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Nutrition intervention using an eicosapentaenoic acid (EPA)-containing supplement in patients with advanced colorectal cancer. Effects on nutritional and inflammatory status: a phase II trial

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Abstract *Goals:* The aim of the study was to assess the impact of an eicosapentanoic acid-containing protein and energy dense oral nutritional supplement (EPA-ONS) on nutritional and inflammatory status, quality of life (QOL), plasma phospholipids (PPL) and cytokine profile, tolerance of irinotecan-containing chemotherapy and EPA-ONS in patients with advanced colorectal cancer (CRC) receiving chemotherapy. *Materials and methods:* Patients with advanced CRC having one prior chemotherapy regimen received 480 ml of EPA-ONS daily for 3 weeks before commencing chemotherapy with folinic acid, 5-fluorouracil, irinotecan (FOLFIRI), and continued for 3 cycles of treatment (9 weeks). All assessments including weight, body composition, C-reactive protein (CRP), QOL, dietary intake, PPL and cytokine analyses were performed at baseline, 3 and 9 weeks. *Results:* Twenty-three patients were enrolled, 20 completed 3 weeks, and 15 completed 9 weeks. The mean EPA-ONS intake was 1.7 tetrapaks (408 ml) daily. There was a significant increase in mean weight (2.5 kg) at 3 weeks (p=0.03). Lean body mass (LBM) was maintained. Protein and energy intake significantly decreased after the commencement of chemotherapy (protein p=0.003, energy p=0.02). There was a significant increase in energy levels (p=0.03), whilst all other QOL measures were maintained. PPL EPA levels increased significantly over the first 3 weeks. Mean CRP increased by 14.9 mg/L over the first 3 weeks (p=0.004), but decreased to baseline levels by the end of the trial. There was a significant correlation between plasma IL-6 and IL-10 concentrations and survival, and between IL-12 and toxicity. *Conclusion:* Dietary counseling and the provision of EPA-ONS may result in maintenance of nutritional status and QOL, however randomized trials are required to evaluate the impact of EPA on toxicity from chemotherapy.

Keywords Nutritional status · EPA · CRP · Chemotherapy · Toxicity · Colorectal cancer

Introduction

Malnutrition in cancer patients is multi-factorial and often goes unrecognized by treating physicians. A pro-inflammatory state, present in advanced cancer patients, is readily identified by elevations in acute phase proteins (APP) such as C-reactive protein (CRP) and α-1 acid glycoprotein (α-1AGP). Furthermore, elevated CRP can predict poorer survival in patients with colorectal cancer (CRC) [1, 2].

Cancer cachexia in CRC has not been well-defined. Resting energy expenditure is a possible mechanism for cancer cachexia, but is elevated in some cancer patients but

not others [3]. Hypermetabolism varies amongst malnourished CRC patients, and appears to be associated with tumour site and duration of disease [4].

A study in CRC showed nutritional counseling by suitably qualified dietitians produced significant improvements in nutritional status and quality of life (QOL) [5]. It remains unclear however, whether the use of standard high protein and energy supplements improves cancer treatment outcomes such as response to treatment, time to progression or survival [6, 7].

The use of eicosapentanoic acid-containing protein and energy dense oral nutritional supplement (EPA-ONS) was shown to reduce weight loss, increase lean body mass (LBM), improve functional capacity, nutritional status and QOL, however not to any greater degree than conventional supplements [8–11]. A post hoc analysis by Fearon et al. suggested that if taken in sufficient quantity, greater improvements could be achieved with the EPA containing supplement [10].

EPA is also an anti-inflammatory agent, which stabilizes the APP response, as measured by CRP, in patients with advanced pancreatic cancer [12]. Interleukin-6 (IL-6), a potent pro-inflammatory cytokine is involved in inducing the APPR [13]. Studies in the non-cancer population show that consumption of long-chain n-3 fatty acids leads to reductions in CRP and IL-6 [14–16].

