

Randomised Controlled Trial of Fish Oil Supplement to Treat Cancer Cachexia

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Abstract

Patients with advanced cancer often suffer from cachexia, a debilitating and complex extreme weight loss syndrome which is also associated with shorter survival times. A pragmatic randomised controlled trial was conducted to determine whether an oral nutritional supplement containing the omega-3 fatty acid eicosapentaenoic acid (EPA) was able to improve quality of life and survival times of patients with advanced solid tumour cancer in a mixed tumour cancer type population.

Keywords: Cancer; Cachexia; Eicosapentaenoic Acid (EPA); Survival.

Patients and Methods

Twenty-seven patients were randomly assigned to receive 2 cartons daily of either an EPA nutritional supplement or a matched supplement (without EPA) for a total period of 8 weeks. Gross weight, body composition, appetite, functional status and quality of life were assessed (baseline, 4 and 8 weeks) and survival data recorded. Factors regarding compliance, tolerability, as well as flavour and serving preferences were also assessed.

Results

Inadequate recruitment of suitable participants together with a deteriorating patient population resulted in inconclusive findings. However, there were interesting observations: Firstly, in either group, consuming between 1.5 and 2 cartons per day of a nutritional supplement (regardless of type) over a 4-week period, resulted in stabilisation of weight loss with a small, but statistically non-significant weight gain and secondly, patients in the EPA survived up to three times longer than those in the non-EPA arm.

Conclusion

Lessons learned from conducting this trial may provide guidance for further studies that are required to firmly establish whether there is a role for EPA nutritional for advanced cancer patients.

Introduction

Cachexia is a distressing syndrome of severe weight loss and is a common manifestation of advanced cancer. Cachexia is a major cause of mortality since cachexic patients usually have a shorter survival time compared to other terminally ill cancer patients [1, 2]. The definitive treatment of cancer is total removal of the causative tumour, but when this is not an option and survival of patients is limited, the focus of any intervention turns to the relief

of symptoms, including cachexia and improving the patient's quality of life.

Eicosapentaenoic acid (or EPA) is an omega-3 polyunsaturated fatty acid which has been associated with a number of reported benefits in patients with cancer including stabilising weight loss, reducing post-surgery infections and prolongation of survival [3]. It has been suggested that since cancer can result in a systemic inflammatory response EPA may have a role to play in both the modulation of pro-inflammatory cytokines production and the mechanisms underlying these effects [4].

The decision to conduct our randomised controlled trial followed the completion of a Cochrane systematic review [5] which revealed a paucity of well conducted randomised controlled trials (RCTs) to adequately determine whether EPA could improve clinical outcomes for advanced cancer patients. On an intention to treat basis, EPA two trials reported EPA as either no better than the control arm for patients with unresectable pancreatic cancer [6] or worse for patients with mixed tumour types where combining EPA with the appetite stimulate Megestrol (MA) resulted in a slight inhibitory effect of MA on the action of EPA so that it was less effective than EPA alone [7]. There was insufficient data to confirm the survival advantage seen in a small placebo randomised controlled study of 60 patients with generalised solid tumour cancer [8].

Patients And Methods

Full ethical approval was obtained prior to conducting a randomised single blind controlled trial over a period of 20 months closing at the end of March 2006. Recruitment of patients was actively sought

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through a number of sources: consultant oncologist, Macmillan nurses, palliative care consultant, other hospice staff, dieticians, specialist cancer nurses, general practitioners, and district and community nursing teams. Adults (over 18 years old, male or female) with advanced solid tumour cancer (with weight loss) were recruited in to the study if they had either a histological proven or a firm radiological or operative diagnosis of solid tumour cancer, defined as either recurrent or metastases or for whom no active curative treatment was planned. Patients were included only if they had a history of on-going weight loss (5% over previous 3 months or more). Concurrent palliative chemotherapy, radiotherapy or taking oral corticosteroids was permitted, but patients were excluded if they were already regularly taken one (or more) oral fish oil capsules/tablets, taking other appetite stimulants or if, at the time of enrolment, they had evidence of gross ascites, jaundice, pyrexia, severe anaemia or suffering acute infection. Patients were not excluded if they had ankle oedema.

