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A systematic review on the role of fish oil for the treatment of cachexia in advanced cancer: An EPCRC cachexia guidelines project

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Abstract

Background: The European Palliative Care Research Collaboration is developing clinical guidelines on cachexia in patients with advanced cancer. A systematic review on the use of fish oil/omega-3-fatty acids (n-3-FA)/eicosapentaenoic acids (EPA) in advanced cancer patients suffering from cancer cachexia was performed as part of the guideline development.

Methods: The systematic literature search in Medline on the use of fish oil/n-3-FA/EPA identified 244 papers, with 38 publications included in the final evaluation. Some smaller trials, often unrandomized and without a control group, reported a good effect of n-3-FA in patients with advanced cancer and cachexia. However, the results of the larger randomized controlled trials could not support the positive results, as they mostly did not find a significant effect.

Results: Adverse effects such as abdominal discomfort, fish belching, fish aftertaste, nausea and diarrhoea were reported with a low incidence. No serious adverse effects were documented, but adverse effects often had an impact on quality of life. This often limited dose escalations or even led to discontinuation of n-3-FA.

Conclusion: There is not enough evidence to support a net benefit of n-3-FA in cachexia in advanced cancer. On the other hand, adverse effects were infrequent, with no severe adverse effects. The results from the review led to a weak negative GRADE recommendation.

Keywords

Cancer cachexia, eicosapentaenoic acids, fish oil, guidelines, omega-3-fatty acids, systematic review

Background

Cachexia has been recognized as a frequent problem in cancer patients, and more specifically in patients with advanced cancer. Cachectic patients suffer from weight loss and appetite loss, as well as from the impairment of physical function and reduced tolerance to antineoplastic therapy, often resulting in reduced time of survival. In addition to the physical symptoms different

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psychosocial problems are related to cancer cachexia. Weight loss is very irksome for some patients in their daily life as well as in their coping with diagnosis and prognosis. Progressive weight loss and inadequate efficacy of the interventions may also be frightening for patients. Body composition and physical appearance are deeply rooted in the self-image and linked to internal representation of state of health and life expectancy in most patients.

While patients have to cope with their own attitudes and emotions on loss of body weight and physical functioning, they also have to cope with the reactions of family members and friends, health care professionals and others. Care givers notice the changes and their worries may be reflected back to the patient. Often they will urge the patient to eat more, adding this as another stress factor.

The European Palliative Care Research Collaborative (EPCRC)[1] has recently defined cancer-related cachexia as follows:[2]

> Cancer cachexia is a multi-factorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism.

In addition to the metabolic disorder that is primarily paraneoplastic, secondary causes such as impaired integrity and function of the gastrointestinal tract from mouth to anus and poorly controlled physical and psychosocial symptoms including pain, shortness of breath, depression, or severe fatigue will contribute to cachexia.

Different therapeutic interventions have been suggested for cancer-related cachexia. n-3-Fatty acids (n-3-FA) such as eicosapentaenoic acid (EPA) are used in clinical practice, though there is no consensus on their benefit in patients with advanced cancer.

The European Palliative Care Research Collaboration (EPCRC) is developing clinical practice guidelines for pain, depression and cachexia in advanced cancer patients. As part of the cachexia guideline development, the evidence concerning the use of n-3-FA was to be evaluated with a systematic review.

Methods

This review was carried out as part of the development of European clinical practice guidelines on the treatment of cachexia in patients with advanced cancer. The work was part of the EPCRC guidelines project.

The objective of the systematic review was to evaluate whether there is a net benefit from therapy with n-3-FA in patients with advanced cancer and cachexia. The net benefit considers the effectiveness in relation to treatment-related burden, for example from adverse events. The review should result in a guideline recommendation according to the GRADE methodology[3] (positive or negative, strong or weak recommendation).

A systematic search was performed in Medline (Pubmed) the search strategy shown in Table 1. The search was restricted to publications in English language and to the time period from 1966 to June 2010.

Papers were included if describing subjects with cancer cachexia treated with EPA, fish oil, or n-3-FA. The evaluation did not differentiate between these terms, as the terminology is not used consistently in the literature and the terms EPA, fish oil and n-3-FA are used interchangeably. The review focussed on clinical studies comparing treatment with n-3-FA in patients with advanced cancer and suffering from cachexia with standard therapy that did not include this enriched supplement. Studies comparing n-3-FA with melatonin, megestrol acetate, or drug combinations were also included, but were evaluated separately, as were studies comparing different dosages of n-3-FA.

