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Title: A novel multimodal treatment strategy for cancer cachexia; rationale and motivation for the MENAC (Multimodal – Exercise, Nutrition and Anti-inflammatory medication for Cachexia) trial

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ABSTRACT

Cancer cachexia is a multifactorial syndrome characterized by an on-going loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support alone. Cachexia has a high prevalence in cancer and a major impact on patient physical function, morbidity and mortality. Despite the consequences of cachexia, there is no licensed treatment for cachexia and no accepted standard of care. It has been argued that the multifactorial genesis of cachexia lends itself to therapeutic targeting through a multimodal treatment. Following a successful phase II trial, a phase III randomized controlled trial of a multimodal cachexia intervention is underway. Termed the MENAC trial (Multimodal – Exercise, Nutrition and Anti-inflammatory medication for Cachexia), this intervention is based on evidence to date and consists of Non-steroidal Anti-inflammatory Drugs (NSAID) and eicosapentaenoic acid (EPA) to reduce inflammation, a physical exercise programme using resistance and aerobic training to increase anabolism, as well as dietary counselling and oral nutritional supplements to promote energy and protein balance. Herein we describe the development of this trial - NCT02330926.

INTRODUCTION

Cancer cachexia is a multifactorial syndrome characterized by an on-going loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support.[1] The effects of cachexia are pronounced including increased mortality, reduced physical function[1] and increased symptom burden affecting quality of life.[2] Additionally patients with cancer cachexia are likely to have increased complications from anti-cancer therapy such as treatment delays and toxicity, which can result in increased health care costs. [3]

Despite the multiple consequences of cancer cachexia there is no licensed treatment for cachexia and no standard of care. Clinical trials in this field have focused on unimodal therapy and as such have had mixed results.[4 5] In recent years there has been an increasingly persuasive argument for trials that employ a multimodal intervention where multiple interdependent mechanisms that cause cachexia can be targeted in unison.[6] However, the evidence to support such a multimodal approach is lacking. We have recently completed a feasibility trial of a multimodal cachexia intervention, termed the preMENAC trial.[7] This was a randomised, phase II, open-label trial of a Multimodal Intervention (Exercise, Nutrition and Anti-inflammatory Medication) plus standard care versus standard care alone to prevent/attenuate cachexia in advanced cancer patients undergoing chemotherapy (clinicaltrials.gov ID; NCT01419145). The latter concept is also in keeping with the argument that practical rehabilitation alongside standard cancer therapies is justified.[8]

Following this we have recently opened the associated phase III trial, MENAC (**M**ultimodal Intervention - **E**xercise, **N**utrition and **A**nti-inflammatory medication in **C**achexia) - NCT02330926. The aim of the MENAC study is to attenuate or prevent weight and muscle loss

and to improve physical function in patients with lung or pancreatic cancer, receiving anti-cancer treatment. Herein we present the rationale and motivation for the MENAC trial. Ethical approval was not required for the present paper however ethical and regulatory approval has been given for the MENAC trial.

RATIONALE FOR KEY COMPONENTS OF THE MULTIMODAL INTERVENTION

ANTI-INFLAMMATORY MEDICATION

It has been demonstrated that cancer patients with cachexia often have increased inflammation and several studies show that pro-inflammatory cytokines such as interleukin 6 (IL-6) are involved.[9 10] Inflammation seems to be one of the main pathophysiological drivers in cachexia and as such, attenuation of the pro-inflammatory response has been argued as a key component of any cachexia therapy. Inflammation can be targeted via the following mechanisms:

- ***NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)***

NSAIDs block cyclooxygenase (COX) which converts arachnoid acid (AA) to prostaglandins resulting in inflammation and pain (via the COX-2 pathway). COX -1 is a consecutive enzyme present in most tissues in the body and blockade of this can increase the risk of gastrointestinal haemorrhage due to reduction of mucosa-protective prostaglandins. It is appealing to use NSAIDs in the treatment of cachexia as they counteract an upstream mechanism for inflammation and thus might influence several pathways (e.g. Interleukin 1 [IL-1] that reduces appetite[11] and Tumor Necrosis Factor α [TNF-α] that might influence muscle and fat catabolism[9]). Furthermore NSAIDs are inexpensive, easy to administer and have the potential of being a treatment option for many patients with cachexia, and which are well tolerated.

