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Lenalidomide in cancer cachexia: a randomized trial of an anticancer drug applied for anti-cachexia

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Abstract

Background Cancer cachexia (CC) impacts quality of life, physical function, anticancer treatment response, and survival. Inflammation is a prominent pathomechanism of CC. This small-scale study sets out to investigate the immunomodulatory drug lenalidomide in inflammatory CC in a randomized, double-blind, placebo-controlled trial.

Methods Patients with advanced solid malignancies, documented weight loss, no or unchanged anticancer treatment, and C-reactive protein > 30 mg/L were included. In a 2:2:1 randomization, patients received either lenalidomide 25 mg once daily or C-reactive protein-guided dose, starting with 5 mg lenalidomide once daily or placebo once a day for 8 weeks. Dose adaption and safety were assessed twice a week. Treatment response was defined as an increase of lean body mass of more than 2% in a lower lumbar computed tomography and an increase in dynamometer-assessed handgrip strength of 4 kg. Secondary endpoints included adverse events, C-reactive protein response, nutritional intake, and symptoms.

Results Of 24 eligible patients, 16 were included (25% female). At baseline, the mean age was 67 (range 51–88) years, and mean body weight was 64.7 kg (range 39.8–87.2 kg). Five were diagnosed with mesothelioma, two with non-small-cell lung cancer, two with renal cell carcinoma, two with neuroendocrine tumours, and five with other malignancies. Mean survival was 43 days. Eleven adverse events (four of which were severe) were recorded with a probable link to study participation. Nine patients completed the study. No participant showed a treatment response. C-reactive protein-guided dosing did not result in lower doses of lenalidomide. Lean body mass decreased less in the treatment groups. For the lenalidomide and placebo groups respectively, handgrip strength decreased by 2.3 vs. 5.5 kg, nutritional intake decreased by 249 vs. 32 kcal/day, and C-reactive protein increased by 35 mg/dL vs. decreased by 17 mg/dL. The study was closed prematurely due to slow accrual and the need for concurrent anticancer treatments.

Conclusions No treatment response on muscle mass and muscle strength was observed with lenalidomide. Because of several limiting factors, including low recruitment caused in part by an ambitious study design and concomitant anticancer treatment, this study did not generate adequate data to draw reliable conclusions.

Keywords Neoplasms; Cachexia; Randomized controlled trial; Lenalidomide

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Introduction

Cancer cachexia (CC) is a major physical, psychological, and social burden in patients suffering from advanced solid malignancy.[1,2] CC is defined by a negative energy and protein balance[3] and is an independent prognostic factor for survival.[4,5] A consensus classification differentiates between pre-cachexia, manifest cachexia, and a refractory stage of cachexia.[6] Pathophysiologic mechanisms vary in combinations of reduced food intake and hypermetabolism, associated with catabolism and inflammation caused by their underlying malignancy. Inflammatory processes manifested as systemic inflammation are thought to be the key mechanism in the development of CC.[7,8] Eating-related symptoms and nutritional intake are known to correlate with inflammatory processes.[9] Lean body mass and handgrip strength are established parameters for the assessment of CC.[10] A large trial testing a multimodal intervention is set up to measure the intervention's effects on lean body mass and handgrip strength after 6 weeks.[11]

Effective anticancer treatment can improve cachexia, whereas ineffective cancer treatment often worsens the signs and symptoms of cachexia.[12] Cachexia-targeted options are limited to conservative interventions, including nutritional support, physical exercise, and psychological interventions.[13,14] A few pharmacological treatments, namely, progestin, corticosteroids, and prokinetic drugs, have shown very limited effect in an insufficiently defined subset of patients.[15] Stabilization under this treatment usually lasts a few weeks only; therefore, new treatment approaches are needed.[16]

Lenalidomide, a derivate of thalidomide, is an immunomodulatory drug.[17] One of its main effects is a decrease in inflammatory cytokines. Lenalidomide is registered for the treatment of multiple myeloma. On the basis of the data on anti-cachexia drugs and the availability of lenalidomide with better tolerability than thalidomide, for which some moderately representative data have been published for cachexia, this randomized trial was designed to compare two different doses of lenalidomide and placebo control.[18]

The aim of the current trial was to test the effect of lenalidomide on muscle mass and grip strength in inflammatory CC in patients with advanced cancer undergoing basic standard of care cachexia management. We hypothesize that the effect of active treatment on lean body mass and handgrip strength will be measurable 8 weeks after initiation of treatment.