Perioperative treatment of cachectic patients with advanced cancer with n-3-FA was not in the primary focus of the review. However, these studies were included, regardless of whether surgery was performed with curative or palliative intent, but were evaluated separately.

Only clinical studies and systematic reviews evaluating clinical studies were included in the review. Thematically fitting reviews, letters, and comments were used as background information, but excluded from the review. Publications were excluded if they reported on animals, on children, or on non-cancer patients.

We designed a spreadsheet with data from each included trial. Information on study design, sample size, setting, study limitations, patient characteristics, outcome measures, and results were entered and evaluated. Meta-analysis was not possible as a variety of outcome measures were used and study designs were not comparable.

Results

The search identified 244 publications (Table 1). After exclusion of trials on animals and non-English papers 157 papers were left; the number was reduced to 86 after excluding publications on children and studies

Table 1. Search strategy for Medline

Search	Most recent queries	Result
#17	Search #16 Limits: Humans, English	157
#16	Search #9 AND ((#12 AND #13) AND #14)	244
#15	Search #9 AND (((#10 OR #11) AND #13) AND #14)	244
#14	Search (("1966"[EDat]: "2009/07/31"[EDat]) AND (English[lang])	13872476
#13	Search cachexia OR "weight loss" OR anorexia OR "appetite loss" OR wasting OR malnutrition OR "muscle loss"	173265
#12	Search #10 OR #11	2772101
#11	Search cancer OR neoplasm OR tumour OR oncol* OR carcinoma* OR malignan*	2741885
#10	Search "palliative care" OR "hospice" OR "terminal care" OR "terminally ill"	57630
#9	Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	28274
#8	Search "Omega-3*"	8861
#7	Search "Omega-6*"	2799
#6	Search "eicosapentaenoic acid*"	5286
#5	Search "fish oil*"	5196
#4	Search "Fatty Acids, Omega-3"[Mesh]	11814
#3	Search "Fatty Acids, Omega-6"[Mesh]	11626
#2	Search "Eicosapentaenoic Acid"[Mesh]	3151
#1	Search "Fish Oils"[Mesh]	14101

("Fish Oils"[Mesh] OR "Eicosapentaenoic Acid"[Mesh] OR "Fatty Acids, Omega-6"[Mesh] OR "Fatty Acids, Omega-3"[Mesh] OR "fish oil*" OR "eicosapentaenoic acid*" OR "Omega-6*" OR "Omega-3*") AND (((palliative care OR hospice OR terminal care OR terminally ill) OR (cancer OR neoplasm OR tumour OR oncol* OR carcinoma* OR malignan*)) AND (cachexia OR weight loss OR anorexia OR appetite loss OR wasting OR malnutrition OR muscle loss) AND (("1966"[EDat]: "2009/07/31"[EDat]) AND (English[lang])))

not using n-3-FA. Full text analysis excluded another 32 reviews, five invited reviews, four comments, five letters to the editor, and two other documents. These papers were not included in the evaluation, leaving 38 papers for the final evaluation (Figure 1).

Most important for the review were three systematic reviews and six randomized controlled trials (RCTs) with comparison of EPA/fish oil/n-3-FA versus standard nutrition without enriched supplement. All of the six RCTs except one were double blinded. Three other RCTs compared omega-3-fatty acids to melatonin, megastrol acetate, and to a combination of several substances. In addition, there were six non-randomized uncontrolled cohort studies, one non-randomized but controlled cohort study, two prospective uncontrolled trials, and three case series. These 12 trials had the same setting; they all investigated a n-3-FA enriched supplement without control group in patients with advanced cancer and cachexia. Eight other papers were related to surgery; four had their main focus on the maximum tolerable dose, and two were related to other issues. One paper compared an n-3-FA enhanced supplement with a high ration of omega3/omega6 with the same supplement but a low ratio of omega3/omega6. The last paper focussed on compliance.