Intervention: Patients were randomised to receive either an oral nutritional supplement containing EPA (Prosure™ supplied from Abbott Laboratories) or standard oral nutritional supplement not containing EPA (Ensure Plus™ supplied by Abbott Laboratories). Both Prosure™ and Ensure Plus™ supplements provided a milkshake type food supplement specifically designed for medical purposes, but there were some differences between the nutritional content of the two supplements. The Ensure Plus™ (without EPA) supplement offered more fat, calories and carbohydrate content than the Prosure™ (with EPA) supplement. In contrast, each carton of Prosure™ supplement contained more protein with the addition of fibre. It was decided to restrict the choices of both the nutritional supplements to two of the most popular flavours of Prosure™ (banana and vanilla flavours), but if patients expressed a flavour preference, arrangements were made for changeover of flavour choice to be supplied.

The decision to provide EPA combined with a protein and energy enriched oral nutritional supplement was based on previous research findings on patients with unresectable pancreatic cancer that suggested that combining EPA with an enriched nutritional supplement could result in weight gain rather than just weight stabilisation when 2 cartons are consumed daily to provide a suggested therapeutic dose of 2.1g EPA [9, 6]. Following an extensive search for a suitable EPA nutritional supplement, Prosure™ appeared to be the best available source at the time. Costs involved prohibited Abbott Laboratories' direct involvement to provide a blinded matched control. Ensure Plus™ was a pragmatic alternative choice since it was both the nearest matched control for nutritional content and, as part of local practice at the time, often recommended as the standard nutritional supplement by clinicians for cancer patients with weight loss. This was a single blind trial where only the statistician was blinded to the group allocation. However, details of the randomisation process were concealed from both the lead researcher and patient until after consent and full enrolment into the study.

Primary Outcome Measures: The primary outcome measures were changes in gross body weight and body composition. The same researcher weighed all the patients at each time point using portable weighing scales (SECA Model 835). All patients were weighed without footwear and wearing light clothing with weight recorded in kilograms. Body composition was assessed using anthropometric measurements to detect a change in lean body fat. Two measurements, mid-arm circumference (MAC) and triceps skin fold (TSF) provided two practical measurements to use and are particularly suitable for objective measurement in more acutely ill patients [10]. These two measurements were combined to provide an indirect determinant of mid-arm muscle area (MAMA = [MAC (cm) - π X TSF (cm)²/4π] - 10 {corrected for males}).

Secondary Outcome Measures: Additional data collected included appetite status, functional status, quality of life status each measured at baseline, 4 and 8 weeks and survival. Appetite was assessed using a 7-scale rating score where 0= No Appetite and 7= Excellent Appetite to provide a measurement of the increase or decrease in appetite status for the previous week. Functional status was measured using the 5-point WHO Zubrod scale [11] where 0 = Normal activity and 4 = Unable to get out of bed. Quality of life status was measured using the EORTC 30 self-administered questionnaire, which includes scales for global health status, quality of life, functionality and symptoms.

Patients recorded daily consumption (i.e., 2 cartons, 1 carton, ½ carton or none) on specifically designed recording charts. In addition, patients were asked to make a note of any side effects or new symptoms that they had experienced whilst on the supplements. Each side effect or new symptom was recorded as one event. Multiple symptoms were recorded as individual events with as much information as possible to describe the event.

CONTENTS PER TETRA CARTON	PROSURE*	ENSURE PLUS*
TOTAL VOLUME	240mls	240mls
CALORIES	300kCal	360kCal
PROTEIN	16g	13g
FAT	6.14g	11g
Saturated Fat	2.93g	
EPA	1.09g	
DHA	0.46g	
CARBOHYDRATE	44g	50g
FIBRE	3g	0g
MINERALS (different types)	17	15
VITAMINS (different types)	13	13

Table 1: Nutritional Values and Contents for Each Supplement

Finally, information regarding flavour and serving preferences were documented to explore in more detail, what factors, both positive and negative, might influence the patient's compliance with consuming the nutritional supplement allocated.