Methods

Study design

This randomized, double-blind, placebo-controlled trial was conducted at the oncology department of the Cantonal Hospital St. Gallen, Switzerland between March 2009 and December 2012.

Setting

At the oncology clinic at the Cantonal Hospital of St. Gallen, patients primarily receive anticancer treatment on an outpatient basis. Patients are admitted to the ward when necessary. An interdisciplinary tumour board decides on treatment indications and treatment type. A clinical trial unit provides access to experimental treatments.

Study population

Inclusion criteria for this trial were a Stage IV metastatic solid neoplasm, presence of CC, and inflammation (*Table 1*). The definition of CC was loss of body weight of more than 5% within the previous 6 months or 2% within 2 months according to patient records of family physicians. Inflammation was defined by a C-reactive protein increase of $>$30 mg/L in the absence of clinical signs of an active infection or any other systemic inflammatory disease. Because of the anti-inflammatory effect of lenalidomide and the plan to have a C-reactive protein-guided arm, a higher cut-off than the typical 10 mg/L was selected.[8] The baseline value was determined by the average of at least three measurements within 4 weeks before study start.

Trial treatment

Lenalidomide (5, 10, 15, and 25 mg), a thalidomide derivate, and placebo were provided by Celgene®. We randomly assigned study participants in a three-arm design to an 8-week treatment with oral lenalidomide of either 25 mg once daily, C-reactive protein-guided dose starting with 5 mg once a day, or placebo once a day in a 2:2:1 ratio. In the C-reactive protein-guided treatment arm, lenalidomide was increased stepwise to a maximum of 25 mg or maintained in case of a $\geq$50% reduction of C-reactive protein, whichever occurred first. C-reactive protein and safety response was assessed twice weekly.

To minimize confounding factors influencing the course of cachexia, a basic cachexia management was implemented for all study participants, starting 10–14 days prior to baseline assessment.[19–22] Nutritional counselling, physical activity counselling, and symptom management was provided in the outpatient cachexia clinic. This multimodal approach was offered systematically to all patients. However, no documentation was made of which patients received which elements, nor were there standardized measurements of the components in order to track progress.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	
Age (years)	>18
Neoplasia	Locally recurrent or metastatic incurable solid tumour
Loss of weight	≥2% in 2 months or ≥5% in 6 months
Inflammation	>30 mg/L
Ability to eat	No simple starvation
Anticancer treatment	None or stable for >4 weeks
No anti-cachexia treatment	
Exclusion criteria	
Untreated secondary cause of cachexia	
Relevant toxicity from anticancer treatment (≥Grade 2 toxicity CTCAEv3.0)	
Parenteral nutrition	

CTCAEv3.0, Common Terminology Criteria for Adverse Events version 3.0.

Safety assessments

Side effects were assessed clinically and in laboratory analysis twice weekly in the first 2 weeks and thereafter weekly at the oncological outpatient department. In the laboratory analysis, haematology and liver and kidney function tests were performed. In case of any clinical side effects of Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3.0) Grades III or IV, trial treatment was reduced or temporarily interrupted until improvement or resolution of the side effect.

Outcome assessments

Lean body mass was assessed by a computed tomography of the lumbar spine at the height of L4/L5 at baseline and after 4 and 8 weeks.[10] Handgrip strength was measured with the hand dynamometer Jamar® on both hands at baseline and after 4 and 8 weeks. C-reactive protein was measured weekly. Nutritional intake was calculated by a nutritionist according to a food protocol recorded for 2 consecutive days at baseline and after 4 and 8 weeks. Patient-reported outcomes were assessed by the Edmonton Symptom Assessment Scale at baseline and after 4 and 8 weeks.[23]

Statistical analysis

The primary endpoint for treatment response was a combined endpoint of improvement of the lean body mass and handgrip strength after 8 weeks. Improvement criteria of lean body mass were set to a minimally important clinical difference of an increase in lean body mass of >2% and the handgrip strength to increase more than 4 kg on either side.[24] Sixty patients were projected to be included into the trial.

