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A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer

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Abstract

Background   Cancer cachexia is a syndrome of weight loss (including muscle and fat), anorexia, and decreased physical function. It has been suggested that the optimal treatment for cachexia should be a multimodal intervention. The primary aim of this study was to examine the feasibility and safety of a multimodal intervention (n-3 polyunsaturated fatty acid nutritional supplements, exercise, and anti-inflammatory medication: celecoxib) for cancer cachexia in patients with incurable lung or pancreatic cancer, undergoing chemotherapy.
Methods   Patients receiving two cycles of standard chemotherapy were randomized to either the multimodal cachexia intervention or standard care. Primary outcome measures were feasibility assessed by recruitment, attrition, and compliance with intervention (>50% of components in >50% of patients). Key secondary outcomes were change in weight, muscle mass, physical activity, safety, and survival.
Results   Three hundred and ninety-nine were screened resulting in 46 patients recruited (11.5%). Twenty five patients were randomized to the treatment and 21 as controls. Forty-one completed the study (attrition rate 11%). Compliance to the individual components of the intervention was 76% for celecoxib, 60% for exercise, and 48% for nutritional supplements. As expected from the sample size, there was no statistically significant effect on physical activity or muscle mass. There were no intervention-related Serious Adverse Events and survival was similar between the groups.
Conclusions   A multimodal cachexia intervention is feasible and safe in patients with incurable lung or pancreatic cancer; however, compliance to nutritional supplements was suboptimal. A phase III study is now underway to assess fully the effect of the intervention.

Keywords   Cachexia; Cancer; Randomised; Multi-modal; Trial; Anti-inflammatory

Introduction

Cancer cachexia is a multifactorial syndrome characterized by weight loss, muscle wasting, and symptoms such as fatigue and anorexia.[1] It is a severe, unrelieved cause of suffering in patients and is associated with increased mortality,[2] increased chemotherapy toxicity, and reduced quality of life.[1] It is estimated that more than 80% of patients with

advanced cancer disease will experience weight loss or cachexia.[3]

The pathophysiology of cancer cachexia is a combination of reduced food intake and altered metabolism resulting from complex interactions between inflammation, hypermetabolism, neuro-hormonal changes, increased catabolism, and reduced muscle/fat anabolism.[4] Despite increased understanding of the mechanisms of cachexia, there is still no standard of care, no licensed drug treatment, and no evidence-based guidelines on the management of cachexia. Thus, clinicians and patients often regard cachexia as an inevitable consequence of cancer. This lack of treatment progress is paradoxical given the importance of this condition in limiting oncology treatment success and contributing to excess morbidity and mortality. New approaches are needed to break the deadlock: approaches that address the complexity of the syndrome and challenge the accepted therapeutic nihilism.

Systematic reviews have shown that uni-modal interventions employing (i) nutritional counselling and oral nutritional supplements (ONS),[5] (ii) physical exercise training,[6] (iii) non-steroidal anti-inflammatory drugs[7] (NSAIDs), or (iv) omega (n-3) polyunsaturated fatty acid supplementation,[8,9] can improve nutritional and functional outcomes. Unfortunately, within each systematic review, there was considerable heterogeneity between studies, and few studies had an adequate sample size. As such, these individual treatment effects have not been sufficiently strong to change clinical practice. To treat cachexia optimally, it has been argued that a multimodal intervention is necessary[10] to enable the multifactorial pathophysiology to be targeted and achieve at least additional, if not synergistic effects.

It has been argued that the optimal time to initiate any cachexia therapy is early in the disease trajectory, indeed before cachexia has become established: preventing cachexia rather than treating it. In practical terms, this means that cachexia interventions should be given alongside tumour-directed treatment. This approach has the advantage that chemotherapy-induced muscle loss may also be reduced.[11] Undertaking cachexia treatment early in the disease trajectory during chemotherapy may provide a therapeutic window where the chances to establish a clinically meaningful benefit are maximal.

Taken together, the aforementioned observations form a persuasive argument that a multimodal cachexia intervention [nutritional therapy with eicosapentaenoic acid (EPA), physical exercise and anti-inflammatory treatment (celecoxib)] should be examined in a robust clinical trial. This intervention should be delivered in tumour groups where cachexia is prevalent (lung and pancreatic cancer) and early in the disease trajectory to achieve optimal clinical benefit.

However, a multimodal intervention such as this is challenging both in terms of compliance with the intervention and in the timing of delivery. Therefore, the aim of this randomized phase II study was to assess the feasibility and potential efficacy of a multimodal intervention to attenuate cachexia in patients with incurable lung or pancreatic cancer.

