Nutrition, Metabolism & Cardiovascular Diseases (2013) 23, S19–S24

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/nmcd

Nutrition, Metabolism & Cardiovascular Diseases

REVIEW

Mechanisms and treatment of cancer cachexia

J.M. Argilés [a,b,*], F.J. López-Soriano [a,b], S. Busquets [a,b]

[a] Cancer Research Group, Departament de Bioquímica i Biologia Molecular, Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain
[b] Institut de Biomedicina de la Universitat de Barcelona, Barcelona, Spain

Received 19 July 2011; received in revised form 12 April 2012; accepted 12 April 2012
Available online 30 June 2012

KEYWORDS
Wasting;
Cancer;
Anorexia;
Nutraceuticals;
Drugs

Abstract According to a recent consensus, cachexia is a complex metabolic syndrome associated with underlying illness and characterised by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss. Cachexia occurs in the majority of terminal cancer patients and it is responsible for the deaths of 22% of cancer patients. Although body weight is, indeed, an important factor to be taken into consideration in any cachexia treatment, body composition, physical performance and quality of life should be monitored. From the results presented here, one can speculate that a single therapy may not be completely successful in the treatment of cachexia. From this point of view, treatments involving different combinations are more likely to be successful. The objectives of any therapeutical combination are two: an anticatabolic aim directed towards both fat and muscle catabolism and an anabolic objective leading to the synthesis of macromolecules such as contractile proteins.

A definition of cachexia

Perhaps the most common manifestation of severe diseases, such as acquired immunodeficiency syndrome (AIDS), chronic heart failure (CHF) and cancer, is the development of cachexia. Although there is no single, generally agreed upon definition of cachexia, a recent consensus states that "cachexia is a complex metabolic syndrome associated with underlying illness and characterized by the loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia. Cachexia is distinct from starvation, age-related

* Corresponding author. Cancer Research Group, Departament de Bioquímica i Biologia Molecular, Facultat de Biologia, Universitat de Barcelona, Diagonal 645, 08028 Barcelona, Spain. Tel.: +34 934021002; fax: +34 934021559.
E-mail address: jargiles@ub.edu (J.M. Argilés).

0939-4753/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.numecd.2012.04.011

loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity" [1]. Indeed, cachexia occurs in the majority of terminal cancer patients and, according to Warren, it is responsible for the deaths of 22% of cancer patients [2]. Cancer cachexia is a multi-organ syndrome associated with cancer, characterised by body weight loss (at least 5%), muscle and adipose tissue wasting and inflammation, often associated with anorexia. Although a plethora of treatments for the cachectic syndrome has been proposed, unfortunately not a single one is completely satisfactory. When treating body weight loss associated with cachexia, two targets have to be considered. On the one hand, the food intake should be controlled with the aim of reducing anorexia (Fig. 1). In addition, contributing factors to decreased food intake could be assessed and treated. This clearly constitutes the first aim of the therapy of wasting. On the other hand, providing complete nutritional requirements by means of total parenteral nutrition does not abrogate the weight loss. It is thus clear that, in addition to control the food intake, the metabolic disturbances associated with tumour burden contribute most importantly to the appearance of cachexia, thereby neutralising the metabolic alterations which include abnormal carbohydrate metabolism, lipid mobilisation, hepatic protein metabolism and, above all, alterations in the rate of skeletal muscle protein breakdown (Fig. 1) [3].

