CANCER CACHEXIA IN THORACIC MALIGNANCY: A NARRATIVE REVIEW

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ABSTRACT

Purpose of review: Thoracic malignancies are amongst the most lethal of all cancers. Cancer cachexia (CC) lacks unanimously accepted diagnostic criteria and therefore is referenced to as a conceptual framework whereby CC is “an ongoing loss of skeletal muscle mass (termed sarcopenia), with or without loss of fat mass that cannot be reversed by conventional nutritional support and leads to progressive functional impairment”. This review summarises the current evidence base in this field, including imaging techniques currently used to define sarcopenia, inflammatory and metabolic changes associated with the syndrome and ongoing research into potential treatment strategies.

Recent findings: Sarcopenia is a key component of the CC syndrome. It is common in patients with both early-stage and advanced NSCLC. Patients with sarcopenia have more treatment-related side effects and poorer overall survival compared with non-sarcopenic patients.

Summary: Early identification of CC may facilitate stratification of patients most-at-risk and initiation of emerging anti-cachexia treatments. If these are proven to be effective, this strategy has the potential to improve tolerance to anti-cancer therapies, improving the quality of life, and perhaps the survival, of patients with thoracic malignancies.

INTRODUCTION

Thoracic malignancies are amongst the most lethal of all cancers and include non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) and malignant pleural mesothelioma (MPM). Previous studies report widely varying estimates of the prevalence of cancer cachexia (CC) in these diseases, with the most data available in NSCLC, but little or no data previously reported in SCLC, MPM and rarer thoracic cancers such as the thymic malignancies. Understanding the significance of CC in these diseases is complicated by the lack of a universally accepted and applied set of diagnostic criteria. In 2011, an expert international panel defined CC as "a multi-factorial syndrome defined by ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be reversed by conventional nutritional support and leads to progressive functional impairment"[1]. CC is also associated with various physiological and metabolic events, including systemic inflammation and alterations in basal metabolic rate. In this review, we report the prognostic significance of CC, or its component parts where data regarding CC *per se* have not been reported. Since the latter situation is common in this field, we have focused particularly on the constituent elements of CC, including weight loss, sarcopenia (as defined by a variety of imaging tools, which are discussed in some detail) and the systemic inflammatory response. We conclude with an overview of emerging therapeutic strategies that seek to prevent or reverse CC in patients with thoracic malignancy, with the ultimate aim of improving quality of life and survival by improving tolerance to anti-cancer therapies.

CANCER CACHEXIA SYNDROME

The prevalence of CC has been reported to range between 50–80% in advanced solid cancers[2, 3], with prevalence reported towards the higher end of this range in patients with

gastrointestinal tract and lung cancers[4, 5, 6]. The prevalence of CC is less well-defined in terms of specific thoracic malignancy sub-types with most paper simply recording data for 'lung cancer' without differentiation into NSCLC (or its sub-types) or SCLC. No prevalence data exist regarding MPM.

WEIGHT LOSS

Weight loss is a principal constituent of the CC syndrome and is common in patients with thoracic malignancy[7–10]. Martin *et al* recently reported a scoring matrix that integrates weight loss with changes in BMI, which could be effectively used to predict survival independently of cancer type, tumour stage, age, sex and performance status in patients with locally advanced or metastatic cancer; 2,561/8,160 (31.4%) of patients in the training set had respiratory cancer[11]. In NSCLC specifically, weight loss has been associated with adverse outcomes independent of disease stage, performance status and age[12]. Conversely, weight gain in advanced NSCLC patients receiving chemotherapy has been identified previously as an early indicator of clinical benefit[13]. In patients with brain metastases from NSCLC and SCLC, being underweight is an independent prognostic factor[14]. In MPM, previous studies relating to weight loss are discordant, with some studies reporting an adverse association with prognosis[15–18] and others not[20, 21].

ANOREXIA

Anorexia or loss of appetite, is common in patients with NSCLC[28] and SCLC[29]. Baseline anorexia has been found to be significantly related to survival in patients with MPM[30]. Anorexia is thought to result from a complex interplay between neuropeptides and cytokines[22]. In animal models, pro-inflammatory cytokines released from tumours induce anorexia by activating neuronal cells expressing anorexigenic pro-opiomelanocortin (POMC)

in the hypothalamus[23]. POMC and interleukin-1 receptor expression are also suppressed by ghrelin, which increases appetite by up-regulation of agouti-related peptide and neuropeptide Y expression[23]. Interestingly, patients with stage III and IV NSCLC and anorexia have significantly higher levels of ghrelin compared to patients without anorexia[24, 25], but despite this, patients with CC do not, in general, report increased appetite. Although researchers have postulated potential reasons for this paradox, mechanisms resulting in increased ghrelin levels in CC remain unclear[26]. Parathyroid hormone-related peptide released by tumours has also been implicated in promoting anorexia and muscle wasting[27].