A systematic review examining the evidence for NSAIDs in the treatment of cancer cachexia, identified thirteen studies, of which six were comparative trials.[12] Most studies examined patients with advanced cancer of various types, however few studies examined NSAIDs alongside concomitant anticancer treatment. Of interest, some studies observed that patients receiving an NSAID had significantly improved body weight compared with controls, with differences ranging from 2.5 kg[13] and 2.9 kg[14] at 6 weeks to 5.1 kg at 12 weeks.[13] Another study, which did not report total weight as an outcome, reported a mean difference in lean body mass (LBM) after 16 weeks of 4.65 kg.[15] There was also evidence that NSAIDs may improve performance status and inflammatory parameters.[15] However, there were also common limitations across studies including small sample sizes and a multitude of outcomes.

This level of evidence was considered insufficient to recommend NSAIDs for the treatment of cachexia outside clinical trials recognising that new interventions should only be introduced when the evidence base is robust, especially considering the known side-effects of NSAIDs, (e.g. stomach ulcers).

As there was no clear guidance on the choice of NSAIDs for cachexia trials,[12] the selective COX-2 inhibitor celecoxib was used in the preMENAC trial, primarily because it had been examined in the greatest number of trials. However using, celecoxib in the preMENAC trial resulted in the exclusion of a large group of patients due to co-existing cardiovascular disease. In comparison, low-dose ibuprofen is often considered the NSAID with the least side-effects and has therefore been chosen as the NSAID in the MENAC study due to its favourable side-effect profile, beneficial effects in cachexia[13 16 17] and ease of availability. Ibuprofen will be taken three times daily and the dose of 1200mg/24 hours is based on previous work. [18]

- ***Ω-3 FATTY ACIDS***

The Ω-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and decosahexaenoic acid (DHA) are found in fish oils. Both EPA and DHA are competitive substrates with arachidonic acid (AA) for the cyclooxygenase pathway which lead to the conversion of less inflammatory lipid modulators than those derived from AA, and are both well recognized for their anti-inflammatory properties.[19] These actions, together with their ability to maintain muscle mass [20], probably account for the effects of Ω-3 fatty acids seen in cancer cachexia, either with EPA alone [21]or a combination of EPA and DHA.[20]

Prior systematic reviews have concluded that there is not enough evidence to determine a net benefit of EPA in cancer cachexia.[22] However, a narrative review reported positive effects[20] with one study demonstrating maintenance or gain of muscle mass in 69% of patients treated with EPA, versus 29% in the control group[23]. A further study reported a difference in muscle mass of 3.2 kg after five weeks treatment.[24] Recently, a recent systematic review concluded that Ω-3 fatty acids supplementation during chemo and/or radiotherapy seems to be beneficial in several outcomes, especially in conserving body weight and muscle mass, but that more studies are needed in substantiate this.[25]

The optimal dose of EPA and DHA supplementation to attenuate cachexia has not been defined, but intervention studies showing positive effects on muscle mass have used ONS providing daily intake of 2-2.2 g EPA and approximately 1 g of DHA.[26] In cachexia trials, oral Ω-3 fatty acids has been administrated either as capsules or as ONS.[27] The advantage of giving ONS compared to capsules is that they provide extra calories, proteins and micronutrients in addition to Ω-3 fatty acids. On the other hand, low compliance with ONS has been reported,[7] and

therefore alternative forms of administrations of Ω-3 fatty acids can be advantageous for the patients to ensure good compliance.