Preventing and treating the toxicities of chemotherapy remains a major challenge for cancer physicians. Irinotecan (CPT-11) may produce life-threatening toxicities in patients with CRC, especially the combination of neutropenia and diarrhoea resulting in treatment delays, dose reduction, and protracted hospitalization for symptom management. Animal studies demonstrate that the consumption of long-chain n-3 fatty acids can improve the therapeutic index of irinotecan [17, 18]. However, no corroborative clinical data are available.

The aim of the current study was to assess the effects of nutritional counseling and provision of an EPA-ONS on nutritional status, body composition, QOL, plasma phospholipids (PPL), CRP, cytokines, and chemotherapy toxicity in patients with advanced CRC receiving irinotecan.

Materials and methods

Patients with histologically confirmed diagnosis of stage IV CRC were eligible for study recruitment. Other eligibility criteria included: WHO performance status of 0–2; no chemotherapy in the previous 4 weeks, no surgery for the past 2 weeks; body mass index <35 kg/m^2; adequate haematological, renal and hepatic status; bi-dimensionally measurable disease; and estimated life-span >3 months. Patients who could have a 3-week delay in administering cytotoxic chemotherapy without impacting disease progression were selected for the trial.

Patients were excluded if they had: previously received irinotecan; pre-existing intestinal disease; psychiatric disorders; oedema; dehydration; or were unable to take an oral intake. The ethics committee for human research at the participating centres approved the protocol and written informed consent was obtained from all participants.

The trial was an open label phase II study conducted between August 2002 and January 2005 at the Royal Prince Alfred and Concord Hospitals, Sydney, Australia. Patients were instructed to consume, in addition to their regular diet, 2 tetrapaks (480 ml) per day of an EPA-ONS (ProSure™, Abbott Laboratories, provided by Abbott Australasia, 300 kCal (1268 kJ), 16 g protein, 1.09 g of EPA and 0.46 g of DHA/240 ml tetrapak) for 9 weeks.

Chemotherapy commenced at week 4 and was repeated every 2 weeks. Nutritional status, weight, LBM and QOL were measured at baseline, and at the end of weeks 3 and 9. The patients were assessed for weight, using a spring balance scale. Height and weight histories were recorded. Nutritional status was measured using the patient generated subjective global assessment (PGSGA) (A=well-nourished, B=suspected of malnutrition, C=malnourished). A score of 4–8 requires intervention by a dietitian, whilst a score >9 indicates a critical need for symptom management/nutrition intervention. Body composition was assessed using a single frequency (50 kHz) four-terminal bio-impedance meter (BIM-4, SEAC Pty Ltd, UniQuest, St Lucia, Queensland, Australia). Fat-free mass (FFM), fat mass (FM) and total body water (TBW) were calculated according to the Lukaski algorithm [19], and FFM was used as the measure of LBM.

The disease and treatment assessment (DATA) form, a simple, valid multi-item QOL tool, was used to assess QOL [Nowak et al., unpublished report, 20]. Measurements included fatigue, appetite, nausea, vomiting, diarrhoea, energy level, physical and overall well-being.

A dietitian instructed patients on how to complete a 3-day food diary at week 1, end of weeks 3 and 9 (coinciding with the first and fourth cycles of chemotherapy). The total energy and protein intake was calculated using FoodWorks professional edition 3.02. Patients were advised to take the EPA-ONS and maintain a high intake of dietary n-3 fatty acids. Compliance to EPA-ONS intake was evaluated by patient self-report and PPL levels measured at baseline, 3 and 9 weeks. Symptoms associated with taking the EPA-ONS were recorded.