Systematic reviews

A recent systematic review[4] evaluated several databases (MEDLINE, EMBASE, Cochrane Library and online version of Healthstar database) for the years 1996 to 2006 on the clinical use of n-3-FA in the cancer setting. From 50 clinical trials and prospective studies, 17 trials met the inclusion criteria.[5–21] Not all of these trials were RCTs, and the authors graded them by level of evidence (Agencia, d'Avaluacio de Tecnologica Medica) and recommendation grade (Canadian Task Force).

There was fair evidence that provision of supplements containing n-3-FA was beneficial in patients with advanced cancer and weight loss. It seemed to be associated with an improvement in various clinical, biochemical and quality of life (QoL) parameters. Apart from one study[22] patients in all trials were suffering from pancreatic and upper digestive tract cancer. The authors neither recommended a standardized combination ratio EPA/DHA nor a standardized dose. The incidence of adverse effects was low and EPA as a part of a low-fat nutritional formula was better tolerated than in the form of concentrated capsules. Conclusions were not possible on the duration of supplementation nor on survival.

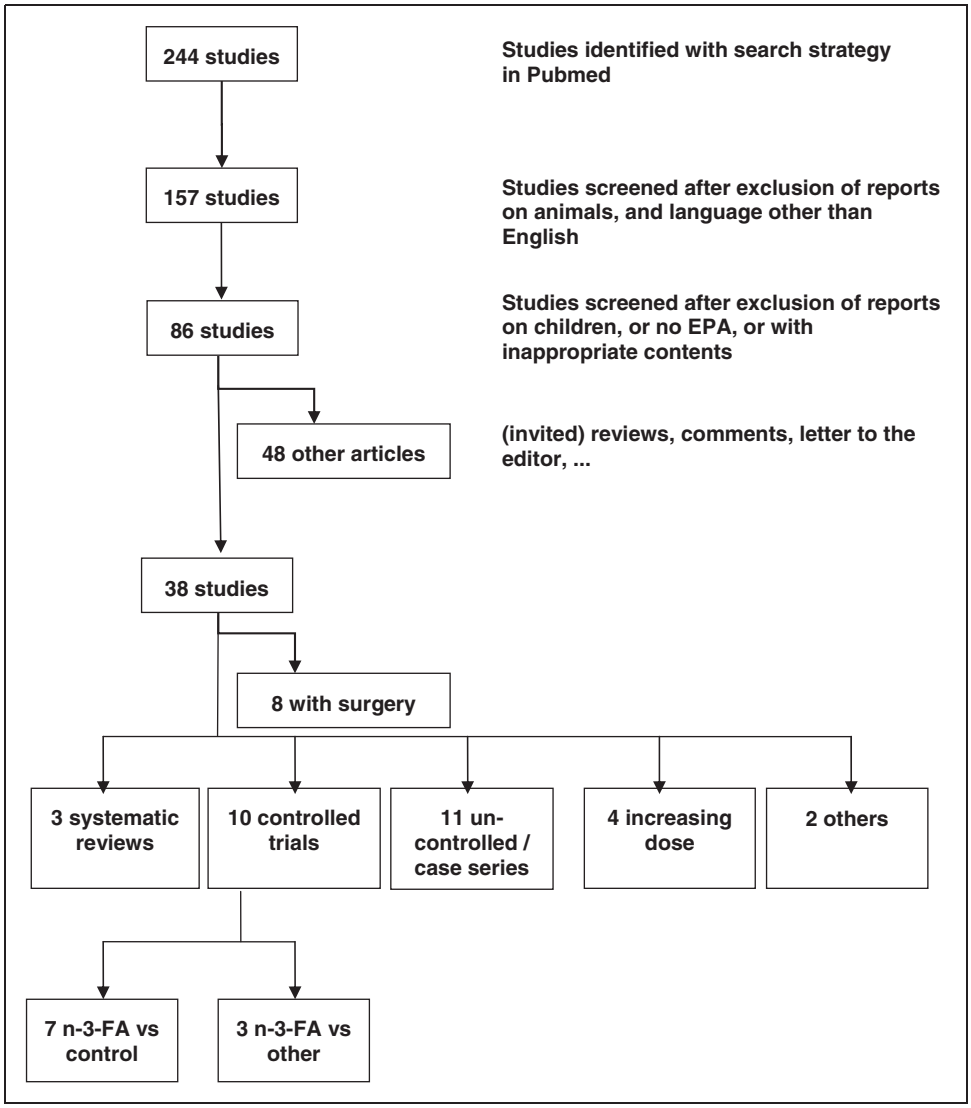

Figure 1. Flowchart for the literature review.

