Editorial

Cancer cachexia research: coming of age

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Cancer cachexia or muscle wasting is a debilitating syndrome that is observed in majority of end stage cancer patients. Patients with metastatic cancer have the highest prevalence and most severe degrees of cachexia or muscle wasting which results in worst prognosis and extremely poor quality of life (1). Unfortunately, the therapeutic options for the management of cancer associated cachexia are limited (2). The last decade has seen some increase in attention towards the topic of cancer cachexia and muscle wasting with steady rise in number of publications each year (>7,000 articles on PubMed search using keywords '*Cancer Cachexia*'). There is also increasing attention from stake holders, thinktanks and funding agencies to help promote research on this topic and implementation of policies focused on cancer comorbidities research (including muscle wasting research). However, more work needs to be done in order to make inroads against this multi-faceted syndrome and requires holistic approaches and interdisciplinary research interactions.

There is now consensus on the definition of cancer cachexia. The uniformly put forward definition of cachexia is "presence of weight loss of 5% or more within 12 months, or body mass index (BMI) less than 20 kg/m^2 when weight change is not known, and the presence of three or more of the following conditions: (I) muscle weakness, (II) fatigue, (III) anorexia, (IV) low lean body mass (LBM), and (V) abnormal biochemical data" (3). After this consensus definition, additional versions were agreed upon on the diagnostic criteria for cancer cachexia. According to newer definition, cachexia can be diagnosed as "a multifactorial syndrome characterized by a persistent loss of skeletal muscle mass (with or without fat loss) that cannot be completely reversed by conventional nutritional therapy and that progresses to functional impairment" (4).

Non-small cell lung cancer (NSCLC) and gastrointestinal cancer patients are more prone to cachectic symptoms (5,6). Cachexia is one of the major reasons for poor performance status and reduced ability to take optimal doses of chemotherapy. For NSCLC patients, cachexia is considered as a complication of common comorbid chronic lung diseases, such as chronic obstructive pulmonary disease (COPD) and direct correlations between the two have been established (7). These observations suggest that cachexia management should be one of the major goals during the treatment of NSCLC or other solid tumors of which the patients demonstrate more pronounced muscle wasting and related comorbidities.

The article from Morita-Tanaka and colleagues (8) is a timely narrative review bringing the reader's attention to the problem of cancer cachexia. Aside from some systematic reviews, majority of existing articles focus on one aspect of the biology of cachexia. Such knowledge (in review format

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or research articles) is dispersed in bits and pieces in the web of science. Morita-Tanaka and team have done an excellent job in bringing several different aspects of cancer cachexia under one review. This article covers in depth the signaling mechanisms supporting muscle wasting and emerging strategies being used in the clinical setting centered around ghrelin agonist anamorelin (as highlighted in *Fig. 1* of the review). The article begins with the detailed description of the various definitions of cachexia. This is followed by passages on the major signaling pathways that have been commonly attributed to manifestation of cancer cachexia. The authors have made sure to make use of simplistic diagrams showcasing the broader range of organs being targeted by these cachexia promoting pathways. The figures also inform readers on common pathways that are guiding cancer cachexia, pulmonary cachexia, COPD, idiopathic pulmonary fibrosis (IPF) and their overlapping roles in lung cancer associated cachexia.

From a generalized account of cachexia and its supporting signaling, their article gradually shifts to a more focused description of the significance of muscle wasting in NSCLC. The authors bring forward relevant information on how comorbidities such as COPD and IPF exacerbates cachexia and vice versa leading to complications in NSCLC patients. This is important for clinical management of NSCLC patients who predominantly present with COPD and IPF. The utility of anamorelin in such comorbid patients has been shown to reduce the complications associated with both COPD and IPF (9).