ALTERED METABOLISM

The catabolic effects of CC result in depletion of skeletal muscle and fat mass[31]. Previous studies have reported that patients with metastatic NSCLC have an elevated resting energy expenditure (REE)[32, 33] which may contribute to the wasting process[34, 35]. In these studies, REE was expressed as per kilogram of fat-free mass[32] and as unadjusted REE (measured by indirect calorimetry) and adjusted REE (measured by dual x-ray absorptiometry (DEXA), potassium-40 measurement and tritiated water dilution[33]. Interesting patients REE have previously been shown to higher again in patients with SCLC compared to those with NSCLC[36]. This observation is concordant with clinical experiences in this classically more aggressive lung cancer sub-type and was associated with higher circulating levels of soluble TNF-receptor 75 and cortisol in the SCLC patients in this study.

SYSTEMIC INFLAMMATION

The above observation emphasises the important link between elements of the CC syndrome and the systemic inflammatory response, which can be defined by single measures (commonly the acute phase proteins CRP and albumin), haematological indices (e.g.

neutrophil: lymphocyte ratio (NLR), platelet: lymphocyte ratio (PLR) or integrated scores, most notably the modified Glasgow Prognostic Score (mGPS; which combines C-Reactive Protein (CRP) and albumin).

In SCLC, measures of a systemic inflammatory response have previously been associated not just with higher REE, but also with adverse outcomes[39]. Hypermetabolic patients with NSCLC who lose weight also have elevated levels of inflammatory mediators, including acute phase proteins[37]. In the same illness, high baseline and progressive increases in NLR have previously been associated with poorer overall survival and weight loss[38]. Elevated NLR also correlates with sarcopenia in post-operative NSCLC patients[40], while a useful prognostic index based on BMI and NLR has been reported in patients with advanced NSCLC[41]. An elevated NLR also confers a poor prognosis in male patients with SCLC[42] and in male and female MPM patients receiving systemic treatment[43]. In MPM, elevated NLR and PLR have also been shown to affect disease-free survival[44].

Pre-operative increased CRP has previously been associated with a poor prognosis following subsequent resection of NSCLC[45]. Similarly, in MPM pre-treatment CRP levels have previously been associated with subsequent clinical benefit from multi-modality treatments incorporating surgical resection[46]. In advanced NSCLC, low serum albumin has been shown to be a predictive marker of chemotherapy toxicity and adverse survival[47]. Low serum albumin is also a significant prognostic factor in patients with MPM[48]. In addition, mGPS, which integrates these values, is predictive of survival in patients with both metastatic NSCLC and SCLC[49].

ALTERED BODY COMPOSITION

Imaging tools are available for the assessment of body composition including Dual-Energy X-ray Absorptiometry (DEXA), Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). DEXA is used to measure total appendicular lean tissue mass and has commonly been used for the evaluation of cancer cachexia in clinical trials. A recent study that utilised DEXA to define pre-sarcopenia (using a definition of appendicular skeletal muscle mass ≤ 7.26 kg/m^2 for men and ≤ 5.45 kg/m^2 for women) identified this in over half of the patients with MPM studied[50]. However, DEXA is not routinely performed in the clinical setting and measures lean body mass which is not equivalent to muscle mass *per se*. CT has the advantage of routine availability, facilitating both easier prospective studies and the ability to perform retrospective analyses on existing cohorts. CT images, typically those acquired at the level of the third lumbar vertebrae (L3) can then be used to directly measure muscle and fat indices using readily available software packages and sex-specific cut-off values (see *Imaging Considerations* for further details).

Sarcopenia

Sarcopenia is defined as a decrease in skeletal muscle mass. It can be defined using sex- and BMI-specific indices based on measurements of tissue density (Hounsfield Units (HU) derived from a single slice, mid-axial CT image (traditionally at L3) using body composition software tools[51, 52]. Previous estimates of the prevalence of sarcopenia in thoracic malignancy vary widely. In advanced NSCLC this has been reported to be as high as 60–80%[7, 50]. However, these studies often do not specify patients' disease stage[54–60], for example, opting for the terms 'unresectable'[60] or 'pre-terminal'[61]. In earlier stage NSCLC, pre-operative sarcopenia has been reported in 13.9–55.7% undergoing potentially curative survival resection[40, 62–66]. A recent systematic review and meta-analysis identified heterogeneity between study populations (Western versus South East Asian populations), the measurements

(total skeletal muscle area versus total psoas muscle area) and cut-points (varying sex- or BMI-specific) used to define sarcopenia[67] as potential reasons for the varying prevalence of sarcopenia reported in NSCLC.