PPL (EPA, DHA, and arachidonic acid) samples were analyzed at weeks 3 and 9, using standard methods [21, 22]. The cytokines were analyzed using the LuminexR 100™ [23], and included interleukins (IL) 1β, 2, 4, 5, 6, 8, 10, 12, eotaxin, granulocyte macrophage-colony stimulating factor (GM-CSF), and RANTES (a beta-chemokine). Standard non-haematological and haematological toxicities were graded according to NCICTC-version 2 during the first 6 weeks of treatment. Response, chemotherapy dose reductions and survival were also recorded. The toxicities

Table 1 Baseline characteristics of 23 patients with advanced colorectal cancer

Patient characteristics	
Age (median±SD) years	61±11.6
Gender	
Male	15
Female	8
Previous surgery and chemotherapy	17
Previous chemotherapy and radiotherapy	1
Previous surgery alone	2
Previous surgery, radiotherapy and chemotherapy	3
Nutritional status (SGA)	
SGA-A	11 (48%)
SGA-B	11 (48%)
SGA-C	1 (4%)
PG-SGA score (mean±SD)	7.5±6.4
Mean weight (kg, mean±SD)	75.9±17.0
Weight loss in previous 6 months (%, mean±SD)	0±5.3
Mean BMI (kg/m^2, mean±SD)	28±6.4

were rated as nil (CTC grade=0), mild (CTC grade=1 or 2) or significant (CTC grade >2). The aim of this Phase I/II prospective study was to gain experience with the tolerance, safety and efficacy of a combination regimen for the treatment of advanced CRC patients receiving FOLFIRI, and to determine appropriate end points, sample size and power for a potential randomised trial. As this was an estimation and feasibility protocol rather than a hypothesis testing protocol, a formal power analysis was not conducted.

Statistical analysis was conducted on intent to treat basis using SPSS version 11.5. For continuous variables, changes were calculated as end of week 3 minus baseline, end of week 9 minus baseline and end of week 9 minus end of week 3. The non-parametric Wilcoxon signed ranks test was performed to determine changes in nutritional status, inflammatory status, cytokines and quality of life parameters. Statistical significance was reported at $p<0.05$. Pearson's correlations were performed between cytokine levels at baseline and survival, chemotherapy toxicity and various nutritional and inflammatory markers.

Results

Table 1 describes the baseline characteristics of the patients ($n=23$) enrolled into the study. Of these, 20 patients completed 3 weeks and 15 continued to take the EPA-ONS until the end of the study period. Eighteen patients completed 3 chemotherapy cycles, including 15 patients who continued to take the EPA-ONS. Three patients ceased taking the EPA-ONS due to intolerance ($n=2$) and disease progression ($n=1$). In total, seven patients had a chemotherapy dose reduction. The average intake of the EPA-ONS at the end of trial was 1.7 tetrapaks (408 ml).

Reasons for patient withdrawal included intolerance to the EPA-ONS ($n=2$), disease progression ($n=4$), admission to hospital with head injury ($n=1$), and severe toxicity to chemotherapy ($n=1$).

Of the 23 patients that commenced the trial, 16 tolerated the EPA-ONS well. Of the remaining patients, 1 experienced loss of appetite, 1 stomach distension, 1 nausea, 2 vomiting, and 2 disliked the taste of the supplement.

According to the PGSGA, 12 (52%) patients presented with a degree of malnutrition and were classified in the B or C category using the PGSGA, whilst 11 (48%) patients had no significant weight loss and were classified as well-nourished. A mean PGSGA score of 7.5 was recorded at baseline.

Table 2 shows the effects of the 9 weeks of nutrition intervention. Mean weight increased by 2.5 kg from baseline to the end of week 3 ($p=0.03$) and remained stable during the chemotherapy phase of the study. No significant changes were noted in LBM or PGSGA scores.

CRP increased significantly between baseline and week 3 ($p=0.004$), however it decreased significantly to baseline levels during chemotherapy between weeks 3 and 9 ($p=0.02$). When analyzed separately, the same significant changes were seen for the patients that continued to take the supplement (>1.5 tetrapaks) for the duration of the study.

Table 2 Mean values (SD) for nutritional, inflammatory markers

	Baseline $n=23$	End of week 3 $n=20$	End of week 9 $n=15$	p value
Weight (kg)	75.9 (17.0)	78.4 (17.5)	78.4 (17.4)	0.03
CRP (mg/L)	18.2 (13.9)	33.1 (32.6)	19.4 (17.7)	0.004* 0.02$^{\#}$
Lean body mass (kg)	50.3 (10.7)	51.4 (10.2)	51.7 (10.6)	NS
Nutritional status (SGA)	A=11 B=11 C=1	A=14 B=6 C=0	A=11 B=5 C=0	–
Nutritional status (PGSGA score)	7 (6.3)	7 (4.5)	7 (4.8)	NS

Significant difference in weight was seen between baseline and end of week 3 ($p=0.03$). Significant difference in CRP was seen between baseline and end of week 3 ($p=0.004$)* and between end of week 3 and end of week 9 ($p=0.02$)$^{\#}$.