Based on current evidence, the Ω-3 fatty acids used in the MENAC trial are given via an ONS containing both EPA and DHA. If patients are not able to take the prescribed oral nutritional supplements (ONS) due to individual taste preferences[7] they will be offered capsules containing EPA and DHA in combination with another ONS without Ω-3 fatty acids to ensure the extra intake of calories and protein provided by the oral nutritional supplement alone. The dose of EPA and DHA is 2 g and 1 g daily respectively, which is in accordance with previous trials which have had positive effects on muscle mass.[23]

DIETARY INTERVENTION AND TREATMENT OF NUTRITIONAL IMPACT SYMPTOMS

Optimising food intake has been advocated as a key modality in the treatment of cancer cachexia.[28] In advanced cancer there are several reasons for patients to experience reduced food intake. Loss of appetite, or anorexia, is probably the most important precursor, but not for all patients.[29 30] One study showed that in patients with weight loss, 39% had no anorexia and 16% had normal food intake, while 12% of patients with anorexia had no weight loss.[31] Other studies have demonstrated that a wide variety of symptoms directly (e.g. oral dryness, taste change, nausea, vomiting) or indirectly (e.g. fatigue, psychological problems) interfere with food intake and energy balance.[29] Reversible causes of reduced food intake should therefore always be targeted in order to improve food intake.[32]

Only a few studies have recorded food intake in patients with advanced cancer and thereafter estimated energy intake and energy balance.[33-40] Although most of these studies show that

energy intake was insufficient to maintain stable weight, no clear association between energy intake and weight loss has been documented. These results reflect the complex causality of weight loss in advanced cancer. [33 34 37]

Evidence to support nutritional interventions in cancer is conflicting and a systematic review considering the effect of nutritional support identified five clinical trials examining the effect of weight and energy intake on dietary counseling.[41] Two of the five studies showed reduced weight loss in patients receiving dietary counseling (+ 1,4 kg vs. -2 kg, $p<0.05$, and +1% weight gain vs. -1.5% weight loss, $p=0.03$). [42,43] The authors concluded that increased energy intake may have some effect on weight loss in advanced cancer. Additionally a systematic review indicated that it was possible to maintain or increase energy and protein intake in patients by dietary counselling, but this was only evaluated in two studies (92% of total caloric need vs. 73%, $p<0.01$ and 1865±317 kcal vs. 1556±497 kcal, ns).[44 45]

Even if there are valid criticisms of the currently available evidence, it seems obvious that positive energy and protein balance cannot be reached without optimizing nutritional intake. In the MENAC trial, the nutritional intervention is dietary counselling (aiming to promote energy and protein balance) combined with ONS. In all patients it is fundamental to address symptoms such as pain and nausea in order to improve and maintain food intake. In the MENAC trial patients will be encouraged to increase meal frequency and intake of food and beverages with high energy density. Additionally, two cans of ONS daily contribute a total of 542 kcal and 30 g of high quality protein.

PHYSICAL EXERCISE

Physical exercise and in particular strength training, has an essential role in human skeletal muscle proteolysis and produces an anabolic effect leading to increased muscle mass and strength.[46] In patients with cancer, it has been demonstrated that exercise can improve muscular strength, reduce fatigue and increase health related quality of life, both during and after anti-cancer treatment.[47] There is a strong rationale for the benefits of exercise as part of multimodal anti-cachexia therapy as it has the potential to attenuate abnormalities in muscle metabolism found in cachexia[48]. In a review of studies exploring the effects of exercise on immunological and hormonal biomarkers in patients with cancer, data suggests that exercise can reduce levels of CRP but has a less consistent effect on other markers of systematic inflammation (e.g. cytokines) and hormones important in the regulation of muscle metabolism.[49] These reviewed studies were limited to early stage cancer patients and thus the therapeutic effects of exercise need to be explored further in defined cachexia populations.

A systematic review[50] examined the effect of physical exercise on muscle mass and strength during anticancer treatment and compared the relative effects of aerobic and resistance training. In total, 16 studies were included but most examined patients with stage I-III breast cancer, prostate cancer or patients undergoing stem cell transplants. Only one trial exclusively studied patients with advanced incurable cancer during palliative treatment and none of the trials characterized the patients as being cachectic or pre-cachectic. Of 13 studies measuring muscle strength, 11 reported significant improvements in both upper and lower muscle strength favouring both aerobic and resistance training. Five studies measured muscle mass and two of these reported significant improvement (5.2 %[51] and 1.0 kg [52]) again favouring exercise. These findings indicate that exercise can effectively maintain or improve muscle strength during anticancer treatment.