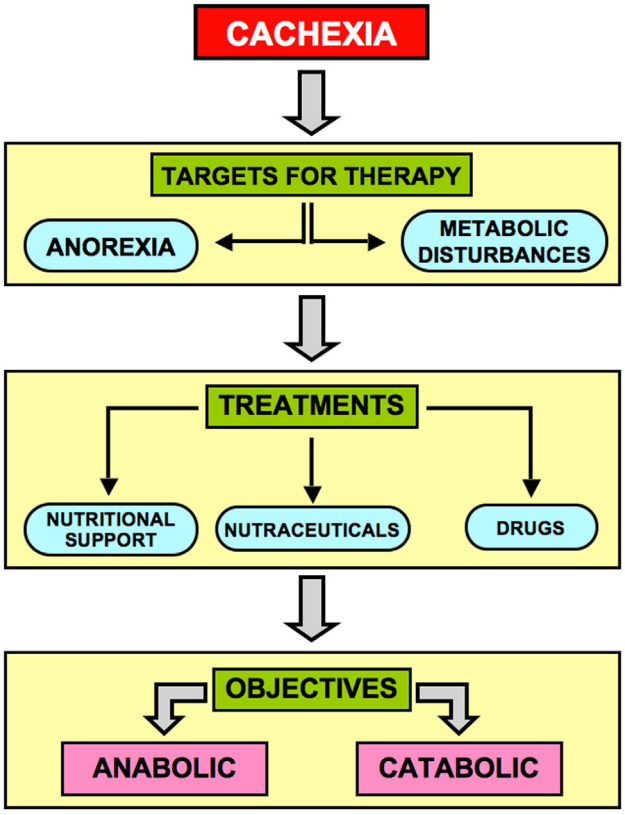

Figure 1 Therapeutical targets for cancer cachexia. There are different therapeutical approaches to fight anorexia and metabolic disturbances based in the combination of nutritional support, nutraceuticals and specific drugs. The objectives for cachexia treatment are two: anticatabolic (directed towards both fat and muscle) and anabolic (leading to the synthesis of macromolecules).

There are approaches for reaching the above-referred targets in addition to nutritional support. The use of the nutraceuticals has lead to interesting results [4—8]. For instance, Ryan et al. in a double-blinded randomised clinical trial, showed that enteral nutrition enriched with eicosapentaenoic acid (EPA) preserved lean body mass in oesophageal cancer patients [8]. Similarly, Read et al. in a phase II trial demonstrated beneficial effects (quality of life) of EPA-enriched nutrition in patients with advanced colorectal cancer [7]. On the other hand, and in order to revert metabolic disturbances, many drugs have been proposed and used in clinical trials, while others are still under investigation using experimental animals. Most likely, the best treatment of the cachectic syndrome is going to be a multifactorial approach. In relation to this, a combination of nutritional support with different nutraceuticals has already been relatively successful [9]. Possibly, a combination of nutritional support and nutraceuticals with specific drugs may lead to optimal results. In any case, the objectives of any therapeutical combination are two: an anticatabolic aim directed towards both fat and muscle catabolism and, an anabolic objective leading to the synthesis of macromolecules such as contractile proteins (Fig. 1).

End points for clinical trials

Independent of the treatment, the monitoring of cachexia is a key issue during therapy. Different parameters can be used but inevitably they rely on the targets mentioned before. In relation to anorexia, food intake, intestinal absorption, delayed gastric empting, and dysphagia constitute important parameters to be monitored. Often, the treatment of the tumour also causes alterations in taste and smell of food; therefore, this should also be taken into consideration. On the other hand, metabolic alterations are varied and complex. Assessment of energy expenditure (both resting and total), inflammation (C-reactive protein), glucose intolerance, fat mobilisation (lipolysis) and protein breakdown are important end points and should ideally be monitored (Fig. 2). Although body weight is one of the most important end points of any cachexia treatment, body composition (lean body mass, fat mass, water) should be analysed by means of body impedance analysis (BIA), dual-energy X-ray absorptiometry (DEXA) or (computed tomography (CT) scanning, since, for instance, an increase in body weight based on fat or water — without an increase in lean body mass — may not be very relevant (Fig. 2). It is very adequate to also include measurements of physical performance such as monitoring of total activity and grip force evaluation. Indeed, physical performance is linked with quality of life — that can be estimated through the use of different specific questionnaires — one of the most important end points of any cachexia trial. Finally, and also related with cancer treatments, survival is an end point that reflects the impact of any cachexia therapy (Fig. 2) [10].

Treating cachexia: fighting anorexia

Megestrol acetate (MA) and medroxyprogesterone (MPA) are synthetic, orally active derivatives of the naturally occurring hormone progesterone. In humans these