Methods

Study design and participants

A phase II, randomised, open-label feasibility trial was conducted—ClinicalTrials.gov: NCT01419145. Eligible patients met the following criteria: age 18–80 years; stage III/IV non-small cell lung cancer or inoperable pancreatic cancer; due to commence chemotherapy; Karnofsky performance status >70; no contraindication to the study interventions (primarily the anti-inflammatory medication); body mass index <30 kg/m^2; and <20% weight loss in the previous 6 months. Patients who had received any systemic anti-cancer therapy in the preceding 4 weeks, or who were taking regular oral steroid medication, were not eligible. Patients who were participating in other interventional clinical trials or who within 30 days prior to inclusion were taking other agents for the prevention or treatment of cachexia (such as megestrol acetate, progestational agents, growth hormone, dronabinol, marijuana, or other anabolic agent) were not eligible. Patients with renal impairment defined as creatinine clearance <30 mL/min were not eligible. Patients with potential contra-indications to celecoxib [New York Heart Association Functional class III or IV heart failure, uncontrolled hypertension (diastolic blood pressure > 95 mmHg at screening), history of previous myocardial infarction, unstable angina, coronary revascularization, uncontrolled arrhythmia, cerebrovascular accident, previous gastrointestinal inflammatory disease and history of gastrointestinal ulceration, history of bronchospasm, asthma, rhinitis, nasal polyps, angioneurotic oedema or urticaria with intake of NSAID or aspirin therapy, history of hyper sensibility related to intake of acetylsalisylsyre, or NSAIDs] were also excluded.

The protocol was approved by ethics committees for human research at the participating centres and written informed consent was obtained. The authors certify that they comply with the ethical guidelines for authorship and publishing of the *Journal of Cachexia, Sarcopenia and Muscle*.[12] Patients were recruited from three centres: St. Olav's Hospital, Trondheim University Hospital, Norway; Oslo University Hospital, Ullevål, Norway; and the Beatson West of Scotland Cancer Centre, Glasgow, UK.

Randomization

A web-based randomization system developed and administered by the Unit of Applied Clinical Research, Department of Cancer Research and Molecular Medicine, Norwegian

University of Science and Technology was used. Randomisations were undertaken in a 1:1 ratio with stratification by centre and tumour type. Following baseline assessments, patients were randomised to the treatment arm (multimodal intervention) or to the control arm. Patients in the treatment arm had detailed counselling and instruction from trial research staff, including nurses, physiotherapists, and dieticians. Patients in the control arm had standard cancer care.

The **treatment arm** consisted of the following:

- Celecoxib 300 mg once daily. Celecoxib was chosen as it is one of the anti-inflammatory drugs most studied in cachexia and it has proved to be beneficial in preserving weight, performance status, and muscle strength and has demonstrated to have relatively few side effects.[7]
- Two 220 mL cartons of ONS (ProSure © Abbott). Each carton contains 1 g EPA, giving a net intake of 2 g/day.
- Nutritional counselling with advice on optimization of nutritional intake that was provided by a dietician and/or trial nursing staff. A nutritional interview (30 min) was performed at baseline, and then patients were given oral and written advice on improving energy and protein intake. Typically, the advice was to increase meal frequency and use energy dense foods.
- Exercise programme including home-based aerobic and resistance training devised by a physiotherapist. The aerobic component consisted of 30 min of aerobic exercise of the patients' choice two times a week. The resistance exercise component consisted of six individualised exercises that follow the same schedule, targeting major muscle groups in the upper body and legs, to be performed three times weekly for about 20 min. The exercises consisted of push ups against the wall, overhead presses, and bicep curls and, for the legs, squats, lunges, and calf raises with use of weights.

Patients in the treatment arm were contacted a minimum of once a week (maximum of twice) by telephone to assess compliance and to encourage adherence to the multimodal intervention.

The control arm was standard cancer care alone and did not include regular nutritional or exercise interventions or NSAIDs. If the treating clinician felt it appropriate, dietician review was carried out. Patients in the control arm were offered the multimodal intervention after 6 weeks (i.e. after endpoint assessments) to prevent them mimicking the multimodal intervention and thus contaminating the control arm.

In both arms, patients had regular oncology review. Typically, this included out-patient appointments prior to chemotherapy (pre-chemotherapy assessments) and also hospital visits (single day) for chemotherapy delivery (most commonly every 3 weeks). The most common chemotherapy regimens were Folfirinox, Vinorelibine-Carboplatin/Cisplatin, Gemcitabine mono, and Pemetrexed-Carboplatin/Cisplatin.

All patients had their symptoms managed appropriately, according to guidelines at each centre.

Procedures

At enrolment, each patient's demographic details and disease-related characteristics were recorded. The following assessments were undertaken at this point (i.e. baseline— prior to randomisation) and then repeated at trial endpoint (6 weeks): body weight and body mass index; physical function [using ActivPAL (physical activity metre worn for 7 days)[13] and the 6 min walk test (6MWT)]; muscle mass (using CT assessment of lean muscle mass)[14]; muscle strength (hand held dynamometer assessing grip strength); nutritional status [using abridged Patient Generated Subjective Global Assessment (aPG-SGA)][15]; nutritional intake [using a 10 point verbal scale assessment of nutritional intake (AveS)][16]; and fatigue [assessed using the Fatigue Severity Scale (FSS)].[17]

Compliance with the EPA enriched ONS was assessed using patient completed logs. Plasma phospholipid EPA was also used as a biomarker of compliance with the EPA-enriched ONS. Compliance with study medication (celecoxib) was assessed by counting the tablets returned by the patient. The type and duration of exercise preformed was registered in a log by the patient. Compliance with the intervention was assessed at <50%, 50–80%, and >80% of full compliance within each component of the intervention.