In SCLC and MPM the prevalence of sarcopenia is even less well defined, with no previous data being published in MPM. In SCLC, South Korean researchers recently reported a prevalence of 79.2%[68] using locally derived cut-points.

The prognostic importance of sarcopenia has been shown in several previous studies of patients with lung cancer[56, 69, 70]. In the radically-treatable NSCLC surgical population, pre-operative sarcopenia has been associated with poorer outcomes in most studies[40, 62, 64, 67]. A single analysis found no such association but had a short median follow-up period of 26.3 months[65]; (compared to 35.5–61 months in the other cohorts). In patients with early stage lung NSLC who are not fit for surgical resection, stereotactic body radiotherapy (SABR) has recently emerged as a means of delivering radical treatment to inoperable patients (often because of severe respiratory or cardiovascular comorbidities). In this setting, pre-treatment sarcopenia has recently been identified as a risk factor for non-lung cancer death[72], but interestingly not associated with increased lung cancer-related mortality.

In more advanced NSCLC, patients with sarcopenia prior to initiation of palliative chemotherapy[73], chemo-radiotherapy[77] and anti-PD-L1 immunotherapy (with Nivolumab)[79] have been shown to have increased mortality relative to non-sarcopenic comparators. Sarcopenia has also been associated with reduced tolerance to chemotherapy[75, 76] and has been shown to predict survival regardless of body weight[52]. Patients with NSCLC receiving tyrosine kinase inhibitors have a slower rate of skeletal muscle loss than those receiving cytotoxic chemotherapy. The may reflect lower toxicity from the molecular targeted therapy,

including less adverse events such as fatigue, loss of appetite and gastrointestinal symptoms that may direct affect sarcopenic change[78]. In patients with SCLC, sarcopenia is also associated with shorter overall survival [68, 71].

Imaging Considerations

As mentioned earlier, skeletal muscle measurements have traditionally been acquired at the level of L3 across many cancer sub-types. However, this convention poses particular limitations in patients with thoracic malignancy, in whom routine CT acquisitions may not extend this inferiorly. This is especially problematic in retrospective studies, where many patients cannot be included, but also adds complexity and cost to prospective research, since routinely acquired imaging cannot universally be employed. Previous thoracic malignancy researchers have therefore sought alternative measures of skeletal muscle area. Total psoas cross-sectional area, for example, has been associated with prognosis in patients prior to pneumonectomy for locally-advanced NSCLC[63]. Axial CT images acquired at T12 have also been used to study skeletal muscle loss pre- and post-surgery for NSCLC[80]. Low pectoralis muscle area at diagnosis of NSCLC, has also been associated with adverse survival in a previous study[81]. The use of location-specific reference muscle areas has been further extended by recent data which reports that temporal muscle thickness on Head CT imaging is an independent predictor of survival in patients with NSCLC patients and brain metastases[83]. This study quoted a high prior correlation between psoas muscle areas and temporal muscle thickness and more data of this sort are urgently required. Validation studies of skeletal muscle measurements made on thoracic CT images, relative to established L3 values, would be a considerable advance in this field – maximising the size and reducing the cost of future studies. Authors from a single centre in South Korea recently reported high correlation

between pectoralis muscle area (measured at the aortic arch and at L1) and L3 muscle index in patients with SCLC[82], but further studies in this setting and in NSCLC and MPM are needed.

Sarcopenic Obesity

Sarcopenic obesity describes a clinical phenotype in which obesity (BMI≥30) and low muscle mass occur simultaneously[56]. At present, there have been few studies that have assessed the clinical significance of sarcopenic obesity in patients with thoracic malignancies. In a cohort of Canadian patients, including some with thoracic malignancies, sarcopenic obesity was an independent predictor of adverse survival[56]. In addition, in a recent study of NSCLC patients receiving carboplatin-based doublets, patients with the highest body surface area: lean tissue ratio (a feature associated with sarcopenic obesity) had a higher rate of dose-limiting haematological toxicity compared with patients having the average overall body surface area: lean tissue ratio[75].