The secondary endpoint for safety was the occurrence of serious adverse events and CTCAEv3.0 Grade III and IV adverse events during and until 4 weeks after administration of the last trial treatment. C-reactive protein response was defined as reduction of the mean C-reactive protein value at baseline of at least 50%. Descriptive statistics were used for the exploratory endpoints of nutritional intake and cancer symptoms.

Ethical considerations

The study protocol was written, and the trial was performed in accordance with the Declaration of Helsinki, the Guidelines of Good Clinical Practice issued by the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and Swiss regulatory authority's requirements. The protocol was approved by the local ethics committee (EKSG 09040) and the national drug administration Swissmedic (SM 2009DR2214).

Results

Subjects

The first patient was enrolled on 27 April 2010, the last one on 25 September 2012. Of more than 200 patients screened, 24 were eligible (*Figure 1*). Nine patients completed 8 weeks of treatment. Mean age at study inclusion was 67.3 years, and mean body mass index was 23.7.

The demographic profiles are shown in *Table 2*. Sixteen patients were included: 12 male and 4 female. The underlying malignancies of solid organs were heterogeneous. Five patients were suffering from mesothelioma, two from non-small cell lung cancer, two from renal cell carcinoma, two from neuroendocrine tumours, and five from various other solid tumours. Mean survival after study termination was 43.4 days, indicating the far advanced stages of malignancies of the study participants.

Treatment response

No participant receiving lenalidomide showed a treatment response as predefined. The mean decrease of muscle strength of both hands was 5.5 kg in the placebo group and 2.3 kg in the lenalidomide arms (*Figures 2* and *3*). The two patients in the placebo arm lost muscle mass (−646 mm/8 weeks and −278mm/4 weeks), one in the C-reactive protein group lost (−974 mm/4 weeks) and one gained slightly (+324 mm/4 weeks), and the two in the lenalidomide arm lost (−948 mm/8 weeks) or stayed stable (−5 mm/8 weeks).

Figure 1 CONSORT flow diagram.