Hospitalizations and adverse events were recorded in accordance with Good Clinical Practice standards. Adverse events were graded according to Common Terminology Criteria for Adverse Events (CTCAE, v3.0).

Routine biochemistry/haematology analyses (albumin, C-reactive protein, Leucocytes, and creatinine) were performed at baseline and endpoint.

Endpoints

The primary endpoint was feasibility. This was assessed by recruitment and retention (number of patients screened and/or consented), compliance with the intervention (based on use of celecoxib, nutritional supplements, and exercise performed), and contamination of the control arm (number of patients who tried to mimic all or part of the intervention). Feasibility of recruitment and retention was assessed by proportion of patients screened vs. those consented and attrition rates. In cancer trials, the percentage of patients recruited vs. those screened varies: we accepted 10% recruitment[18] and an attrition rate of <26%[19] as feasible. Compliance with the multimodal intervention was assessed according to individual components and thresholds of <50%, 50–80%, and >80% were used. Compliance of ≥50% of the specific intervention in ≥50% of patients was

considered acceptable. The secondary endpoints were assessment of weight, muscle mass (assessed by CT measurement of muscle mass), physical activity (ActivPAL and 6MWT), hand grip strength, nutritional status (AveS and aPG-SGA score), and fatigue score. These were assessed at baseline and after 6 weeks (endpoint). Safety and survival were also assessed as secondary endpoints.

Muscle mass was assessed using CT scan images performed as part of patient management, which were retrieved from digital storage in the picture archiving and communication system. Muscle mass levels at L3 are highly correlated to total body muscle mass (r2 = 0.86).[20] Axial images at the L3 level were selected out and analysed using the 'Automated Body Composition Analyzer using Computed tomography image Segmentation' (ABACS) software.[21] Using Hounsfield unit thresholds of −29 to 150 for skeletal muscle, −50 to 150 for visceral adipose tissue, and −190 to −30 for subcutaneous adipose tissues, the program recognized shapes and predictable patterns to accurately predict values. The sum of skeletal cross-sectional muscle areas was normalized for stature (m2) and reported as lumbar skeletal muscle index (cm2m-2).

The primary endpoints were chosen to assess the feasibility of a delivering a multimodal intervention for cancer cachexia. The secondary endpoints were regarded as exploratory to inform future trial design, should the primary endpoints be positive and future trials be deemed worthwhile.

It was anticipated that most patients entering the trial would have non-small cell lung cancer. Independent of the treatment given, the majority of these patients have 2 cycles of chemotherapy over a total of 6 weeks. The endpoint after 6 weeks was chosen to reflect the standard chemotherapy treatment regimens in the UK and Norway and enabled the trial to use existing radiological data (CT scans) and assessments to coincide with hospital visits. Further, the trial duration of 6 weeks was chosen in consideration of selective attrition that occurs in this advanced cancer population. Baseline assessment was before randomization and prior to the start of chemotherapy.

Statistical analysis

An intention to treat approach was used for the primary endpoints. A per protocol approach was used for secondary endpoints. A sample size of approximately 40 patients, 20 for each arm, was chosen based on an estimation of providing sufficient information to inform the primary endpoints; feasibility of recruitment and compliance.

In this phase II study, the primary endpoints were mainly regarded as descriptive, and unless otherwise stated, presented as medians and inter-quartile ranges or percentages, as appropriate. For secondary endpoints, to explore the potential that there might be differences between the two

arms, parametric (2 sample *t*-tests) and non-parametric tests (Mann–Whitney) were done. Survival analysis was performed using Kaplan–Meier methods with log-rank test applied. EPA is expressed as % of total fatty acids quantified in plasma at baseline and week 6. Because of the small sample size and multiplicity of testing, *P*-values should be interpreted with caution.

Results

Primary endpoints

From November 2011 to April 2014, 399 patients were screened resulting in 46 patients being included (*Figure* 1—Trial Profile). Recruitment rate (screened vs. consented) was 11.5% (46/399), and this is in keeping with other trials in this patient population.[22] The main reasons for patients not being eligible were as follows: contraindications to celecoxib, prior cardiovascular disease/gastric inflammatory disease (19%) or taking an anti-inflammatory medication (7%); too frail to receive chemotherapy (12.5%) and over 80 years of age (13.0%). The attrition rate of those recruited was 10.9% (5/46): 8.0% (2/25) in the treatment arm and 14.3% (3/21) in the control arm.