Sample Size Calculation

The sample size calculation was based on previously published small clinical trials looking at the use of EPA versus placebo in pancreatic cachexic patients [12, 13]. Assuming an underlying normal model, estimates of the mean weight loss derived from these papers, suggested expected values of 2.8-2.9 kg/month with a standard deviation of 1.50-1.90 kg/month for a control group. With a standard deviation of 1.5 kg/month, a parallel study involving 37 subjects per arm would be expected to provide a power of 80% in detecting a difference of 1 kg/month in mean weight loss between two groups when tested at the 5% significance level. This figure was rounded up to 40 per group. Allowing for a 20% attrition rate, the total number of patients required was 100 participants; 50 in the treatment group and 50 in the control group.

Randomisation Of Participants

A computer generated randomisation table was created by the study statistician (BH) with a copy of the randomisation sequence kept in a locked cabinet. Patients were randomised at enrolment in permutation blocks of four using a sequential series of numbered sealed envelopes containing the computer generated random assignments.

Procedure

Patients were invited to take part in the study by means of an introductory letter and written information and written informed consent obtained. The researcher visited all patients in their home with subsequent visits at 4 weeks and 8 weeks. On entry to the study, two baseline measurements of nutritional status were carried out: the Patient-generated Subjective Global Assessment of Nutritional Status questionnaire (or PG-SGA) as well as calculation of the patient's body mass index (or BMI).

Data Analysis

Data were analysed on an intention to treat basis using SPSS (Statistical Package for Social Sciences, Chicago, Illinois, USA version 14.5). Differences in mean weight loss were compared using a Student's t test, Quality of Life data compared using the Mann-Whitney U test and categorical data compared using Fisher's exact test. Survival rate curves were constructed using the product limit (Kaplan Meier) method and comparisons between treatment groups made using the Log-rank test.

Results

A total of fifty-seven participants were identified as eligible to take part in the study. (Figure 1) shows the flow of participants through the study.

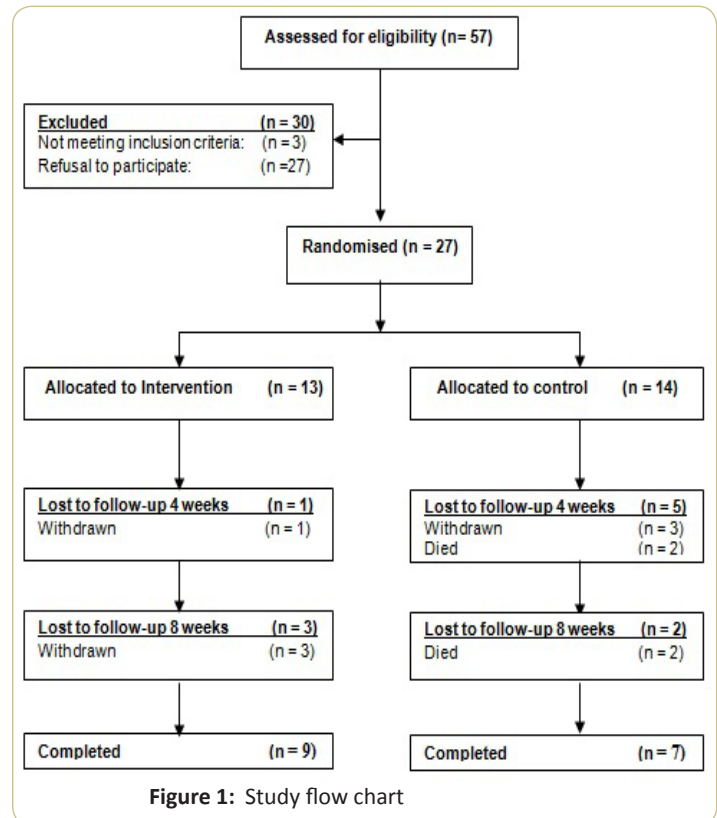


Figure 1: Study flow chart

Thirty patients did not take part in the study. Three did not meet the inclusion criteria and twenty-seven patients declined to take part. (Table 1) summarises the reasons patients were excluded from the study.

REASON GIVEN FOR NOT TAKING PART IN STUDY	FREQUENCY
Decline in medical condition	6
Changed mind about taking part	11
Prescribed nutritional supplement by GP	1
No reason given	9
Excluded 1 = Not Solid Tumour type 1 = Gained Weight 1 = Refusal to stop own fish oil capsules	3
TOTAL	30

Table 2: Patients excluded from the study

The 27 participants recruited into the trial were randomised to one of two groups. Descriptive statistics summarising their demographic characteristics and baseline assessments are presented in (Table 2).