Immunotherapy has changed the treatment landscape for NSCLC. With Food and Drug Administration (FDA) approval to nivolumab in 2nd line, pembrolizumab in patients with PD-L1 >1% in second line and atezolizumab between 2015–2017, there has been an increase in the armament of options for patients with NSCLC (10). Nevertheless, immunotherapies have to be carefully designed for patients with cachexia. As highlighted by Morita-Tanaka and colleagues, several studies indicate that patients with cachexia and sarcopenia have lower progression-free survival (PFS) compared to those without (8). Strategies such as nutrition and exercise from early on may help manage symptoms in order to improve the quality of life of patients undergoing treatment.

Given the background knowledge on pathways supporting cachexia, cross talk with common comorbidities such as COPD and IPF, impact on choice of treatment, and outcome studies with immune checkpoint inhibitors, some discussions on available treatments are warranted. Addressing this, the authors bring forward background knowledge on discovery and development of ghrelin agonist as an anti-cachexia agent. The article carries a section on pathways under the regulation of ghrelin especially related to diet promoting switch vis a vis growth hormone secretagogue receptor (GHS-R1a). The section highlighting clinical progress of ghrelin agonist anamorelin is well balanced and covers the challenges and successes during the early stage drug development process. A number of studies are highlighted including ONO-7643-04 in which 100 mg of anamorelin daily for 12 weeks showed improvement in cachexia parameters and increase in diet. Other studies highlighted in this section are two phase III trials (NCT03743051 and NCT03743064) that are ongoing. The point raised by authors on drug-drug interactions and side effects particularly related to impact on sodium channels is helpful for clinicians planning to put their patients on anamorelin trials.

Despite considerably expanded use in cancer patients, ghrelin agonist cannot increase muscle strength. Anamorelin works indirectly through appetite stimulation thereby improving muscle mass. Addressing this issue, the authors describe the Nutritional and Exercise Treatment for Advanced Cancer (NEXTAC as well as NEXTAC-Two and NEXTAC-3) studies that are inter institutional trials incorporating diet and exercise in patient with cachexia. Some suggestions include better monitoring and reporting of weight loss, appetite loss and related symptoms that require appropriate education to caregivers, patients and family members.

While there is some progress in management of cancer cachexia through nutritional supplements and agents such as anamorelin, we are still a long way from finding curative therapies for cachexia. Therefore, novel biomarkers need to be identified urgently with the goal to directly enhance muscle strength in cancer patients. The authors have dedicated a short section to discuss novel therapeutic targets covering molecules such as Growth/Differentiation Factor 15 (GDF-15), mammalian target of rapamycin complex (mTORC), muscle growth factor inducible 14 (Fn14), muscle RING finger 1 (MuRF1), SPRY domain-containing SOCS box protein 1 (Spsb1), serum amyloid A1 (SAA1), and ZRT/IRT-Like Protein 14 (ZIP14). This section could have been further enhanced with in-depth discussion on the biology of each target that was superficially described. Additionally, another short section on biomarker development could have made this review more comprehensive. Especially, there was no description

of epigenetic regulators of cachexia and sarcopenia and utility of such markers in diagnostic or treatment strategies were not covered. A number of studies on non-coding RNA mediated regulation of muscle wasting are emerging and have been reviewed recently in the same journal (11). Addition of microRNA related information would have further enhanced the breadth of this narrative review.

Nevertheless, the article by Morita-Tanaka and colleagues is a one stop shop for readers interested in learning about the various molecular mechanisms guiding cancer cachexia (8). This article also guides the reader towards latest clinical developments in terms of new therapies that are emerging for muscle wasting syndrome. Some hints on future research and holistic approaches including patient and caregiver education makes this article of broader interest to the biomedical field. Cachexia is a multifaceted syndrome and a complex unmet clinical problem. A cumulative effort at all fronts starting from basic scientists, pharmaceutical industry, clinicians, hospital caregiving staff, hospice facility staff, and educators is needed to address this complex problem. Such concerted effort is absolutely necessary in order to successfully find effective new drugs and better management strategies to improve the lives of advanced cancer patients that predominantly suffer from cachexia.

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