The analysis was based on the 25 and 21 patients randomly assigned to the treatment and control arms respectively. The baseline characteristics are shown in *Table* 1. Groups were well matched with respect to baseline Karnofsky performance score, cancer type, and prior weight loss. Patients randomized to the treatment arm were, however, slightly older, had more advanced stage lung cancer, greater prior tumour treatment and higher plasma levels of C-reactive protein.

Compliance with the multimodal intervention is shown in *Table* 2. Compliance (deemed as >50% of individual components in 50% of patients) was 76% (19/25) for the celecoxib, 60% (15/25) for the exercise components and 48% (12/25) for the ONS. Therefore, acceptable compliance was achieved in all but the ONS. Three patients had >80% compliance to all components of the intervention. In terms of combinations, eight (38%) patients did >80% of the aerobic and resistance components. Nine (43%) patients took >80% of the ONS and celecoxib components and nine (43%) patients took/did >80% of the resistance and celecoxib components. Two patients reported reduced compliance with all three components during hospitalisations. Some patients reported low compliance with the exercise component because of fatigue or not having the time to perform the intervention. Other reported doing some exercise, but not enough to be compliant. On the basis of the patient logs, patients tended either to take the ONS as prescribed or not take them at all with the main reason for not taking ONS was that they did not

Figure 1 Trial profile.
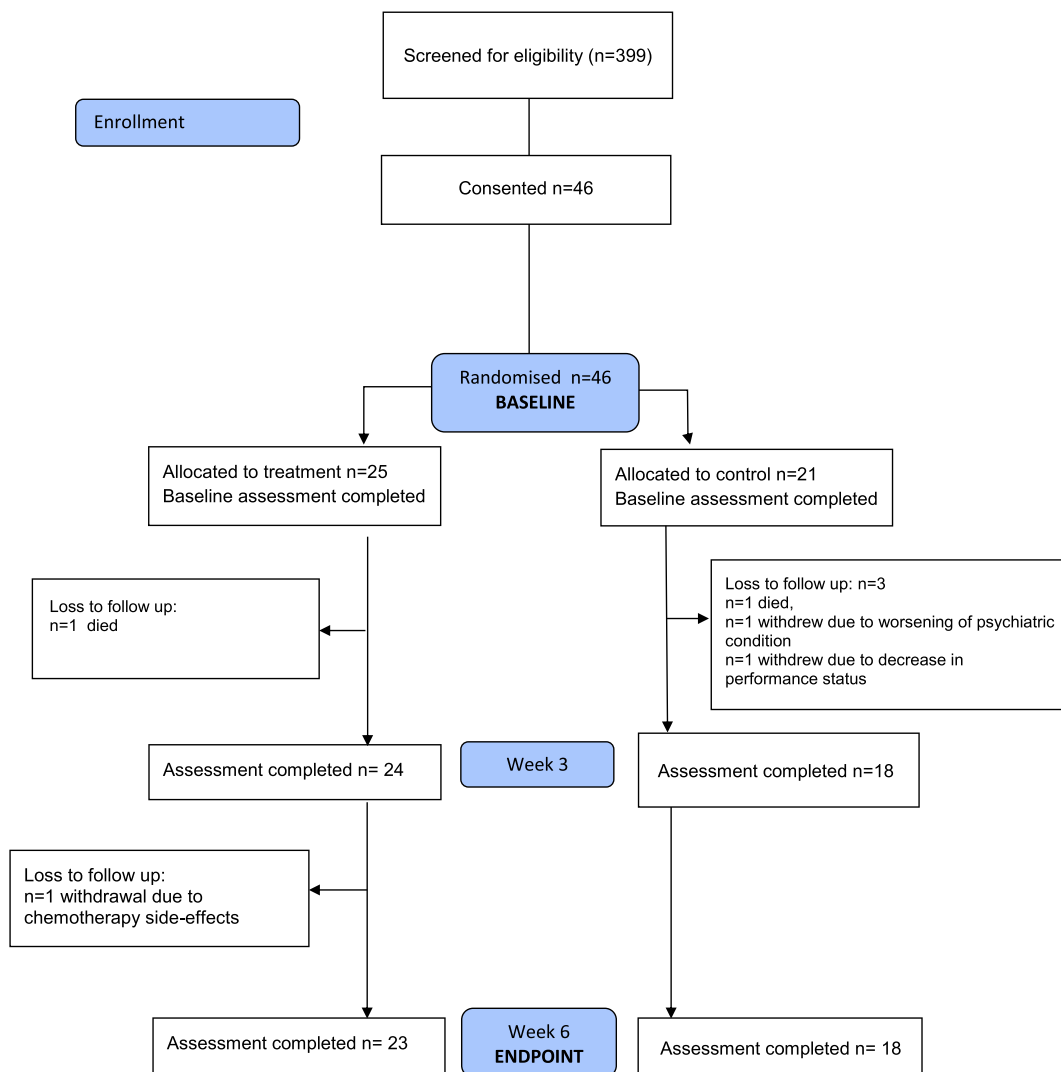
find it palatable. At baseline, plasma EPA levels were similar: 1.5% (0.34–4.5%) in the treatment arm ($n = 22$) and 1.0% (0.65–2.2%) in the control arm ($n = 18$) ($P = 0.21$). At week 6, the plasma EPA level increased to 3% (0.56–8.57%) in the treatment arm vs. 1.5% (0.63–3.76%) in the control arm ($P = 0.001$).