BASELINE CHARACTERISTICS	INTERVENTION (N=13)	CONTROL (N=14)
Gender (Males: Females)	9M: 4F	10M: 4F
Age: mean (SD) years	73.1 (9.3)	65.6 (11.5)
Median (range)	72 (58-87)	68 (40-77)
Tumour Types		
Lung	8	
Mesothelioma	4	8
Oesophagus	1	
Pancreas		2
Prostate		2
Myeloma		1
Stomach		1
Initial Staging of Disease:		
Local	11	7
Loco-regional	1	1
Disseminated	0	3
Missing Data	1	3
Radiotherapy	1	0
Chemotherapy	1	3
History of Steroids use	7	5
Weight - Mean (SD), kg	56.4 (9.2)	60.7 (10.8)
% weight loss kg from usual weight Mean(SD),%	12.9 (4.2)	13.4 (8.6)
Body Mass index – Mean (SD), kg/m²	20.4 (2.3)	21.1 (2.6)
Ankle Oedema	2	1
Anthropometric measurements: Mean (SD)		
Mid-arm circumference, cms	25.7 (2.8)	27.0 (2.5)
Skin fold measurement, mms	12.7 (4.5)	12.7 (4.0)
Lean Body Mass (adjusted for gender) cm ²	18.0(30.2)	14.9(32.2)
PG-SGA Stage:		
Stage B= moderately malnourished	12	12
Stage C=severely malnourished	1	2
PG SGA Score:		
4-8 = Requires Intervention	1	2
>9 = Critical Need of Intervention	12	12
Appetite Status Median (range) (0= no appetite to 7= excellent)	3.5 (1-7)	3.2 (2-7)
Zubrod Performance Score Median (range) (0=Normal to 4= unable to get out of bed)	1.0 (0-2)	1.0 (1-2)
EORTC QLQ-C30 Mean (SD)		
Global Health score	48.10 (26.4)	47.62 (15.9)
High scores= high level of function & Quality of Life		

Table 3: Patient characteristics at baseline by treatment regimen

The majority of study participants were male (19 males, 8 females). Eighteen patients were classified as being at a localised stage of disease; two with loco-regional stage and three with disseminated. No data on stage of disease were available for four patients. At baseline patients had lost an average of approximately 13% of their pre-illness stable weight. On entry to the study one patient was receiving palliative radiotherapy and four patients receiving palliative chemotherapy. Ten patients received concomitant oral corticosteroids with two having used them in the previous 2 weeks. Using the (PG-SGA) questionnaire, twenty-four patients were classified as moderately malnourished and three as severely malnourished. The PG-SGA nutritional management score indicated that twenty-four patients had a critical need for nutritional or pharmacological interventions and in general, other values showed below average scores of physical function and global health status. Baseline characteristics of the two study groups were similar.

Withdrawals And Dropouts: Although twenty-seven patients (13 intervention and 14 control) were assessed at baseline, only 21 were available to be assessed at 4 weeks (12 intervention and 9 control) and 16 patients at eight weeks (9 intervention and 7 control). Among the patients who took part in this study a number of minor new symptoms as well as side effects were reported (Table 3).

New Symptoms/ side effects	NUMBER OF PATIENTS		
	Intervention (EPA) Group (n=13)	Control (without EPA) Group (n=14)	*P value
Sense of fullness and eats less	7	3	0.120
Vomiting	0	3	0.222
Nausea	2	0	0.222
Constipation	1	1	1.000
Loose stools/ diarrhoea	1	1	1.000
Abdominal Pain	1	0	0.481
Flatulence	0	1	1.000
Metallic Taste	0	1	1.000
Fishy Smell/ Taste	1	0	0.481

Table 4: Reported new symptoms or side effects of supplement

* Fisher's Exact Test

The most common new symptom reported was that of a sense of fullness that usually resulted in patients eating less. This effect was mentioned slightly more frequently in the intervention arm than the control arm. However, there were no statistically significant differences in the number of patients who experienced either new symptoms or side effects between the study arms.

