short review

memo (2021) 14:20–23
https://doi.org/10.1007/s12254-020-00637-6

memo
magazine of european medical oncology

Sarcopenia in cancer—a focus on elderly cancer patients

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Received: 3 June 2020 / Accepted: 7 July 2020 / Published online: 29 July 2020

Summary Geriatric assessments, nutritional counseling and monitoring of muscle health before and during therapy are of high clinical significance in the management of elderly cancer patients. Criteria, data and cut-offs characterizing cancer-related geriatric sarcopenia are sparse and no consensus about definitions exists to date. We hence highlight a need for clinical trials focusing on sarcopenia in elderly cancer patients, based on its high prevalence and potential negative consequences on therapy outcomes, mortality, quality of life and physical mobility.

Keywords Muscle loss · Muscular atrophy · Muscle strength · Nutritional therapy · Treatment outcome

Sarcopenia is a pathological condition appearing with advanced age and defined as a progressive decline in muscle strength due to loss of skeletal muscle mass and quality. It is associated with adverse impact on survival and increasing disability, immobilization, falls and infections and consequently leads to higher rates of hospitalization [1]. The prevalence of sarcopenia ranges from 5–13% for people aged 60–70 to 50% for people aged older than 80 years [2]. Medical grading systems define presarcopenia, sarcopenia and severe sarcopenia based on the appearance of low muscle mass alone or the combination of low muscle strength and/or physical performance. In some cases, sarcopenia is accompanied by an increase in fat mass termed "sarcopenic obesity", which may balance body weight and hinder detection of the condition. Sarcopenia can be considered "primary" when no cause can be detected or "secondary" when caused by evident and often multifactorial causes.

Secondary sarcopenia is frequently detected in elderly cancer patients and is a pathophysiological feature of cancer cachexia, a metabolic syndrome, characterized by cytokine-mediated degradation of muscle mass [1]. Etiologic factors of cachexia are higher levels of energy consumption through metabolic changes and inflammation, combined with malnutrition and decreased muscular activity [1]. In this state, the tumor and its microenvironment secrete pro-inflammatory and catabolic cytokines such as TNFs, IL-1 and proteolysis-inducing factor (PIF), which in turn lead to release of several myofibrillar proteins that activate cascades resulting in muscular atrophy. Furthermore, cancer is suggested to result in the release of inflammatory proteins reducing appetite and of proteins such as hormone sensitive lipase, adipose triglyceride lipase, protein kinase A and the lipid-mobilising factor (LMF), which all induce lipolysis of adipose tissue [3–5].

The prevalence of sarcopenia among cancer patients differs between cancer types and stages and is more common in males [6, 7]. Villaseñor et al. determined a prevalence of 16% in nonmetastatic breast cancer patients, while Stene et al. reported a frequency of 71% in patients with advanced lung cancer. Pretherapeutic sarcopenia was found in 38.6% of cancer patients, with highest penetrance in patients suffering from esophageal and small-cell lung can-

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cers [8]. Geriatric assessment before cancer treatment including the identification of sarcopenic symptoms was hence recommended by the Society of Geriatric Oncology (SIOG). Assessing sarcopenia and adapting therapy regimens to the physical status of elderly cancer patients is recommended since sarcopenia was associated with chemotherapy toxicity, treatment complications and cancer-related fatigue [9].