Contamination in the control arm

Only one patient allocated to the control arm tried to mimic the intervention by taking anti-inflammatory medication, nutritional supplements, and exercising. A further three patients took anti-inflammatory medication on their own initiative; thus, a total of 4/21(20%, CI 6%–48%) patients in the control arm took an NSAID. There was no evidence of patients in the control arm taking EPA based on analysis of EPA levels in blood. There was no evidence of increased

nutritional status (based on both AveS and aPG-SGA scores) and no evidence of increased physical activity (based on ActivPAL recordings) in the control arm. No patients in the control arm were referred to a dietician.

Based on assessments of recruitment, retention, compliance (except for ONS), and contamination, the trial was feasible.

Secondary endpoints

Weight, muscle mass, physical activity (ActivPAL and 6MWT), grip strength, nutritional status (aPG-SGA and AveS scores), and fatigue score per trial arm are shown in *Table* 3.

Patients in the treatment arm had a mean (SD) increase in body weight by 0.91 kg (2.47) whereas those in control arm

Table 1 Baseline patient demographics and clinical characteristics by trial arm

Characteristic		n	%	Median	IQR	n	%	Median	IQR
		\multicolumn{4}{c}{Treatment arm (n = 25)}			\multicolumn{4}{c}{Control arm (n = 21)}	
Age (years)				63.0	54.5–68.0			59.0	52.5–67.0
Male gender		15	60			11	52.4		
Ethnicity									
Caucasian		24	96			21	100		
Other		1	4.0			0	0		
Primary tumour									
NSCLC	III	2	8			3	14.3		
	IV	13	52			8	38.1		
Pancreatic	III	6	24			5	23.8		
	IV	4	16			5	23.8		
Site of metastases									
Bone		4	16			4	19		
Liver		2	8			4	19		
Lung		4	16			3	14		
Lymph node		12	48			8	38		
Brain		1	4			0	0		
Other		4	16			1	5		
Prior treatment									
Surgery		4	16			2	9.5		
Chemotherapy		4	16			1	4.8		
Radiotherapy		4	16			3	14.3		
Biochemical parameters									
C-reactive protein (mg/L)				12.0	5.0–43.0			6.5	0.3–29.2
Albumin (g/L)				38.5	34.3–42.5			38.0	35.0–43.0
Leucocytes (10^9/L)				9.0	6.5–11.0			8.0	5.5–9.5
Creatinine (μmol/L)				64.5	55.3–72.8			59.0	55.5–64.5
Assessments									
KPS				90.0	80.0–100.0			90.0	80.0–90.0
BMI				24.2	21.4–27.0			24.0	21.9–25.3
Weight loss (%)[a]				5.7	0.6–13.3			5.4	1.6–11.7

[a]In the previous 6 months

BMI, body mass index; IQR, interquartile range; KPS, Karnofsky performance status; NSCLC, non-small cell lung cancer.

Table 2 Compliance levels per intervention component (n = 25)

Intervention component				<50%		>50%		>80%	
				n	%	n	%	n	%
Celecoxib				6	24	2	8	17	68
ONS				13	52	2	8	10	40
Resistance				10	40	3	12	12	48
Aerobic				10	40	3	12	12	48
Aerobic	Resistance			14	56	3	12	8	32
Aerobic	Resistance	ONS		15	60	2	8	4	16
Aerobic	Resistance	Celecoxib		17	68	2	8	6	24
Aerobic	ONS			15	60	1	4	5	20
Aerobic	ONS	Celecoxib		15	60	1	4	5	20
Resistance	ONS			18	72	2	8	5	20
Resistance	Celecoxib			14	56	2	8	9	36
Resistance	ONS	Celecoxib		18	72	2	8	5	20
ONS	Celecoxib			15	60	1	4	9	36
Aerobic	Resistance	ONS	Celecoxib	22	88	0	0	3	12

lost 2.12 kg (2.50). *Figure* 2A shows percentage change in weight per trial arm. Patients in the treatment arm had a mean (SD) weight increase of 1.29% (3.42) whilst those in the control arm lost weight, mean (SD) −3.19 (3.67); $P < 0.001$.

In terms of muscle mass, patients in the both arms lost muscle. Assessment of muscle mass (using CT derived measures) between the trial arms is shown in *Figure* 2B, and there was no statistical difference between the groups.

There were no notable differences in physical activity (ActivPAL and 6MWT), grip strength, PG-SGA, and AveS per trial arm. C-reactive protein was also assessed at follow up and there was no difference between groups, $P = 0.94$.

Table 3 Weight, muscle mass, physical activity (ActivPAL and 6MWT), grip strength, aPG-SGA score, AveS score, and fatigue score per trial arm.