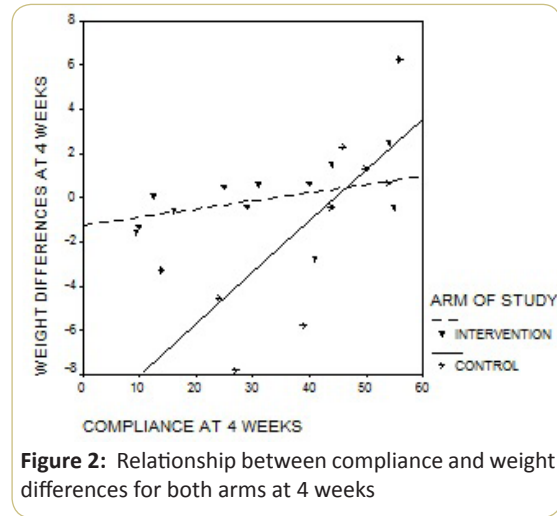
Primary and Secondary Outcomes

We failed to find significant differences between the groups for gross body weight, body composition, appetite, functional status or quality of life between patients taking the EPA supplement compared to those taking the non-EPA supplement in this study. The observed differences are presented in (table 4) below.

It should be noted that, since we were unable to achieve the target sample size, this study lacks statistical power. Moreover, the absence of a statistically significant difference between treatments is not evidence of equivalence.

For this reason, we discuss the findings in order to explore the observed changes further.

Exploring the data: Trend towards weight stabilisation and improved survival: Exploration of the data was undertaken to



Variable	Intervention Group (EPA)	Control Group (Without EPA)	Difference	95% Confidence Intervals & P value
Gross Weight (kg)	0.11 (1.42)	1.25 (4.45)	-1.14	(-4.61 to +2.34) *p=0.479
Lean Body Mass (cm ²)	4.1 (21.2)	25.3 (32.9)	-21.2	(-5.8,44.5) *p=0.1265
Appetite Status:	3.58 (1.55)	3.54(1.38)	-0.04	**p=0.42
Functional Status	1.23(0.60)	1.29(0.47)	-0.06	**p=0.25
Global QoL Status:	48.08 (26.39)	47.62(15.91)	-0.46	**p=0.46

Table 5: Change from baseline at four weeks by treatment regimen

Figures written as means with standard deviation unless otherwise stated

* Independent samples t test

** Mann Whitney U Test

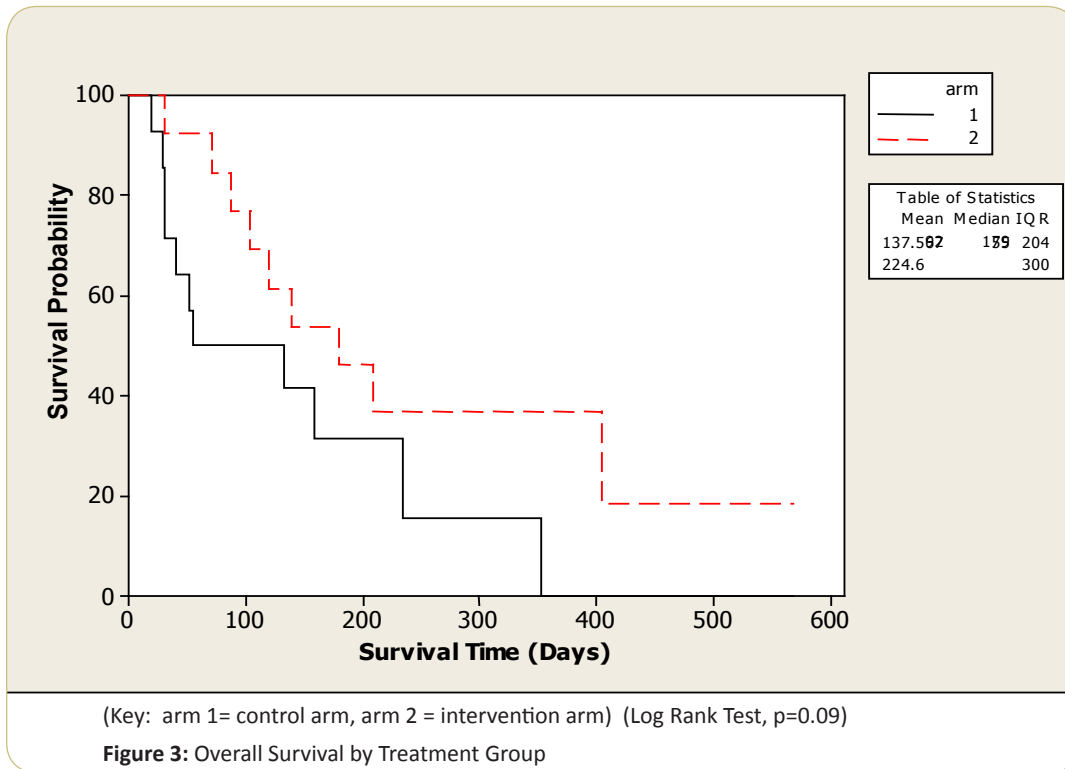
NB: Data not shown for 8 weeks measurements due to small numbers of patients involved

