



Hot Topic

Towards a simple objective framework for the investigation and treatment of cancer cachexia: The Glasgow Prognostic Score



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ABSTRACT

Progress in the treatment of progressive involuntary weight loss in patients with cancer (cancer cachexia) remains dismally slow. Cancer cachexia and its associated clinical symptoms, including weight loss, altered body composition, poor functional status, poor food intake, and poorer quality of life, have long been recognised as indicators of poorer prognosis in the patient with cancer. In order to make some progress a starting point is to have general agreement on what constitutes cancer cachexia. In recent years a plethora of different definitions and consensus statements have been proposed as a framework for investigation and treatment of this debilitating and terminal condition. However, there are significant differences in the criteria used in these and all include poorly defined or subjective criteria and their prognostic value has not been established.

The aim of the present review was to examine the hypothesis that a systemic inflammatory response accounts for most of the effect of cancer cachexia and its associated clinical symptoms on poor outcome in patients with cancer. Furthermore, to put forward the case for the Glasgow Prognostic Score to act as a simple objective framework for the investigation and treatment of cancer cachexia.

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Introduction

Cancer is the most common cause of death worldwide with on average one in three people in the United Kingdom developing cancer in their lifetime. Treatment of cancer is most successful if detected and treated at an early stage. With more advanced disease there is an increased incidence of progressive involuntary weight loss i.e., cancer cachexia and related clinical symptoms including weight loss, altered body composition, poor functional status, poor food intake, and poorer quality of life. These are, in turn, associated with poorer outcome and survival, independent of tumour stage.

There are long established and routine standardised methods of staging the cancer that, for example TNM stage, describe the extent of tumour spread and its impact on outcome. In contrast, standardised objective methods that can routinely establish the extent of cachexia (e.g., imaging for muscle and fat mass) and related symptoms and their impact on outcome are not established. The objective definition of cancer cachexia and its clinical symptoms has remained problematical since the most commonly used assessments weight loss, performance status and quality of life do not have standardised objective measurements.

This problem is highlighted by a recent proposal that “Cancer cachexia is defined as a multifactorial syndrome characterised by

an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism [1].” Despite being the result of a consensus of experts in the field, this definition, with a reliance on patient recalled weight loss, was not composed of routine objective and well standardised measurements that had established prognostic value. Also, due to the lack of an effective treatment weight loss remains a problematic therapeutic target. Therefore, it is not surprising that progress in the treatment of cancer cachexia remains slow and illustrates the maxim of Lord Kelvin, “I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind”, Lord Kelvin (1824–1907).

A detailed examination of the mechanisms underlying the relationships between poor food intake, the systemic inflammatory response and the GPS have been previously reviewed [2,3]. The focus of the present review is to examine how such information might be used to provide a simple, objective, and clinically relevant framework for the identification and treatment of cancer cachexia. Furthermore, to put forward the case for the Glasgow Prognostic Score (Table 1), a systemic inflammation based scoring system, to

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Table 1
The Glasgow Prognostic Score (GPS) is proposed to form the basis of an objective framework for the assessment and treatment of cancer cachexia (proposed for use in all patients with cancer).

Score	Measurements	Framework	Intervention
GPS = 0 No Cachexia	Albumin (>35 g/l ¹) C-reactive protein (<10 mg/l ¹)	Weight loss uncommon-no metabolic upset.	If weight loss then assessment of other cause of weight loss and dietary intervention if necessary.
GPS = 0 Undernourished	Albumin (<35 g/l ¹) C-reactive protein (<10 mg/l ¹)	Weight loss common-no metabolic upset.	If weight loss then assessment of other cause of weight loss and dietary intervention if necessary.
GPS = 1 Pre cachexia	Albumin (>35 g/l ¹) C-reactive protein (>10 mg/l ¹)	Weight loss uncommon-metabolic upset.	If weight loss then anti-inflammatory and dietary intervention.
GPS = 2 Refractory Cachexia	Albumin (<35 g/l ¹) C-reactive protein (>10 mg/l ¹)	Weight loss common-metabolic upset.	If weight loss then anti-inflammatory and dietary intervention. Referral for palliative care.

act a simple objective framework for the investigation and treatment of cancer cachexia.