		Treatment arm Mean (SD)	Control arm Mean (SD)	P^a
Weight (kg)		$n = 23$	$n = 21$	
	Baseline	70.18(13.03)	66.63 (10.46)	
	6 weeks	70.82 (14.07)	64.93 (9.88)	
	Difference	0.91 (2.47)	−2.12 (2.50)	
	% difference	1.29 (3.41)	−3.19 (3.67)	<0.001
Muscle Mass (CT) cm^2		$n = 23$	$n = 20$	
	Baseline	133.79 (25.24)	129.91 (29.61)	
	6 weeks	130.96 (26.82)	123.07 (31.78)	
	Difference	−2.82 (9.41)	−4.97 (7.80)	
	% difference	−0.02 (0.071)	−0.042 (0.062)	0.030^b
ActivPAL Steps (no of steps)		$n = 11$	$n = 11$	
	Baseline	5407 (3485)	3651 (2609)	
	6 weeks	4872 (2523)	4632 (3171)	
	Difference	−536 (2296)	981 (1694)	0.50
Six minute walk test (meters)		$n = 19$	$n = 21$	
	Baseline	474.3 (79.1)	470.2 (87.2)	
	6 weeks	474.4 (103.3)	490.5 (101.1)	
	Difference	0.14 (65.2)	20.3 (53.9)	0.32
GripStrength (kg)		$n = 21$	$n = 17$	
	Baseline	35.7 (11.5)	32.3 (12.5)	
	6 weeks	35.3(9.9)	31.5(12.4)	
	Difference	−0.43 (7.24)	−0.71 (5.0)	0.69
PG-SGA score (0–36)		$n = 20$	$n = 17$	
	Baseline	8.64 (6.34)	10.12 (6.27)	
	6 weeks	7.70 (7.85)	10.24 (5.52)	
	Difference	−0.80 (5.29)	0.12 (6.67)	0.65
AveS score (0–10)		$n = 21$	$n = 16$	
	Baseline	7.74 (2.2)	7.00 (2.42)	
	6 weeks	7.74 (2.34)	7.06 (1.84)	
	Difference	0.00 (1.65)	0.06 (1.77)	0.91
Fatigue score (0–10)		$n = 22$	$n = 15$	
	Baseline	3.15 (1.84)	3.51 (1.54)	
	6 weeks	3.85 (1.85)	3.73 (1.94))	
	Difference	0.69 (1.14)	0.22 (1.77)	0.33

For weight and muscle mass, the P value is based on the percentage change. For the other parameters, the P value is based on raw change.
aPG-SGA, abridged Patient Generated Subjective Global Assessment; AveS, 10 point verbal scale assessment of nutritional intake
[a]2-sample *t*-test.
[b]Mann–Whitney.

The median (SD) survival in the treatment arm was 10 (7) months and in the control arm was 8 (10) months, $P = 0.57$. The most common grade 1 and 2 adverse events were nausea, pain, anorexia, constipation, dysgeusia, and dyspnoea in both trial arms. The most common grade 3 events (*Table* 4) were neutropenia and pain. There were in total 101 grade 1 and 2 events in the control arm and 113 grade 1 and 2 events in the treatment arm. None of the reported events (any grade) were related to cardiac disorders, ulcer, or renal function or reported related to the study drug. There were eight Serious Adverse Events in the control arm and 13 in the treatment arm, but none were related to the multimodal intervention.

Discussion

This randomized trial integrating nutrition, anti-inflammatory treatment, and exercise to target cancer cachexia demonstrates that it is feasible to administer a multimodal intervention for cancer cachexia in patients with lung or pancreatic cancer, alongside standard anti-cancer cytotoxic chemotherapy, with the exception of ONS where compliance was below the minimum expected. The multimodal intervention was safe, and the majority of patients completed the trial. There was limited evidence of contamination in the control arm (including plasma EPA measurement, AveS, and aPG-SGA score) again supporting the feasibility of the trial design. We also observed that the intervention resulted in a stabilization of body weight whilst those patients who did not receive the intervention, lost weight. However, this finding must be interpreted with caution as the trial was not powered to examine this.

The importance of cachexia as research priority has long been advocated and this is evidenced by the numerous consensus statements and reviews. In particular, multimodal trials have been recommended; however, the majority of cachexia trials have used single agents in isolation, or have lacked a comparator arm.[23,24] Where multimodal trials have

Figure 2 *(A)* Change in body weight (%) from baseline to endpoint per trial arm. Patients in the treatment arm had mean (SD) increase in weight of 1.29% (3.41) whilst those in the control arm lost 3.19% (3.67). *(B)* **Assessment of muscle mass per trial arm.** Patients in the treatment arm had a mean (SD) loss of muscle mass of 0.02% (0.071) vs. those in the control arm who had a mean (SD) loss of 0.042% (0.062).

A - Change in body weight (%) from baseline to endpoint per trial arm.
Patients in the treatment arm had mean (SD) increase in weight of 1.29% (3.41) whilst those in the control arm lost 3.19% (3.67).