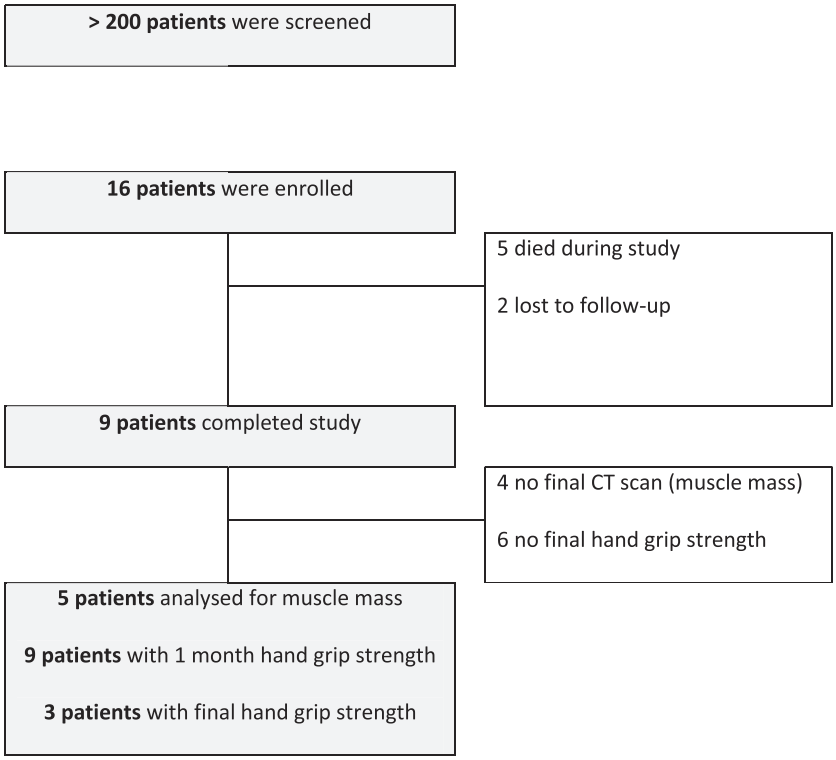

Table 2 Demographics

Participants: $n = 16$	Mean (min/max)
Gender (f/m)	4/12
Ethnicity	European
Malignancy (Stage IV)	Mesothelioma 5, lung 2, cervix 1, oropharyngeal 1, renal 2, neuroendocrine 2, anal 1, urothelial 1, endometrial 1
Age (years)	67.3 (51.3–88.5)
Weight (kg)	64.7 (39.8/87.2)
Height (cm)	168.4 (154/186)
BMI	23.7 (16.2/30.1)
Anxiety (value)	6.2 (1/12)

BMI, body mass index; f, female; m, male.

Safety

No adverse events were definitely related to the investigational product. Eleven adverse events were rated as 'probably related' (*Table 3*). Two adverse events occurred in the placebo group, three adverse events in the C-reactive protein guided, and six adverse events in the continuous lenalidomide group. Four adverse events fulfilled the criteria of being severe. One severe adverse event occurred in the placebo group and three in the fixed dose group, namely, leucopenia, dehydration, pulmonary infection, and renal failure. None of them was judged to be related to the investigational product. All probably related non-serious events resolved completely or with sequelae.

C-reactive protein response

A C-reactive protein response could not be observed (*Figure 4*). The mean difference of C-reactive protein between baseline and study termination was a decrease of 17 mg/dL in the placebo and an increase of 35 mg/dL in both lenalidomide groups. Additionally, C-reactive protein guiding did not result in lower doses of lenalidomide.

Other secondary endpoints

Concerning nutritional intake, data are available on five patients after 4 weeks and three patients after 8 weeks. Mean decrease of caloric intake was 32 kcal/day in the placebo and 249 kcal/day in the lenalidomide group. Nutritional intake was observed to be lower in the intervention groups. The WHO performance scores were stable. Patient-reported outcomes and symptoms, measured by the Edmonton Symptom Assessment Scale, did not show any patterns or trends (*Figure 5*). All symptoms of the patient with C-reactive

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Figure 2 Handgrip strength in kilogrammes (left hand).

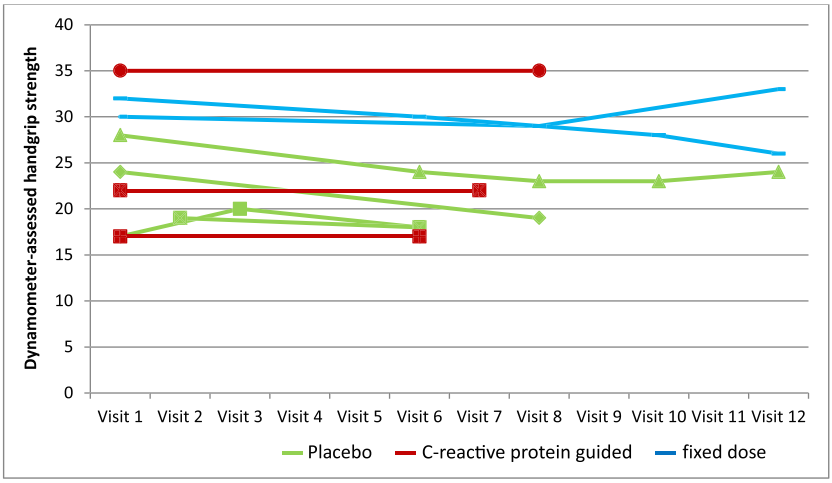
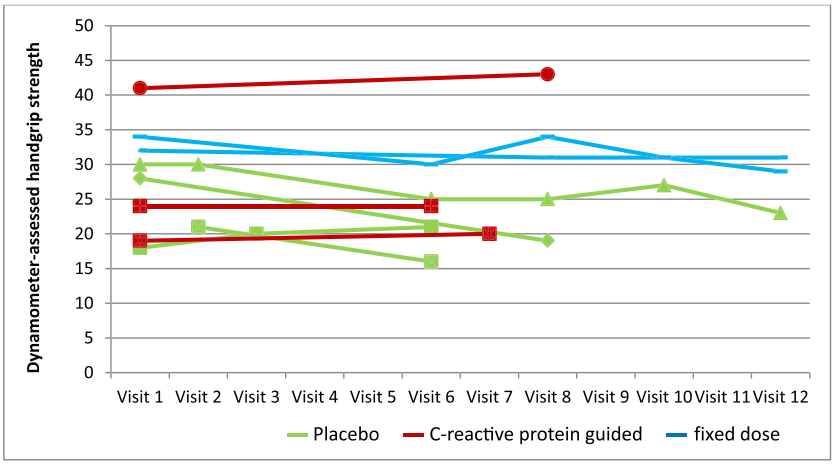