Table 3 Mean values (SD) for energy and protein intake at 3 time points

	Week 1 $n=19$	End of week 3 $n=16$	End of week 9 $n=12$	p value
Total kJ intake (kJ/kg/day)	132 (38.1)	108 (40.8)	125 (47.7)	0.02
Total protein intake (g/kg/day)	1.6 (0.5)	1.2 (0.5)	1.4 (0.6)	0.003[a] 0.03[b]
Meal protein intake (g/day)	118 (25.4)	96 (33.7)	101 (31.0)	0.01[§] 0.02[μ]
Meal energy intake (kJ/day)	9,930 (2,333)	8,459 (3,285)	9,487 (2,512)	0.04

Significant differences in total kJ intake were seen between week 1 and end of week 3.
[a]Significant difference in total protein intake seen between week 1 and end of week 3.
[b]Significant difference in total protein intake seen between week 1 and end of week 9.
Significant difference in meal protein intake seen between week 1 and end of week 3 ($p=0.01$)[§], and between week 1 and end of week 9 ($p=0.04$)[μ].
Significant difference in meal energy intake seen between week 1 and end of week 3 ($p=0.04$).

Table 3 shows the change in protein and energy intake during the study. Some of the patients were unable to complete food records sufficiently to be included within the analysis. There was a significant decrease in both total and meal energy ($p=0.02$, $p=0.04$) and protein ($p=0.003$, $p=0.01$) intake when comparing the first week of taking the supplement and week 4, when chemotherapy commenced. Total and meal energy intake improved by the end of the study with no significant change from baseline levels. By the end of the study, although total and meal protein intake improved compared to end of week 3, the change remained below baseline levels ($p=0.03$, $p=0.04$).

Energy levels increased between end of weeks 3 and 9 ($p=0.03$), but all other QOL measures were maintained. The QOL for overall well-being showed a trend towards improvement during the full course of therapy ($p=0.05$) (Table 4).

Patients' dietary intake of n-3 fatty acids increased at week 3, coinciding with the commencement of the EPA-ONS ($p<0.05$) and was maintained through to week 9. No significant change in n-6 fatty acid intake was seen (Table 5).

Of patients who complied with taking the EPA-ONS ($n=15$), only 2 patients (13%) experienced grade 3 diarrhoea. Of those that were non-compliant and continued with chemotherapy ($n=5$), 2 patients (40%) had grade 3 diarrhoea and 1 patient (20%) experienced grade 4 neutropenia and leucopenia.

PPL fatty acids are expressed as change from baseline to weeks 3 and 9 (median, ± range). EPA levels significantly increased over the study period from 0.53% (0–3.62%) to 5.3% (0.3–7.4%) at the end of week 3 remaining high at 4.8% (1.6–7.1%) by the end of week 9 ($p=0.002$). Similarly, DHA increased significantly from 2.6% (1.0–7.9%) to 7.04% (1.5–8.6%) between baseline and the end of week 3 ($p=0.005$). This remained high with a recording of 6.8% (1.6–9.2%) at the end of week 9. Arachidonic acid decreased from a baseline of 7.7% (1.3–12.7%) to 7.2% (0.7–9.4%) at week 3 ($p=0.06$), and was similar at the end of week 9.