see whether there was any underlying trend of weight stabilisation and survival data. Patients in each arm were asked to consume 2 cartons a day (total 56 cartons) over a four-week period to provide (in the Intervention group) a daily EPA dose of 2.2g/day. At week 4 participants in the intervention arm reported consuming, on average, approximately 1 carton per week more (7 over 4 weeks) than the control group, although this difference was not statistically significant ($t = 1.01, p = 0.33$).

In the Intervention group 6 patients either become weight stable or increased their weight after consuming 10 or more cartons. Maximum weight gain in the Intervention group was seen after consumption of 50 or more cartons. In the Control group, 3

patients increased their weight after consuming 40 or more cartons. Selecting those patients that took 42 or more cartons (to give the recommended dose of 1.5 to 2 cartons per day in the Intervention group) and comparing the mean weight gain with the control group of similar compliance, showed a trend towards weight gain in both arms (Daily: Intervention group: 1.18 cartons SD=1.51; Control Group: 2.03 cartons SD=2.56). However, the numbers involved were too small to complete any meaningful significance testing.

Survival data were recorded of each participant with observations censored beyond 15th March 2006. Survival curves were constructed using the product limit (Kaplan Meier) method and presented in (Figure 3). Treatments were compared using the Log-rank test.



Although patients in the intervention arm survived three times longer on average than those in the control arm (median 179 days versus 55 days), the difference failed to reach statistical significance ($p = 0.09$).

Flavour and serving preferences Although However, in the control arm at the end of the 8 weeks study, the majority of the patients (6 out of 7 patients) said that they would like to continue to use the nutritional supplement and in particular would like to try other flavours. In the intervention arm half of the patients (4 out of 8 patients, data missing for 1 patient) expressed a desire to continue using the supplement despite the lack of flavour choice. The majority of patients in both arms preferred to take the nutritional supplement chilled from the refrigerator (Intervention Arm: n=11, Control Arm: n=7) and straight from the tetra carton (intervention arm: n=8, control arm: n= 7). None of the patients in either arm had tried any of the recipe sheets given, but one patient in the intervention arm added ice-cream sauce to the vanilla to disguise the taste and used the banana flavoured nutritional supplement as pouring custard over fruit. Nutritional supplements were generally well tolerated. The majority of patients in both arms did not have a particular taste preference although in the intervention arm banana flavour was a more popular flavour than vanilla. Some patients (in both arms) said that, by the end of the study period, they were “tired of the flavours” offered.

Discussion

The key findings from this study were that there were no significant differences in either the primary or secondary outcomes measured after the administration of the Intervention (Prosure™ an EPA nutritional supplementation) compared to that of the control group (Ensure Plus™ a nutritional supplement without the addition of EPA). This study was, however, underpowered due to poor recruitment and higher than expected attrition rates resulted in too few patients being available for assessment. It cannot, therefore, be concluded that EPA supplements are ineffectual.

However in both groups, consuming between 1.5 and 2 cartons per day over the 4-week period resulted in a corresponding weight gain. This suggests that high-energy protein rich nutritional supplements (with or without EPA) may provide additional support for advanced patients with mixed tumour cancer types, but further research is necessary to establish which type (and if this matters at all) of nutritional supplement is more useful.

In line with previous findings [8], patients taking EPA in this study survived longer on average, although our findings failed to reach statistical significance. For those patients who prefer not to pursue palliative treatment, it is possible that EPA could provide an acceptable alternative or adjunct to chemotherapy regimes, but further studies are still required to see whether it can provide a realistic option that is acceptable to the patient and meets their needs and expectations.