Figure 3 Handgrip strength in kilogrammes (right hand).



protein-guided treatment improved except appetite. Interestingly, in participants receiving 25 mg every day, symptoms worsened gradually.

Discussion

This is the first trial investigating the immunomodulatory effect of once daily oral lenalidomide against inflammatory CC in patients with Stage IV solid malignancies. Our double-blind, placebo-controlled trial with a 25-mg fixed dose and a C-reactive protein-guided dosing arm did not detect any treatment responder with regard to lean body mass increase or handgrip strength. There was less decrease in muscle mass and strength in the intervention group.

There was no response of C-reactive protein, nutritional intake, and no improvement of cancer-associated symptoms. However, conclusions are limited due to the early closure of the trial because of slow accrual. This trial did not result in major responses as many other anti-inflammatory cachexia trials showed, even though a multimodal management was applied as a backbone to this study.

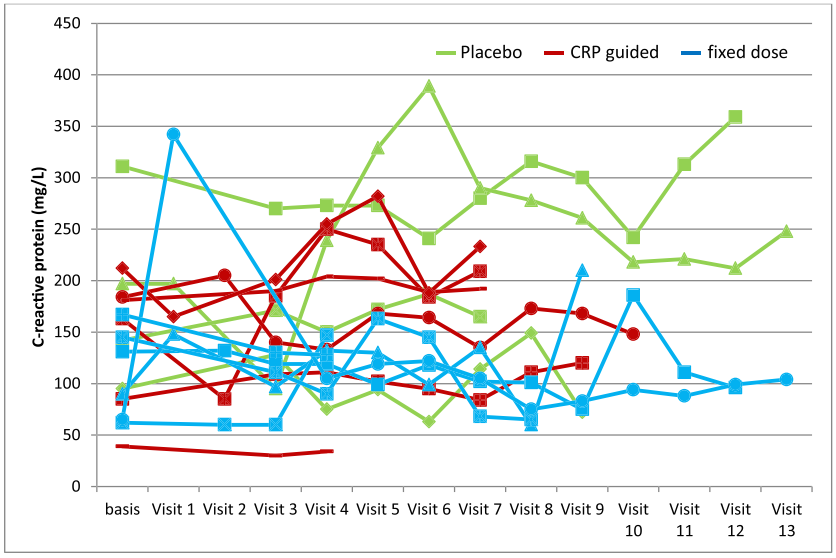
The CTCAEv3.0 Grades III and IV adverse events in advanced cancer patients are relatively common, in particular in those under conventional anticancer treatment. There was no clear difference of incidence and severity of adverse events between our intervention and the placebo arms. Possibly related adverse events seemed to be evenly distributed, although this could be due to chance. From our clinical experience, we judge the toxicity of lenalidomide in our setting with this severely morbid population, prone to

Table 3 Safety

	Total	Group 1 (Placebo)	Group 2 (C-reactive protein-guided dose)	Group 3 (fixed dose)
IP-related adverse events (*n*)	11	2	3	6
Definitely related to IP (*n*)	0	0	0	0
Probably related to IP (*n*)	11	2	3	6
Severe AEs (*n*)	4	1	0	3
Type of severe AEs	Leukopenia 1, dehydration 1, pulmonary infection 1, renal failure 1			
Non-severe AEs (n)	7	1	3	3
Type of non-severe AEs	Insomnia 1, bleeding 3, infection 1, tachycardia 1, hypokalaemia 1			

AEs, adverse effects; IP, investigational product.