Another systematic review tried to evaluate the effectiveness and safety of n-3-FA in relieving symptoms associated with the cachexia syndrome in patients with advanced cancer from publications until 2005.[23] The review was based on five trials.[11,14–16,21] All trials were randomized controlled studies, included patients with incurable or advanced cancer and either weight loss of $\geq$5% or clinical diagnosis of cachexia. These trials included a total of 587 patients. They either compared oral fish oil supplementation containing n-3-FA against placebo[11,15,21] or against active matched control without n-3-FA.[14,16] The primary outcomes were weight gain, body composition and median survival.

In comparison with placebo there was only nutritional status as a common outcome measure, so the data was insufficient to determine whether oral n-3-FA was superior to placebo. Bruera et al.[11] reported a non-significant weight gain with n-3-FA and Gogos et al.[15] reported a significant increase in survival in the n-3-FA arm. In comparison with active control both studies provided no evidence that n-3-FA improves symptoms associated with the cachexia syndrome.

A third systematic review[24] evaluated several databases (MEDLINE, EMBASE, The Cochrane Database) including publications until 2006 in order to identify the clinical efficacy of EPA and DHA for the management of anorexia–cachexia syndrome (ACS) in cancer patients.

The review included patients with cancer regardless of type and ACS; EPA and/or DHA as main treatment; measurable clinical outcomes related to symptoms or survival or QoL. Only RCTs were included in the analysis, other papers were only identified. If a study focussed on biochemical factors only it was excluded.

Table 2. Systematic reviews

First author, year	Title	Narrative summary of results
Colomer, 2007 [4]	n-3 Fatty acids, cancer and cachexia: a systematic review of the literature	Improvement of various clinical, biochemical and QoL parameters; good results were reported after 8 weeks
Dewey, 2007 [23]	Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia (review)	Data were insufficient to establish whether oral EPA was better than placebo. Comparison of EPA versus megesterol acetate as an appetite stimulant provided no evidence that EPA improved cachexia-related symptoms
Mazzotta, 2009 [24]	Anorexia–cachexia syndrome: A systematic review of the role of dietary polyunsaturated fatty acids in the management of symptoms, survival, and quality of life	No clear advantage in the use of either EPA or DHA on weight, lean muscle mass, symptoms, QoL, or survival was reported. Studies that reported statistically significant differences found small clinical differences that would not have justified the use of EPA and DHA alone as a treatment option. However, it seemed evident that multidimensional treatment is the most useful approach for cachexia in advanced cancer

Mazzotta and Jeney identified ten studies and analysed seven RCTs.[6,11,14–16,25,26] In total there were 1319 participants treated for a mean duration of 5 weeks.

The trials did not use uniform outcome measures, and outcome included the following categories: anthropometric measurements (e.g. weight, lean body mass, and others; five studies), performance status (e.g. Karnofsky, Eastern Cooperative Oncology Group [ECOG], and others; four studies), symptoms (e.g. nausea, appetite, tiredness, and others; three studies), QoL (four studies), and survival (five studies).

Although the review was restricted to seven well-designed RCTs, there was no clear advantage in the use of either EPA or DHA alone in terms of weight, lean muscle mass, symptoms, QoL or survival. Statistically significant differences in the RCTs represented only small clinical differences that would not justify the use of EPA and DHA as a treatment option for ACS. The authors concluded that a multidimensional approach to ACS is likely the most useful method (Table 2).

Randomized controlled trials of n-3-FA compared to standard therapy without n-3-FA

Six randomized controlled trials were identified (Supplementary Table 1). Five studies were double blinded, comparing an n-3-FA enriched supplement with a control treatment without n-3-FA or the standard diet without n-3-FA. Fearon and colleagues performed two trials with similar settings in 2003 and 2006. In both trials EPA supplementation was compared with standard supplementation without EPA over 8 weeks in patients with advanced cancer and full cachexia. In the first trial[14] 88 patients were asked to consume two cans of supplement (each with 1.1 g EPA) and 97 control group patients received identical cans with a supplement that was without n-3-FA and enhanced antioxidants. Assessment at the end of week 8 was available from 110 of the 185 patients. In the second study[26] 175 patients took capsules with 2 g EPA, 172 patients received capsules with 4 g EPA and 171 patients were treated with placebos. The 8-week study period was completed by 270 patients. In both studies the results indicated no statistically significant benefit of the EPA enriched supplement. Intention-to-treat analyses did not provide a therapeutic advantage nor a statistically significant improvement in weight, lean body mass, Karnofsky performance status, or survival.