B. Assessment of muscle mass per trial arm.
Patients in the treatment arm had a mean (SD) loss of muscle mass of 0.02% (0.071) versus those in the control arm who had a mean (SD) loss of 0.042% (0.062).
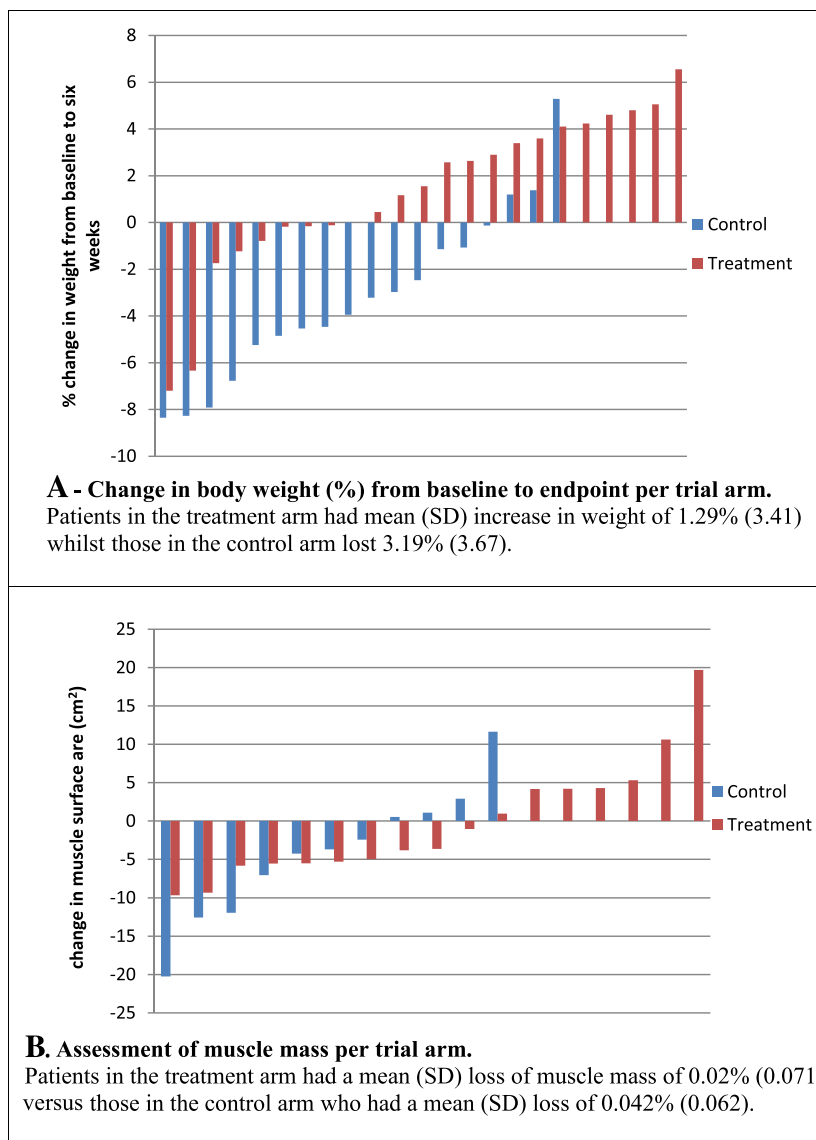
Table 4 Adverse events

Non-related adverse event (CTCAE 3.0)	Treatment arm (*n* = 25) Grade 3	Control arm (*n* = 21) Grade 3
Pain	2	2
Neutropenia	2	2
Infection	2	0
GI stricture: intrahepatic duct	0	1
Rectal bleeding	1	0
Total single events	7	5

been done,[25–27] these have examined two or more components, and whilst some findings have been encouraging, to date, there have been no randomised trials integrating all the components we consider to be appropriate and this has resulted in a failure to advance cachexia treatment.[28] Our findings suggest that multimodal cachexia intervention is safe and feasible and support further examination of this approach to fully assess effects on weight and lean body mass in larger trials.

There are several reasons why cachexia research has been challenging, and the present study has sought to address

these. Defining endpoints in cachexia research has been the subject of much debate, and at present, there is no consensus on what the optimal endpoint should be. The US Food and Drug Administration and the European Medicines Agency suggest that lean body mass gain and improved muscle strength/power should be used as co-primary endpoints for the treatment of cancer cachexia. However, this differs from agreed endpoints in rehabilitation studies for other chronic wasting conditions [e.g. chronic obstructive pulmonary disease (COPD)] where patient-centred outcomes such as physical activity level are used.[29]

We observed a positive effect on weight in the present trial; this is encouraging as cachexia-related weight loss is a key component of cachexia. Body weight is easily measured in the clinic and it is important to have end-points that can be implemented in clinical practice. From a patient perspective, weight loss is associated with psychosocial distress[30,31] whilst deteriorating physical function (e.g. performance status) is associated with reduced quality of life.[32,33] Based on our observations and supported by previous work, we propose that weight loss and physical function are favourable endpoints in cancer cachexia trials, being meaningful for both patients and oncologists. Whilst we have demonstrated that such endpoints are feasible, adoption into practice requires ratification.