Only 3 of the 16 recorded cytokines changed in a statistically significant manner during the trial. Eotaxin, one of the inflammatory and immunoregulatory cytokines, increased from a median of 185 to 204 at week 3 ($p=0.03$) with no further increase at week 9. The median GM-CSF decreased significantly from a median of 16.5 to 7.4 at week 3 ($p=0.028$) and then increased to 11.1 by week 9 ($p=0.03$). RANTES also increased from 15,390 to 16,300 at week 3 ($p=0.04$). A significant correlation was seen between survival and median values at baseline for IL-10

Table 4 Mean values (SD) for quality of life measures

	Baseline $n=23$	End of week 3 $n=20$	End of week 9 $n=16$	p value
QOL–appetite	6 (2.2)	6 (2.2)	6 (2.5)	NS
QOL–fatigue	4 (2.0)	4 (2.3)	4 (2.7)	NS
QOL–diarrhoea	1 (1.9)	1 (1.7)	2 (2.4)	NS
QOL–energy	5 (2.0)	5 (1.7)	6 (2.4)	0.03
QOL–physical well-being	6 (2.4)	6 (1.7)	7 (1.7)	NS
QOL–overall well-being	7 (2.2)	7 (1.7)	8 (1.7)	0.05

For fatigue and diarrhoea 0=no trouble at all, 10=worst I can imagine
For appetite, energy, physical well-being and overall well-being 10=best possible, 0=worst possible
A significant improvement in mean QOL scores for energy was seen between end of week 3 and end of week 9 ($p=0.03$). An improvement (not significant) was seen in QOL mean scores for overall well-being between end of week 3 and end of week 9 ($p=0.05$)

Table 5 n-3/n-6 intake from diet—mean values (SD)

	Baseline $n=22$	End of week 3 $n=17$	End of week 9 $n=13$	p value
n-3 (g)	0.81 (0.4)	4.2 (1.1)	4.6 (1.2)	0.00* 0.03[#]
n-6 (g)	8.6 (6.1)	6.1 (3.2)	8.1 (3.6)	NS
n-6:n-3 ratio	10:1	1.4:1	1.9:1	

A significant difference in n-3 intake from the diet was seen between baseline and end of week 3 ($p=0.00$)*, and between end of week 3 and end of week 9 ($p=0.03$)[#]. n-3 and n-6 ratio shows a change between baseline and end of week 3 and end of week 9.

($p=0.03$, $r=0.488$) and IL-6 ($p=0.003$, $r=-0.63$) (Fig. 1), and between toxicity and IL-12 at baseline ($p=0.023$, $r=0.533$). There was a significant correlation between baseline CRP level and IL-6 ($p=0.004$, $r=0.609$).

Discussion

The purpose of this study was to assess the nutritional status, QOL, and toxicity of FOLFIRI in patients with advanced CRC taking EPA-ONS. The patients recruited into the study were not all weight-losing patients, although all had metastatic disease and had received prior chemotherapy. All previous studies looking at the effects of EPA supplementation in cancer patients have assessed the results in weight-losing patients. The results clearly demonstrate that patients were able to improve or maintain weight and LBM whilst taking the EPA-ONS in association with counseling from a suitably qualified dietitian. The mean PGSGA score of 7.5 at baseline suggests that colorectal cancer patients require nutritional intervention before commencing chemotherapy.

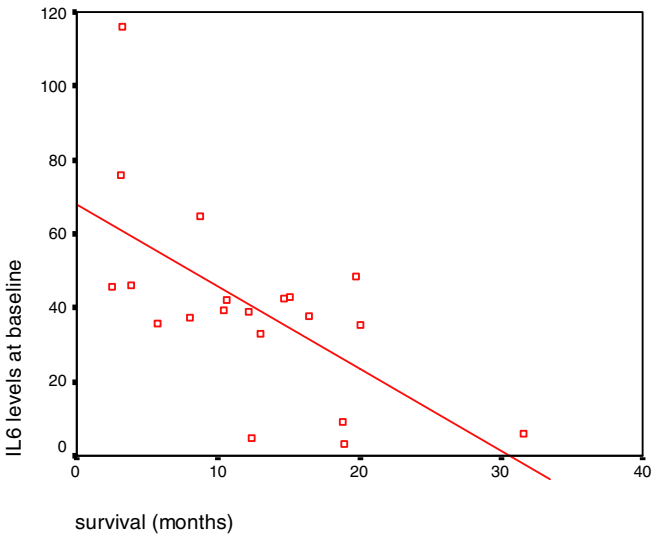

Fig. 1 Correlation between survival and IL-6 levels at baseline. A significant difference was seen between survival and baseline levels (median) of IL-6 ($p=0.003$, $r=-0.63$). The same could be seen for IL-10