In the first trial from 2003 further analysis reported significant correlations between the amount of supplement intake and weight gain and increase in lean body mass for the patients on EPA supplement. These correlations were not statistically significant in control patients. Increased plasma EPA levels in the EPA group were correlated with weight gain and lean body mass gain. Weight gain was related to improved quality of life in the EPA group.

In a controlled trial with 91 patients with advanced cancer and full cachexia, half of the group was treated with fish oil capsules and the other half with placebo for 2 weeks.[11] The authors reported that fish oil did not significantly influence appetite, tiredness, nausea, well-being, caloric intake, nutritional status, or function within this short treatment period.

A similar setting was selected for a trial in 60 patients with advanced cancer and full cachexia comparing EPA/DHA enriched nutrition versus placebo. The trial included well-nourished and malnourished patients,[15] resulting in four study groups with 15 patients each: well nourished with EPA/DHA (WNA), well nourished placebo (WNB), malnourished with EPA/DHA (MNA) and malnourished placebo (MNB). The ratio of T-helper cells to T-suppressor cells was significantly lower in malnourished patients. n-3-FA had a considerable immunomodulating effect by increasing this ratio in the subgroup of malnourished patients. There were no significant differences in cytokine production among the four groups, except for an increase in tumour necrosis factor production in malnourished cancer patients which was reduced by n-3-FA. The mean survival was significantly higher for the well-nourished patients in both groups, whereas n-3-FA prolonged the survival of all the patients. No data on weight changes were reported.

In the trial by Moses et al.[5] 15 patients received supplement and nine patients EPA enriched supplement for a treatment period of 8 weeks. Moses determined total energy expenditure (TEE), resting energy expenditure (REE) and total energy intake (TEI) in addition to weight: Parameters such as physical activity level (PAL = TEE/REE) and energy expenditure of activity (EEA = TEE − REE) were calculated from the data. After 8 weeks TEE and PAL increased significantly in those who received the EPA enriched supplement, but not in control group patients. No significant changes were reported for REE and weight.

In a controlled trial of 33 patients EPA enriched supplement in 17 patients was compared to oleic acid enriched supplement in a control group of 16 patients for 1 week.[21] The authors focussed on energy intake, whole body lipolysis (rate of appearance of H5-labelled glycerol in plasma), palmitic acid release (rate of appearance of ^{13}C-labelled palmitic acid in plasma), palmitate oxidation rate, free fatty acid concentration in plasma and plasma triacylglycerol concentrations, but found no significant effects of the EPA treatment.

One controlled, but non-randomized study was included in our review.[6] In a sequential series, 18 patients with pancreatic cancer were treated with a supplement containing 2 g EPA and 1 g DHA per day for 3 weeks while another 18 received supportive care only. Acute phase proteins (APPs) were measured before and after the intervention period. In patients receiving fish oil, no significant change from baseline in serum APP levels was reported, whereas in patients receiving full supportive care, there was an increase in APP levels. There was a significant difference in weight loss. Patients receiving the supplement gained a median of 1 kg, whereas those with supportive care lost a median of 2.8 kg.

Randomized controlled trials of n-3-FA versus other substance/mix versus both/mix

Three randomized trials were identified that compared n-3-FA not with placebo, but with an active substance or a combination of several substances (Supplementary Table 2).

In a large trial ($n = 412$) Jatoi et al. compared an eicosapentaenoic acid supplement with megestrol acetate (MA) and with a combination of both substances in advanced cancer patients with full cachexia.[16] EPA supplement, either alone or in combination with MA, did not improve weight, appetite, survival or quality of life more than MA alone.