Weight loss and the systemic inflammatory response

Progressive involuntary weight loss has long been recognised as a major element of cachexia in the patient with cancer. Indeed, Hippocrates (460–370 BC) described such a patient in the terms of “the shoulders, clavicles, chest and thighs melt away. This illness is fatal.” In 1932 Warren, in a post mortem study of 500 patients, described cachexia as the most common cause of death across a variety of cancers [4].

In the more recent era, Dewys and co-workers in 1980 assessed the effects of weight loss in 3047 patients prior to undergoing chemotherapy. They reported an increase in the percentage involuntary loss of weight in patients was independently associated with poorer survival. Furthermore, that the presence and amount of weight loss observed varied between different tumour types, specifically pancreatic, gastric and lung cancer being more likely to have a greater loss of weight. This work attempted to give an objective assessment of patients and quantify a threshold where the degree of weight loss (between a minimum of 5% and 10%) would become significant in patient survival [5].

Since then, although the classical presentation of a patient with an advanced malignancy of being emaciated and wasted from the loss of body tissue is still commonly seen by medical practitioners, little progress has been made on defining the amount and type of weight loss and over what period it is associated with poor outcome.

In contrast, there is now good evidence that the systemic inflammatory response, objectively defined, is one of the main factors associated with weight loss and the loss of skeletal muscle in patients with cancer [6–11].

Body composition and the systemic inflammatory response

Following on from the clinical assessment of weight loss, work has focused on the objective measurement of separate components of body composition and their relationship with patient outcome. This is primarily based on the rationale that a reduction in lean tissue would be associated with a corresponding functional decline [12]. Methodologies used to assess lean tissue have included Total Body Potassium [13], Bioelectrical Impedance Analysis (BIA) [14–16], Air Displacement Plethysmography (ADP) [17], Dual-energy X-ray Absorptiometry (DEXA) [16,18] and more recently CT and MRI scanning [19,20].

Much of the initial assessment of body composition was carried out using DEXA scanning. The advantage is that a low dose of radiation is required to assess both fat mass and lean mass of soft tissue and total body bone mineral. DEXA has been long utilised and has been validated in the assessment of body composition in patients with cancer [18].

In more recent times the use of routine CT and MRI scans as part of the routine tumour staging of the patient with cancer has facilitated more routine assessment of body composition in the patient with cancer. Specifically, the benefit of CT scanning is the ability to objectively assess both visceral and subcutaneous fat as well as that of skeletal muscle [21].

Recent work has reported that, using CT scans, sarcopenia is associated with an increase in chemotherapy toxicity [12,22–24]. The presence of both sarcopenia and obesity in pancreatic, respiratory and gastrointestinal cancers was associated with poorer survival [25,26]. For example, a low muscle mass was associated with poorer outcome in patients undergoing liver transplantation [27]. In patients undergoing liver resection for colorectal metastasis sarcopenia was associated with a 3-fold increase in risk of post-operative complications but no significant change in cancer recurrence and has been found to predict post-operative infectious complications in patients with colorectal cancer [28,29]. Therefore, it is of interest that an analysis of pre-operative CT scans carried out in 174 patients with colorectal cancer patients showed that a reduced skeletal muscle mass was associated with the presence of a systemic inflammatory response as evidenced by the GPS [30]. However, it remains to be established whether a CT derived skeletal muscle mass has additional prognostic value to that of the GPS.

Functional status and the systemic inflammatory response

In 1982, The Eastern Cooperative Oncology Group published their assessment of patient's functional deterioration or performance status [31]. This was a simplified version of the patient assessment proposed by Karnofsky [32]. The ECOGps scale is a five point scale with 0 being fully active and 5 being death. The ECOGps has been cited more than 3000 times in the literature and has been used in a wide variety of clinical scenarios. Although ECOGps has been widely used it is a subjective measurement with associated variability. Little progress has been made in the objective classification of functional status.

A series of studies have shown that the systemic inflammatory response, as evidenced by the objective GPS, had equivalent or superior prognostic value compared with the subjective ECOG in patients with lung, and gastrointestinal cancer [33–36]. Recently, Laird and co workers reported that, in two cohorts of 1825 patients (test) and 631 patients (validation) with a variety of advanced tumours across eight European countries, the GPS was directly associated with ECOGps and had equivalent or superior prognostic value compared with the subjective ECOGps [37].

Poor food intake and the systemic inflammatory response

A reduction in food intake and symptoms of anorexia, are common in patients with progressive cancer. Measurement of these has focused on actual dietary intake with the use of food records

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