POTENTIAL TREATMENT OF CC IN THORACIC MALIGNANCY

Better understanding of the biology underlying CC in thoracic malignancy and development of early detection strategies, as described above, provides an opportunity for therapeutic intervention. The goal of these strategies is to improve QoL, tolerance to cancer therapies and ultimately to improve survival. At present, corticosteroids are the most commonly used CC treatment, having been shown in randomised trials conducted decades ago to improve appetite and QoL[87, 88]. However, these drugs are powerful agents with potent immunomodulatory effects and significant toxicities that limit both dose and treatment duration in many patients. They are also contra-indicated, at all but very small doses, in patients receiving immunotherapies, which are becoming increasingly important in the anti-

cancer armamentarium. Simple nutritional interventions have been shown to increase weight and lean body mass in patients with lung and pancreatic CC receiving chemotherapy[85]. Early, intensive nutritional intervention combined with antiemetics has also been shown to prevent weight loss in patients receiving chemotherapy for NSCLC[86].

Increasing interest and understanding of CC biology has recently driven a more targeted approach to CC drug development, including the evolution of more specific appetite stimulants, anabolic/catabolic transforming agents, anabolic therapies and multi-modal interventions that combine different approaches.

Appetite Stimulation

Anamorelin is a novel selective ghrelin receptor agonist which has anabolic and appetite-enhancing activities. Anamorelin significantly increased lean body mass but not handgrip strength in the ROMANA 1 & 2 trials[9], which enrolled x patients with inoperable stage III/IV NSCLC and CC. The ROMANA 3 study found that Anamorelin was well tolerated and safe over 12–24 weeks[90] in a further x patients. Anamorelin is not currently approved for use and two further Phase III studies are currently underway.

Anabolic/Catabolic Transforming Agents

Espindolol which has three pharmacological targets[91]: blockade of non-selective β-receptors (thus reducing catabolism), antagonism of central 5-HT1a receptors (potentially reducing fatigue and thermogenesis) and partial agonism of β2 receptors (increasing anabolism). The ACT-ONE trial tested two doses of twice daily Espindolol in a randomized, double-blind,

phase II multicentre trial, which recruited n patients with advanced colorectal or NSCLC-related CC. In 2016, the trial reported their primary endpoint of a positive weight slope of 0.54 kg/4 weeks for the high-dose Espindolol group compared with weight loss in the placebo group (negative weight slope of -0.21 kg/4 weeks). They also reported improvement in fat free mass and maintenance of fat mass in patients with advanced NSCLC and CC. Espindolol is not currently approved for use but Phase III study is planned.

Anabolic Therapies

The complex interplay between androgens and androgen receptors can have positive effects on muscle mass and strength by promoting tissue anabolism[92]. Unfortunately, the Prevention and Treatment of Muscle Wasting in Cancer Patients (POWER) 1 and 2 trials, which assessed the efficacy of a non-steroidal selective androgen receptor modulator (Enobosarm) against a placebo in patients with Stage III and IV NSCLC, did not meet the primary endpoints of improvements in total lean body mass or physical function at 3 months[93, 94].

Multimodal Interventions

A feasibility study of Multimodal Exercise/Nutrition/Anti-inflammatory treatment for Cachexia (Pre-MENAC) was a randomised, phase II study designed to determine the feasibility of a multimodal intervention which included exercise, n-3 polyunsaturated fatty acid nutritional supplements, and an anti-inflammatory agent in patients with advanced lung and pancreatic cancer[95]. The authors recently reported positive feasibility results and a phase III efficacy study is underway; change in body weight at 6 weeks has been selected as the primary end-point[95]. Similarly, the Nutrition and Exercise Treatment for Advanced Cancer (NEXTAC) programme found that early introduction of multimodal interventions was

associated with high levels of compliance and safety in elderly patients receiving chemotherapy for pancreatic cancer and NSCLC[96].

CONCLUSION

CC remains an understudied complication of the thoracic malignancies, including NSCLC, SCLC and MPM. Estimates regarding the prevalence of CC in NSCLC vary greatly and little data exist in SCLC or MPM. From the data that have been reported, there is general agreement that CC is associated with reduced tolerance to cancer therapies and poorer overall survival. Future research in this field should include more practical and precise definitions of the CC syndrome, making best use of available data, including cross-sectional imaging, circulating measurements and serial weight and BMI recordings. A better understanding of the origin, clinical significance and targetable vulnerabilities associated with CC in thoracic malignancy is required for development of specific treatments. This will require integration of both tumour (e.g. volumetric staging, genomics)97 and host biology and the conduct of large scale randomised clinical trials.

KEY POINTS:

- Cancer cachexia (CC) remains a largely understudied and untreated condition
- CC results in reduced tolerance to treatment and poorer overall survival
- Future steps in the identification of CC should combine routinely available clinical tests such as serial weight and BMI measurements, inflammatory indices and cross-sectional imaging

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