There is currently insufficient evidence to determine the optimal type and dose of exercise in order to counteract cachexia in patients with advanced cancer[53] especially as both the cardiorespiratory and muscular systems, are affected.

The design of the physical exercise component of the MENAC trial was thus based on evidence relating to safety and efficacy of exercise interventions trialed in all cancer populations, guided by international guidelines for cancer survivors[54 55] and modified to be feasible to offer with light supervision to an advanced cancer population. The main goal of the exercise intervention is to contribute to the prevention of muscle loss and to improve or maintain physical function. Therefore, in the MENAC trial the intervention will consist of functional resistance training three times each week in addition to aerobic training two times each week. This is a home-based exercise programme prescribed during an interview by a trained health professional and supported by a standardised instruction booklet. The intervention is based on experience from the preMENAC trial where compliance (deemed as $\geq$50% of individual components in $\geq$50% of patients) was 60% for the exercise component and was considered feasible[7]. It was observed that many patients in the intervention arm were more physically active than they otherwise would have been, but not enough to be compliant. To further optimise compliance, dependent on patient preference and centre service provision, exercise in the MENAC trial may be supervised on occasion. In addition the exercises have been modified from those in the preMENAC trial, so they can be performed without specialist equipment (free weights) so to become easier to implement across settings.

TREATING CACHEXIA ALONGSIDE ANTI-CANCER THERAPY

Cancer cachexia cannot be treated in a vacuum and the best way to treat cancer cachexia is to treat the underlying cancer. However, both chemotherapy[56] and targeted therapy[57] may cause

significant loss of muscle, a side effect for which there previously has been little attention. In patients with advanced cancer the motivation for giving chemotherapy is often to delay disease progression and thereby delay or reduce symptoms to maintain function and quality of life. It is therefore of importance to focus on possible side effects that might increase symptoms, instead of alleviating the total symptom load as intended. If chemotherapy is to be delivered, it is vital to develop strategies to minimize its side effects.

It is increasingly acknowledged that cachexia treatment needs to be initiated at an early phase of cachexia[6 20] and at this time co-treatment with anti-cancer therapy is inevitable. Some evidence exists that tumour-related outcomes or toxicity are improved where EPA[25], NSAIDs[58], nutrition[59] and physical exercise in isolation, are given alongside anti-cancer therapy. (Figure 1) Based on the above considerations, participants in the MENAC trial will enter when they are commencing anti-cancer therapy.

Systematic reviews on key components of the multimodal intervention have been completed by our group. [50 60-62]

MENAC TRIAL DESIGN

The MENAC trial is a prospective multi-centre randomised controlled trial of a multimodal therapy (oral nutritional supplements plus Ibuprofen plus exercise) versus standard care. Following randomisation, patients will be allocated to either the intervention or the control arm and key endpoints will be assessed after six weeks – Figure 2. After this, patients in the intervention arm will be allowed to continue and those in the control will be offered the multimodal intervention. This latter step is mainly to reduce contamination of the control arm with the aim of limiting those patients mimicking the intervention.

Although the six week time period may be considered short, data from previous studies showed that it is possible to achieve meaningful changes in weight in this time frame[14 16 63] whereas increasing it may result in unacceptable levels of attrition.[13] A cancer cachexia intervention is probably more likely to succeed at an early phase. Thus in the MENAC trial the aim is to include patients with a high risk of developing cachexia, or who are early in the cachexia trajectory.

Patients will be recruited from multiple sites in Europe and Canada. In order to have clinically meaningful findings it is necessary to demonstrate both effectiveness and feasibility of the multimodal treatment programme.

MENAC has received ethical and regulatory approval in countries where it is being conducted. Southampton Clinical Trials Unit (SCTU), a UK Clinical Research Collaboration registered CTU, is coordinating the trial in the United Kingdom with worldwide trial coordination from the Norwegian University of Science and Technology. An independent Trial Steering Committee and Independent Data Monitoring Committee has been set up to monitor trial progress and safety. The MENAC Trial Management Group includes representatives from medical and paliative care oncology, patients and CTU staff involved in the day-to-day running of the trial.