Limitations of the study and future research: There were a number of limitations in the execution of this study. These included insufficient recruitment, high attrition rates and poor compliance.

With a small sample size the study findings are at risk of small imbalances in baseline characteristics, and so could have benefitted from stratification of randomisation. However there is no one clear predictor for weight loss in people with cancer cachexia [14] and so until more is known about the aetiology of the condition it is difficult to identify suitable factors for stratification.

Despite the use of a comprehensive recruitment strategy we were unable to accrue sufficient patients into the study. There are a number of possible explanations for poor recruitment. Firstly it is possible that low referral rates were due to insufficient identification of potential participants. At the time of the study, patients were not routinely weighed, referred for dietary assessment, advice or supplementation. In a separate qualitative study [15] we have since explored management of patients with advanced cancer and weight loss through audio-taped semi-structured interviews with fourteen nurses (both hospital and community settings). Analysis of the findings revealed that many nurses interviewed did not routinely provide early identification and assessment of weight loss, nor did they continue to monitor the patient's nutritional status. In addition, many of the nurses were reluctant to initiate conversations with cancer patients about weight loss, but instead waited for patients and relatives to raise their concerns.

It is also possible that potential health care referrers acted as "gate-keepers" to suitable patients for the study. All potential health care referrers were contacted periodically in order to maintain the profile of the trial, but it was difficult to maintain a high level of contact. Highest recruitment figures were achieved with those healthcare professionals who were actively involved in project supervision as part of the Trial Steering Committee.

While initially many health care professionals showed interest in referring patients, over time further discussions suggested some healthcare professionals were sceptical about the benefits of entering patients in to the study. Views were expressed about the lack of effect of any nutritional supplementation, regardless of type; belief that patients who are already very ill would be burdened by a commitment to consume large quantities of nutritional supplementation as well as concerns about the possibility of additional side effects.

Another problem was the higher than expected attrition rate. The target for recruitment was 100 to allow for an anticipated attrition rate of 5-10%. Recruitment of patients into the study proved more difficult than anticipated and we were only able to assess eligibility of just over half of the patients we required to take part in the study (N=57). Once randomised into the study, the number of patient withdrawals and dropouts were higher than anticipated (41% in the

Intervention Arm and 50% in the Control Arm). In the majority of cases, this was due to rapid decline with patients either dying or being too ill to continue. We adopted a number of strategies to address potential problems of compliance. Regular telephone contact with home visits by the same researcher throughout the study enabled a good patient/researcher rapport and was felt to enhance compliance (and minimise attrition rates) in both arms of the study. In addition all supplements were supplied to the home and patients were able to change flavour choices delivered to the home if they wished to do so. Despite our efforts, many patients (in both arms of the study) did not regularly consume the nutritional supplementation. This may be due to a number of factors. Although both supplementations were generally well tolerated it is reasonable to anticipate that patients may take more of the nutritional supplement if they feel it is working or less if it is not working. However, since consumption was fairly consistent over time it is more likely that this reflects the deteriorating condition of the patient's ability to tolerate the nutritional supplement allocated. Typically patients were initially enthusiastic to try nutritional supplements, but poor appetite and early satiety resulted in some patients finding it difficult to fit meals around taking two supplements. It may be that taking the nutritional supplement further suppressed appetite and usual food intake. In this case, the nutritional supplement would be replacing the energy generally supplied by usual food intake and failing to provide the substantial increase in total energy intake required. Although the results from our Cochrane systematic review [5] suggest that combining the appetite stimulant, Megestrol Acetate with EPA may result in a slight inhibitory effect, it is possible other appetite stimulants, such as corticosteroids, may prove more useful to use in conjunction with nutritional supplementation use. Future trialists might also consider collecting additional information to assess impact of the timing of supplement consumption on both appetite and food intake or whether patients were using nutritional supplements as a replacement for other food.

Conclusion

Cancer cachexia remains under-investigated, despite significant morbidity and mortality. The role of an EPA nutritional supplement as an effective intervention remains uncertain. There is a need for further investigation, but the challenge will be identifying and recruiting suitable cancer patients into such a study.

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