
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<tr>
<td>QLQ-C30 Fatigue</td>
<td>37</td>
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<tr>
<td>QLQ-C30 Pain</td>
<td>8</td>
</tr>
<tr>
<td>QLQ-C30 Appetite</td>
<td>33</td>
</tr>
<tr>
<td>Chemotherapy (Folfox: Capecit.)</td>
<td>4:2</td>
</tr>
<tr>
<td>SGA (Good: Risk)</td>
<td>4:2</td>
</tr>
</tbody>
</table>

**Nutritional, laboratory and dietary assessment**

After 12 weeks of intervention, the supplemented group presented a statistically significant weight gain, compared to controls (4.94 vs -1.17; p=0.045).

Laboratory assessment showed that parameters were always inside normal ranges in both groups (data not shown). Plasma proteins, total cholesterol and other routine parameters did not change significantly. No variations in the SGA were found either.

Only the supplemented group reached energy and protein requirements, previous and after chemotherapy cycles, consuming on average 312 kcal and 18 grams of protein more than patients only receiving dietary counseling, although there were no statistical significant differences between groups.

**Quality of life assessment and chemotherapy tolerability**

Among the different domains of HRQOL (fig. 1), we did not find significant differences in the GHS/QoL scale between treatment and control groups (3.33 vs -6.94; p=ns). Although both groups decreased their physical function (-4 vs -15.56; p=ns), only the control group had a worsening over 10 points, considered clinically meaningful. For role function, the supplemented group experienced an improvement in this domain (13.33 vs 2.78; p=ns). The social function scale was positively affected by the experimental intervention,
with statistical significant differences between groups (16.67 vs -13.89; p=0.038). Changes over 10 points were also found in some symptoms, with the control group experiencing more fatigue (-4.44 vs 11.11; p=ns) and pain (-10 vs 2.78; p=ns). Unexpectedly, the loss of appetite worsened in the supplemented group (6.67 vs -16.67; p=ns). We did not find any clinical or statistical significant differences in the rest of scales or single items. The assessment of food related chemotherapy side effects did not show any differences between groups (data not shown).

As for chemotherapy compliance, although no significant differences were found, we observed that none of the 5 patients in the intervention group had to delay or stop their chemotherapy series during the intervention period, whereas 4 of 6 patients in the control group experienced some sort of interruption in their treatment due to toxicity.

Discussion

The present study, although limited by the small sample size, points out towards an improvement in weight gain and some important domains of HRQOL in advanced CRC patients taking an EPA-ONS, plus dietary counseling. The significant difference in the evolution of weight between both groups after the 12 weeks of intervention, matches results from studies with cancer patients treated with an EPA-ONS

It is a known issue that the intake patterns of cancer patients may lead to low energy and protein intakes, both in ambulatory and, as we have studied, hospitalized patients. In our study design, we tried to seek the maximum effect of nutritional support comparing an EPA-ONS plus dietary counseling versus dietary counseling alone, which, the latter, constitutes the standard treatment for non weight-losing cancer patients in our hospital. It is important to note that although both groups received the same dietary counseling, only the experimental group fulfilled energy and protein requirements. Significant increases in protein and energy intake have been previously reported without decline in meal protein and energy intake with the administration of an EPA-ONS

Although previous studies have found improvements in plasma proteins, after consumption of an EPA-ONS, in our study, these were always inside normal ranges, which could explain the lack of differences. Besides, variations within limits of normality have little clinical relevance.

As an indirect sign of chemotherapy tolerability, the supplemented group showed a general improvement in HRQOL compared to the control group. Although, globally, we did not find statistically significant differences in most of the scales and single items, there were some important clinically meaningful differences. Other studies have also reported improvements in the overall well-being and HRQOL of advanced cancer patients treated with EPA. In our study, we observed better scores for the supplemented group in the physical, role and social domains, and also fatigue and pain, compared to the control group. Our findings are paralleled by those of Moses et al., where the intake of an EPA-ONS correlated positively with physical function and HRQOL. Although we could not observe significant differences in the GHS/QoL scale, we believe that better scores in scales such as physical and social function, and the symptom fatigue, may reflect an improved HRQOL. This seems backed up by Kopp et al., who have suggested that physical function and fatigue may be more sensitive than GHS/QoL to detect differences in treatment effects.

Regarding chemotherapy compliance, the supplemented group showed a better compliance without...
reaching statistical significance, probably due to lack of statistical power. We believe that this could also be an indirect indicator on better tolerability. Preliminary studies suggest that EPA and DHA could increase the efficacy of antineoplastic drugs while decreasing toxicity to the host. One of the potential limitations in our study could be supplement compliance, with a mean daily intake of 1.6 g of EPA. Nowadays it is still considered that there is insufficient data to define the optimal dose of EPA to have a therapeutic effect. Clearly, the main limitation of our study is related to the small number of patients included, falling short of the intended number. Important problems with the recruitment compelled us to terminate the study. Although a specifically homogeneous group of patients were studied and the results of statistical analyses gave comparable groups, the reduced sample size clearly lowers the study power for associations. A bias due to an open-label design could be present too, but the type of interventions used made impossible the blinding of groups and researchers.

Although our study could not demonstrate strong differences between groups, the intervention with an EPA-ONS plus dietary counseling seemed to exert a positive effect on weight maintenance, HRQOL and chemotherapy tolerability in advanced CRC patients. We release these inconclusive but interesting results, in the hope that other research groups can conduct larger randomized controlled trials to evaluate the effects of an EPA-ONS in improving nutritional status and chemotherapy tolerability in cancer patients.

References
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