Persson et al. compared fish oil (FO) containing EPA and DHA with melatonin (MLT) and with the combination of both in 24 patients with advanced cancer and full cachexia. In a cross-over design patients were treated with either FO or MLT for 4 weeks then switched over to the combination of both for another 4 weeks. No statistically significant changes in weight and KPS were reported after 4 weeks, but statistically significant lower KPS was found in the fish oil group after 8 weeks. The authors concluded that FO, MLT or their combination did not induce major biochemical changes indicative of a strong anticachectic effect. Nonetheless, the interventious used may have had a weight-stabilizing effect.[25]

In a randomized clinical trial, 110 patients with cancer cachexia were given polyphenols plus antioxidant agents, α-lipoic acid, carbocysteine, and vitamins A, C and E, all orally as basic treatment. Patients were randomized to one of following five arms for a treatment duration of four months: (1) medroxy progesteron acetate/megestrol acetate, (2) pharmacological nutritional support containing eicosapentaenoic acid, (3) L-carnitine, (4) thalidomide, or (5) 1 + 2 + 3 + 4. Concentrating on the results of treatment groups with EPA, there was a significant increase in MFSI-SF score (fatigue symptoms) and REE, a decrease in EQ-5D index as well as improvement in ECOG PS score in arm 2. In arm 5 total body weight and appetite increased significantly and MFSI-SF, REE, and ECOG performance status score were improved.[27]

Uncontrolled trials

Eight uncontrolled trials[6,8,10,13,28–31] and three case series[7,32,33] focussed on the effect of fish oil and n-3-FA on cachexia in patients with advanced cancer (Supplementary Table 3).

Two trials tested the reaction of high-purity and high-dose n-3-FA on patients with advanced cancer

and full cachexia. Using high-dose n-3-FA capsules ($n = 13$: 0.3 g/kg/day; $n = 30$: 0.15 g/kg/day) the majority of 43 patients treated for a median duration of 1.2 months experienced weight stabilization.[13] Only few patients either gained or lost weight. Patients with weight gain reported higher quality of life scores in the FAACT questionnaire. The second trial investigated the down-regulation of the acute-phase response in six patients with pancreatic cancer cachexia treated with oral high-purity eicosapentaenoic acid in escalating dosage (2–8 g/d).[34] In these patients CRP fell significantly and IL-6 production was significantly reduced.

Another four cohort studies[28–31] and two prospective studies[8,10] reported results from a total of 159 patients. Patients were treated with EPA, DPA, marine phospholipids, fish oil or n-3-FA. The application included cans or tetrapaks with enriched supplement, or pills. Treatment duration ranged from 3 weeks to 4 months. Weight increased significantly in three studies and was stable or slightly increased in the other three. Lean body mass was increased in the four studies that reported this outcome, and similarly appetite was increased in four studies. Laboratory values such as CRP or cytokines were reduced in several studies.

Three case reports[7,33,32] with a total of 36 patients treated for 3 to 8 weeks were included in the review. Again, these studies reported weight gain or at least stabilization and improvement of other parameters with n-3-FA treatment.

Second-line trials

Two randomized trials covered n-3-FA treatment in advanced cancer, but not with the focus on the main question of this review (Supplementary Table 4).

In one trial 65 participants suffering from advanced cancer and full cachexia were divided into two groups receiving a high omega-3/omega-6 ratio and a low ratio, respectively.[35] No significant differences in plasma proteins (albumin, prealbumin, transferrin) nor in other variables were reported after 12 weeks of treatment. Both groups experienced weight stabilization and good gastrointestinal tolerance. The study did not allow any conclusion whether n-3-FA attenuated cachexia.

In a large trial of 185 advanced cancer patients with full cachexia half of the patients were asked to consume two cans per day of EPA supplement and the other half received control supplement for a period of 8 weeks.[36] However, the study focussed on compliance only, differentiating a compliant and a non-compliant group, and a comparison of EPA and placebo groups was not provided.

n-3-FA in context with surgery

Eight trials with a total of 601 cancer patients compared n-3-FA against standard nutrition without n-3-FA in the perioperative setting.[37–44] All were controlled trials, and all but one were randomized. Patients were treated with n-3-FA 5 days preoperatively in one study[41] or 7–14 days postoperatively in the others. n-3-FA were delivered parenterally in one study[37] and enterally in the others, and were compared to standard diet, enteral supplement with glutamine, or parenteral nutrition (Supplementary Table 5).