Endpoints

The primary objective of the MENAC trial is to prevent the development of cachexia and/or to attenuate cachexia progression. From a patient perspective a short term effect will be to improve physical and psychological function, to reduce symptom burden and to improve survival; in other words to live a longer and better life, during and after chemotherapy.

Defining the key endpoints in cancer cachexia is challenging and a lack of consensus from regulatory agencies (FDA and EMA) has failed to progress this. The FDA argue that any cachexia intervention must benefit both lean muscle mass and function; however defining how best to assess this is challenging and recent studies in this area have failed to meet end-points that assess muscle function.[4] Therefore it is important that the optimal way of assessing muscle function in cancer cachexia is decided with the caveat that traditional measures such as hand-grip strength may not be appropriate in this setting. As there is no consensus, the primary endpoint in the MENAC trial has been chosen on a pragmatic basis. Weight loss has been chosen as it is a key defining factor of cachexia and is meaningful for both patients and clinicians.[1]

It is expected that a difference in weight between the treatment groups is followed by a parallel increase in muscle mass and physical activity. These important factors are chosen as secondary outcomes in this trial.

Weight gain alone does not take into account increased oedema, increased tumour weight or the muscle loss that can remain undisclosed due to adiposities. Muscle mass, which is an essential factor in cachexia, will therefore be assessed by Computerised Tomography (CT) which is a validated, objective method.[64] CT scans were the chosen method over Dual-energy X-ray absorptiometry (DEXA), as CT scans are more available in most clinical centres and are usually done as part of routine care, leaving minimal additional burden for the patient and healthcare system. Physical activity level is objectively measured by ActivPAL™, a physical activity meter which assesses mean daily step count and time spent upright, using a small monitor attached to the anterior mid-thigh.

There will also be several exploratory endpoints investigating other consequences of the treatment. One set of exploratory endpoints is measured by Patient Reported Outcome Measures (PROMs - [appetite, physical activity and fatigue] using the European Organistaion for the Research and treatment of Cancer Quality of Life Questionnaire C30 [EORTC QLQ C-30])[65]and Health Status (EQ-5D-3L)[66]. Informed by findings from studies investigating effects from nutritional[67] and NSAID[12] interventions, our hypothesis is that various PROMs will improve with the multimodal intervention. There is however a non-negligible risk that the patients will feel overburdened by the treatment and that quality of life might be reduced. Therefore, the satisfaction and burden of the intervention will also be assessed.

NSAIDs are drugs commonly in use and major side-effects are relatively rare. There are however no large-scale evaluations of side-effects in this frail patient population, and side-effects are not necessarily transferable from other patient populations. Side-effects described by the patients will therefore be reported**.**

CONCLUSION

Currently there are no established treatments for cachexia and the condition is often neglected. Moreover, there is increasing evidence that current intensive oncological treatments are both exacerbating cachexia and are being curtailed by increased toxicity due to cachexia. There is consensus that cachexia is a multidimensional problem and that a multimodal approach to treatment is necessary. The intervention in the MENAC trial is based on thorough systematic literature reviews. It aims to establish a practical rehabilitation program that will provide the first evidence-based method to reverse this currently intractable syndrome that affects more than 50% of advanced cancer patients and reduces their quality of life and life expectancy[68].

Successful management of cachexia could have a major impact on supportive oncology, but could in addition also improve the tolerance and probability of completing chemotherapy and radiotherapy treatment. This trial, that will include patients from multiple countries, will hopefully help improve standardisation of nutritional and metabolic care of patients undergoing anti-cancer therapy.

The novel treatments developed in this project may subsequently benefit other diseases, as cachexia is not specific to advanced cancer. Common conditions such as heart failure, chronic kidney disease, rheumatoid arthritis and COPD would potentially also benefit from this research.

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CONTRIBUTIONS

TS, BL, SK, KF led the manuscript writing. KF conceptualised the MENAC trial. TB, AB, GS, VB, MM, MF, FS and GG had significant input in manuscript preparation. All authors approved the submitted manuscript.

COMPETING INTERESTS

The authors have no competing interests.

LICENCE

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FIGURE LEGENDS

Figure 1 – components of optimum cachexia management.

Figure 2 – MENAC trial schema.

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