Most weight-losing patients would have been ineligible for the trial because they typically had more rapidly progressive disease. The 3 week delay in administering the chemotherapy regimen was deemed essential as at least 3 weeks of supplementation is required to achieve incorporation of EPA [24]. A significant increase in dietary n-3 fatty acids was seen between baseline and week 3, associated with the commencement of the EPA-ONS.

The PPL EPA incorporation increased significantly after 3 weeks of EPA-ONS and was maintained throughout the study period. No significant change in PPL n-6 fatty acids was observed from baseline to week 9. This effect was attributed to the dietary advice provided by the experienced dietitian.

Diarrhoea occurs in 20–25% of patients receiving irinotecan for the treatment of CRC although it varies with the schedule of administration. Due to the small number of patients involved in the study, no firm conclusions can be made, however it was interesting to note that a greater percentage of patients who did not comply with taking the EPA-ONS, experienced CTC grade 3 diarrhoea compared to those who did comply. In addition, a greater percentage of the patients not taking the EPA-ONS experienced grade 3 fatigue compared to those who complied. Only 1 patient experienced grade 4 toxicity (including neutropenia and leukopenia), and this patient had opted not to continue the EPA-ONS. Randomized trials are required to confirm the impact of supplementation on toxicity from irinotecan.

Patients receiving chemotherapy often experience side effects including nausea, vomiting and loss of appetite, which preclude them from taking an adequate intake. Patients' intake decreased significantly, coinciding with first and fourth cycles of chemotherapy commencement at the end of weeks 3 and 9. This did not coincide with the mean increase of 2.5 kg during the first 3 weeks, as the food diaries were distributed to patients on the day their weight was recorded. Their dietary intake was recorded for the following 3 days, coinciding with the commencement of chemotherapy. Over time there was no significant change between both the total energy intake and the meal energy intake between baseline and the end of trial. This supports other observations that the use of EPA-ONS in cancer patients does not inhibit meal intake [25] and demonstrates the importance of using highly skilled

dietitians to counsel patients regularly to maintain dietary compliance.

Most of the patients tolerated the EPA-ONS well, and only 2 patients requested withdrawal due to an inability to drink the EPA-ONS. Individualized dietary counseling was shown to be effective in maintaining patients' nutritional status and reducing the severity of symptoms [5]. A dietitian specialized in treating patients with cancer provided regular counseling to these patients during the trial, whilst the oncology physician reinforced the importance of the EPA-ONS, which may be the reasons why only two patients withdrew due to EPA-ONS intolerance. There was little change in cytokines between the three different time points, except for eotaxin, GM-CSF and RANTES. These changes were not large, although statistically significant, and are unlikely to be clinically relevant.

The significant correlation found between IL-6 and survival, and IL-6 and CRP reflects the mediation of the acute phase response as previously reported [26]. Previous studies in healthy subjects have found an association between PPL long-chain n-3 fatty acids and lower levels of pro-inflammatory markers (IL-6, TNFα, IL-1 and CRP) [27], however no significant correlations were observed, possibly due to the small numbers within the trial.

Maintaining or improving patients' QOL is extremely important and was correlated with nutritional status in cancer patients [9, 28]. A poor nutritional status, particularly weight loss, was also correlated with shorter survival and poorer tolerance to chemotherapy treatment [29]. All the measures of QOL were either maintained or improved in this study, but again this requires evaluation in randomized trials.

In summary, dietary counseling by suitably qualified dietitians, and the provision of the EPA-ONS in patients with advanced CRC receiving FOLFIRI helps to maintain weight and possibly improve symptom control, nutritional status and QOL. This study demonstrates that with sufficient dietary counseling and support, good patient compliance can be achieved in trials of nutritional supplementation.

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