These trials did not focus on weight and body composition, but rather on evaluation of the anti-inflammatory effect of n-3-FA on laboratory parameters or on the prevention of postoperative complications such as impaired wound healing or infections. Five studies found significantly fewer postoperative complications in subjects with n-3-FA compared to controls,[37,39,41–43] whereas two studies were not able to demonstrate an advantage of n-3-FA.[40,44] The study by Braga[38] focussed on laboratory parameters only.

Weight change was addressed in two studies. Whereas a trial with 150 patients found that mean loss of body weight was 3.1%, but without difference between treatment groups,[39] the other study with 70 patients reported that patients with n-3-FA maintained body composition, whereas the control group with standard nutrition lost significant amounts of fat-free mass.[40]

Trials with increasing dose of n-3-FA

Four trials with a total of 71 patients used increasing dosages of n-3-FA in order to ascertain the maximum tolerated dose (Supplementary Table 6). Treatment duration was up to 12 weeks. Patients tolerated a median maximum dose of 12 g of fish oil per day equivalent to a dose of 2 g of EPA per day.[19] In a subsequent study the same authors tested a maximum dose of 6 g EPA per day which was also tolerated.[20]

Even higher dosages were used in the other two trials. Burns et al.[12] established a maximum tolerated dosage of 0.3 g/kg/day and Barber and Fearon[9] reported that a dose of 18 g EPA was tolerated by most patients for a substantial period.

Adverse effects with n-3-FA

Adverse effects of EPA and other n-3-FA were reported in only a few studies. Most often gastrointestinal effects such as mild abdominal discomfort, flatulance, nausea or vomiting, transient diarrhoea or steatorrhoea were reported. Some studies reported abnormal taste of food, sometimes with a fish aftertaste, or fish belching.

Toxicity of the central nervous system and severe paraesthesia were reported in one patient each in a randomized study. The four studies with increasing dosages only reported cramping abdominal pain as an additional adverse event.

Discussion

The literature search retrieved a high number of papers on the use of n-3-FA in cancer cachexia, showing considerable interest in this area in recent years. Thirty-eight papers were included in the final evaluation. This number also included uncontrolled studies, case series and studies in the postoperative setting with a different focus. Only few studies with high quality methodology were available for the final evaluation. In addition, three systematic reviews had been published, evaluating the literature until 2006.

Assessment of cachexia varied widely among the studies, and a vast range of different outcome measures and indicators was used, ranging from quality of life, body composition, nutritional status, or survival, to laboratory parameters. Recently a consensus definition on cachexia has been presented,[45] but this definition is not cancer specific. Recent work from the EPCRC has presented a definition of cancer cachexia.[2] Similarly, the EPCRC has proposed a classification system describing cancer cachexia as an ongoing continuum with a progression from pre-cachexia to cachexia and finally to refractory cachexia. This classification system is currently under evaluation. However, neither the definition nor classification system has been used in clinical research until now, and thus cannot be used in the present evaluation. The scope of different outcome measures impaired meaningful comparisons and prevented meta-analysis of the data.

Three systematic reviews were published in recent years; only one of them formulated a weak recommendation for n-3-FA for patients with advanced cancer and weight loss,[4] stating that there was a fair evidence to recommend it (recommendation grade B). The other two reviews found no clear advantage of treatment with n-3-FA (Table 2). Our review included the evidence from these systematic reviews, supplemented with an update of the literature of the last 4 years. In addition, the present review provides a more comprehensive overview as not only randomized controlled trials were included, but also other studies that contribute to the evidence. Moreover, we examined all six randomized controlled trials for the first time in one review. They had already been analysed in the other reviews, but none of the former reviews included all six studies.

Similarly, four of the six high-quality randomized controlled trials found no significant benefit from the administration of n-3-FA[11,14,21,26] (Supplementary Table 3). In the trial by Bruera et al.[11] additional outcome measures were appetite, weight, and performance status, all of which did not change significantly. Two trials additionally reported on quality of life[14,26] but without significant improvements. The trial by Zuijdgeest-Van Leeuwen et al.[21] focussed on a more cellular level and determined energy intake, whole body lipolysis, palmitic acid release, and other laboratory parameters. However, this study also found no detectable advantage of EPA in comparison to treatment with oleic acid.