Figure 4 C-reactive protein response.

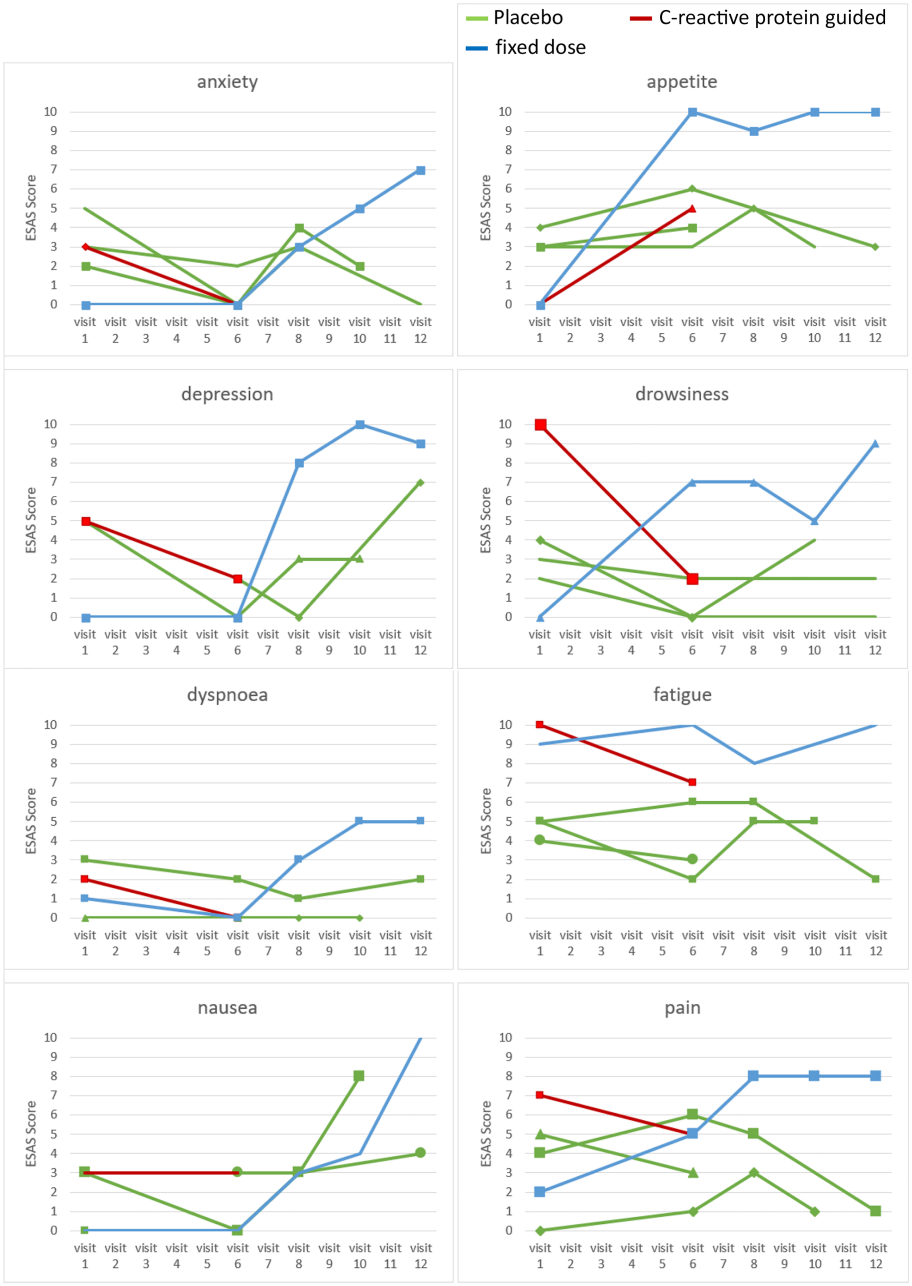


haematological toxicities, as within an acceptable range. The workup with twice weekly clinical and laboratory follow-up of side effects in the outpatient department and dose adaptation of lenalidomide however was substantial, although necessary to guarantee patient safety. For this study, it was paramount to have close collaboration between treating oncologists, the palliative care team, and the investigators. Future anti-cachexia trials should be designed in light of the rapidly changing developments in the field. The effect of lenalidomide on inflammatory cytokines such as tumour necrosis factor alpha and interleukin-8 should be assessed in future research. Furthermore, future study designs require very careful consideration about how to integrate clinical trials on anti-cachexia treatment with modern oncology.

Lessons learned

Accrual of study participants turned out to be much more difficult than projected when the study was planned. The main limiting factor was competing new anticancer treatment in Phase 1 drug development studies, which were preferred. Among them were several oral preparations. These were often given priority over lenalidomide, which was not designed to tackle the underlying disease. Lenalidomide is a drug with haematological toxicities; therefore, patients with cytotoxic cancer drugs could not be included in this trial due to the risk of additional toxicity. Additional reasons for the limited accrual was a lack of interest of patients to follow a study protocol at a late stage of disease with high morbidity and

Figure 5 Edmonton Symptom Assessment Scale (ESAS) symptom scores.



mortality. This led to the decision to close the trial due to low accrual.

Methodologically, using computed tomography of the lower lumbar spine to assess lean body mass assessment would have allowed for objective data and comparability between groups. However, many patients find this procedure exhausting. The investigation is relatively expensive, and calculations require special software and know-how, making it inconvenient for clinical practice. Handgrip strength measurement with Jamar is simple and can be easily adopted in daily business. Multimodal cachexia management was applied but not standardized.

The lack of generalizable results prompted the study team to reflect on the lessons that could be learned from this research. Preclinical research would have provided a firmer foundation on which to develop a study with human subjects. With the benefit of hindsight, we see that the study design of the clinical research was overcomplicated. During the research planning phase, we viewed the three-arm design as the only approach for answering our intended research