One of the challenges in delivering complex interventions in cancer patients has been compliance and the present study provides valuable information on this. As expected, compliance with the anti-inflammatory medication was the highest of all the interventions. With the exercise component and the nutritional supplements, patients either had very high compliance or were not compliant, and this is expected in a real-life clinical setting. It must be anticipated that in a trial consisting of multiple interventions, compliance with each individual component will be reduced compared with compliance in a trial consisting of a single intervention. This was the case in the present trial, and the experience gained will help refine the multimodal intervention in any future studies. To illustrate, in patient in whom compliance in the ONS was low, it may be that ONS that are not enriched with EPA could be used, and instead, EPA supplementation given via oral capsule. Previous intervention studies have also demonstrated that compliance with ONS[34] and exercise[35] can be challenging, and there is an obvious risk that the control group may adopt the intervention. However, contamination in the control arm was limited in the present study, and this clearly bodes well for future trial designs adopting this approach.

Patients in general complied well with study assessments, with the exception of the ActivPAL physical activity metre that had variable compliance. Using an objective measure of physical function (ActivPAL), as opposed to subjective measures such as performance status, places the former in a favourable light; therefore, its role and measures to optimize compliance will be investigated further in future work.

The present trial has limitations. The open label design is not optimal, however, beyond blinding those analysing the CT scans and physical activity data, blinding patients or the staff involved in delivering the multimodal intervention is challenging; however, it could be argued that a placebo anti-inflammatory, an inert nutritional supplement, and/or stretching exercises could be used in the control arm. This unblinded design may also impact on the subjective outcomes employed. The design has the risk of control arm contamination, but in the present trial this was minimal. The sample size is considered large enough to inform on feasibility; however, the multiple comparisons performed in the context of the small sample size mean that firm conclusions on the secondary endpoints cannot be drawn. The observation of improvements in body weight may in part be explicable due to water retention caused by the NSAID, (0,5–1.0 kg reported previously).[36] However, the absence of signs of gross clinical oedema (increasing ankle swelling, ascites, and pleural effusions) provides some supporting favourable evidence that weight gain was not entirely due to expansion of the extracellular water space. Of note was that plasma C-reactive protein levels were higher in the treatment arm, and as higher C-reactive protein concentrations have been related to adverse survival, this may have counterbalanced any survival advantages conferred by the intervention.[37] Clearly the sample size was not designed to assess such aspects however this would be of interest in future studies.

Compliance with exercise was assessed using patient logs. There are clearly some disadvantages with this approach as these logs may not be completed accurately. Other measures to assess compliance could have been employed for instance constant assessment of physical activity (frequency, duration and intensity) over time using wearable activity meters embedded in armbands or watches (or 'new generation' technology such as SMART phones). However, the present trial involved multiple interventions in the context of a new cancer diagnosis and treatment plan; therefore, we chose minimize patient burden by keeping the activity assessment simple. Changes in step count are also worthy of mention. There may have been compensation in both groups with reference to physical activity as measured by ActivPAL. To illustrate, step count increased in the control arm, but decreased in the treatment arm. One possible reason is that those in the treatment arm walked less because they exercised more whilst those in the control arm walked more, by nature of the unblended intervention; this means that some control arm contamination may have been present. However, the small sample size makes interpretation difficult.

Although we recorded which factors affected compliance, it would have also been of interest to know how satisfied patients were with the multimodal intervention and/or any benefits that they got. Clearly, this is fundamental, as the benefits of any treatment only will be realized if patients take it.

Conclusions

This trial is the first to demonstrate that patients with advanced cancer who have a high risk of developing cachexia are willing and able to participate in a randomized controlled trial of a complex intervention that includes a defined exercise programme. The positive effect of the multimodal cachexia intervention on weight provides grounds for optimism that cachexia need not be an inevitable consequence of advanced cancer but rather may be attenuated through a multimodal intervention targeting its genesis. A larger, pragmatic, multimodal phase III trial assessing the effectiveness of anti-inflammatory treatment (EPA/NSAID), nutrition and exercise in cancer cachexia is now underway (EudraCT 2013-002282-19). Should this demonstrate that such an intervention can prevent or attenuate cancer cachexia; this would have considerable implications for clinical cancer care

Contributors

TS, BL, KF, and SK were responsible for the conception, design and interpretation of the data. TS, BL, KF, SK, PF, TRB, AB, and GS drafted the protocol. Drafting of the manuscript was led by BL and TS. Recruitment was done by BL, TS, SK, TRB, GS, and AB. MF contributed to study design and interpretation of the data. CT analysis was undertaken by NJ. EPA analysis was undertaken by TRB and CP. Data analysis was led by BL and supervised by PF.

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Conflicts of interest

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