Two of the randomized controlled trials found some statistically significant results in favour of the use of n-3-FA,[5,15] reporting a significant increase in survival in the n-3-FA group in one study and an increase in physical activity in the other. However, no significant weight changes were reported in these studies. The controlled but unrandomized study by Barber et al. also reported positive results from n-3-FA treatment, but looked at laboratory parameters only.[6]

Two trials with large patient numbers as well as a smaller trial comparing n-3-FA with other substances or combination treatments also found no major benefit.

In contrast to these results from larger trials with high methodological quality several other trials reported positive effects of n-3-FA. However, the study methodology was much less stringent in these trials, as most had small sample sizes and lacked control groups.

Following the GRADE methodology, no positive recommendation could be formulated for n-3-FA treatment in advanced cancer from the present review. Patients with advanced cancer are likely to suffer from refractory cachexia, and it is likely that the anti-inflammatory effects of n-3-FA are not effective in refractory cachexia. In addition, the treatment time recommended by several authors was at least 8 weeks. As patients with advanced cancer often have a prognosis of short survival, this might also shift the balance from benefit to burden, even if adverse effects were mild in most cases, and no severe or serious adverse events were recorded. In one study the side effects were dose limiting for some patients.[11] However, in four studies high dosages were tolerated for several weeks of treatment.

Considering the weak evidence for benefits of n-3-FA, the incidence of mild side effects, but also the lack of severe adverse events, a therapeutic trial seems to be justified in individual patients, if prognosis of survival is considerably longer than 8 weeks and the stage of cachexia is not refractory. In consequence an individual approach is recommended for patients with advanced cancer receiving palliative care, taking into account potential benefits and burden and considering the effects of n-3-FA treatment on quality of life in the individual patient.

Some trials were published in the perioperative setting, describing the use of the anti-inflammatory effect of n-3-FA for prevention of wound infections (Supplementary Table 5). This resulted in fewer complications and faster wound healing, so that the use of n-3-FA in this setting can be recommended. Further studies are warranted in this setting to confirm the effectiveness.

Some of the studies that were included in the review seemed to be flawed in their methodology. The small sample size of some studies was a major problem. Similarly, a missing control group should be considered critical, as well as a lack of randomization. In addition to the study design some of the instruments of measurement used raised concerns. Most studies used the bioelectrical impedance analysis for assessment of the body composition. It is a non-invasive and economic method, which has limited variations between observers. As the device is portable, it can be adopted to use in many settings. Measurement works well in healthy subjects with stable water and electrolyte balance. However, it is not recommended for patients at extreme BMI ranges or with abnormal hydration, where it can both over- or underestimate muscle mass significantly. The results had to be interpreted with caution in cachectic cancer patients with very low BMI.[46]

As a new alternative for measuring body composition abdominal computer tomography scans (L4-CT scan) have been recommended. However, full discussion of emerging diagnostic tools is beyond the scope of this review.

The evaluation of the review has been impaired not only by the lack of common outcome measures but also by a lack of common definitions. The EPCRC has proposed a definition as well as a classification system for cancer-related cachexia. An assessment tool for this classification system is currently being tested. Use of these instruments in future studies would ensure that results are comparable and that data can be pooled for meta-analysis. More research is needed not only on drugs such as eicosapentaenoic acid or other n-3-FA, but also on multimodal approaches combining drugs and non-drug interventions.

Conclusion

This review found evidence of a net benefit of n-3-FA on cachexia in advanced cancer only in trials with lack of methodological stringency, and no evidence of a clear benefit in studies with higher methodological quality. This resulted in a GRADE recommendation of weak negative.

For selected patient groups the use n-3-FA may be beneficial; for example, in cancer patients receiving surgery with palliative or curative intention, where n-3-FA can support postoperative recovery and reduce complications such as impaired wound healing and infections.

Weak methodology of most studies impaired the evaluation of this systematic review. For further research more evidence, uniformity and valid measuring tools are preferable. Research on treatment of cachexia in advanced cancer needs to build a basis with a common terminology and a toolbox for diagnosis and assessment, before more evidence can be produced with studies with high quality methodology.

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Conflict of interest

The authors declare that there is no conflict of interest.

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