question. However, it was not plausible given the challenges of recruiting from a heterogenous population with very far advanced illness. Stratifying by Eastern Cooperative Oncology Group (ECOG) performance status could have helped to include patients at different points in the end-of-life trajectory. As it was, the patients included in the study were often too weak for a routine CT scan and/or were in such poor condition that it was not possible to obtain handgrip strength measurements. Even if we could have put measures in place to improve recruitment, the sample size calculation upon which this research was based was not realistic for generating data that could be analysed in a statistically robust way. This emphasizes the importance of defining intended analysis techniques before estimating the required sample size.

Our stated aims were ambitious, and we would have done better to create a project with a more limited scope but a more clearly defined structure. In particular, the trial should have focused in tightly as a proof of concept trial, leaving safety and efficacy to future research. Furthermore, defining co-primary endpoints introduced additional complication into the study design. In retrospect, it would have been better to select an elegantly simple endpoint, such as body weight, and create a study that could generate initial evidence for or against the use of lenalidomide for CC. By trying to combine all elements into one study, we failed to generate any reliable results about the use of lenalidomide in palliative setting. For future research, designs that are simpler and more practicable should be prioritized.

Conclusions

Treatment with lenalidomide required close monitoring. There was no increase in muscle strength for people with advanced illness and CC taking lenalidomide, but a trend to slow the decrease was observed. These observations must be interpreted in light of the very small patient numbers. Efforts should continue to explore different options for these CC patients to improve care and their quality of life. However, this study did not provide any indication that lenalidomide has the potential to improve cachexia among this patient group.

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Conflict of interest

D.B., C.H., R.O., S.d.W.-L., M.J., C.D., and F.S. declare that they have no conflict of interest.

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Ethical guidelines

The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.[25]

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