Sarcopenia as a risk factor for poor outcome

The importance of assessing sarcopenia is indicated by the findings of numerous studies, which investigated sarcopenia as a risk-factor for increased mortality and linked it to reduced progression-free and/or overall survival (OS) in women with breast cancer [10] and ovarian cancer [11] as well as patients suffering from lung cancer [12], acute myeloid leukemia [13] or head and neck cancer [14]. In addition, Lee et al. reported sarcopenia as an independent prognostic factor for poor OS of elderly patients with gastric cancer, exhibiting a median survival of 6.8 months compared to 10.3 months for patients without sarcopenia [15]. Similar results were shown for colorectal cancer patients suffering from sarcopenia (median OS 14.6 months for the sarcopenic cohort versus 38.6 months for the nonsarcopenic cohort) [16]. It was reported that the emergence of sarcopenia in the early postoperative period in elderly esophageal cancer patients was associated with a higher risk of tumor recurrence and worse survival. In this study 64% of patients suffered from loss of body weight of more than 10% after surgery. In addition, patients with the most prominent postoperative decline of skeletal muscle mass suffered from more extensive blood loss and a higher extent of lymph node metastases [17]. A recent preliminary retrospective study reported that nonsarcopenic non-small cell lung cancer patients treated with PD-1 inhibitors (nivolumab or pembrolizumab) had better overall and long-term responses than sarcopenic patients [18]. Since nonspecific immune reactions during disease progression may be involved in muscle wasting, sarcopenia is under further suspicion of negatively influencing the outcome of immune therapies. Increased release of IL-6 and TNF-α leading to elevated neutrophil/lymphocyte ratios or specific T-cell profiles such as a minor presence of $CD8^+$ recent thymic emigrants and $CD8^+$ effector memory cells are hypothesized to favor muscle destruction [19, 20]. Aside from comparably poorer survival, sarcopenic cancer patients also suffer from reduced quality of life and are more susceptible to develop depression and anxiety symptoms [21].

Sarcopenia and cancer treatment

Secondary sarcopenia is often caused by oncological treatments. Long-term use of hormone deprivation therapy, which is commonly used in prostate and breast cancer treatment, for instance, is a major driver of sarcopenia. It was found to be associated with a significant drop of whole-body tissue composition, muscle and bone mass [22]. Glucocorticoid treatment given to reduce chemotherapy side-effects or to alleviate cancer-related symptoms is further considered a strong mediator of sarcopenia [23], having said that chemotherapy and targeted therapy themselves are able to cause the development of sarcopenic symptoms [24]. Sugiyama et al. reported a prevalence of baseline sarcopenia of 89% within 118 metastatic gastric cancer patients, with one third developing severe muscle loss during therapy. Interestingly, sarcopenia was an independent predictor of disease progression and mortality in patients without baseline sarcopenia. Muscle degradation upon treatment was significantly associated with shorter time to treatment failure and OS [25].

Several studies investigated sarcopenia as a predictive factor for chemotherapy-induced toxicity. The FIGHTDIGO study, for instance, determined a higher risk of dose-limiting neurotoxicity in digestive cancer patients with sarcopenia detected prior to treatment initiation [26]. Capecitabine toxicity was found to be elevated in 50% of sarcopenic females with metastatic breast cancer compared to 20% of nonsarcopenic patients and was associated with early disease progression in the sarcopenic cohort [27]. Similar results showing increased toxicity in sarcopenic patients were obtained for the FOLFIRINOX chemotherapy regimen in pancreatic and esophageal cancer patients [28, 29]. Palliative systemic treatment regimens in sarcopenic metastatic colorectal cancer patients were found to stabilize, reduce or gain muscle mass at times, based on treatment intensity. Interestingly, in this study, loss of muscle mass was reversible through treatment protocol changes or therapy breaks [30]. In conclusion, the mentioned findings advocate for pretherapeutical diagnosis, monitoring and targeted intervention of sarcopenia during cancer treatment.

Assessing and monitoring muscle mass and function in cancer patients

Diagnosis of sarcopenia can be achieved by measuring muscle mass with different techniques, such as imaging, validated measurements of muscular strength or by using performance status scales or anthropometric measurements. The latter include body mass index (BMI), which describes a simple way to assess nutritional status. It is widely used in clinical practice, but lacks information about muscle/fat ratios [31]. Karnofsky index, ECOG performance status or clinical frailty index are scales that enable the classification of patients based on their functional impairment. They are used to compare the effectiveness of therapies and are predictive of cancer survival [32].

Objective measures of physical function include hand grip strength, gait speed or balance. Although these methods are inexpensive, noninvasive and easily implementable in the clinical setting, they lack information about fat mass and might have ceiling or floor effects. An accepted standard of measuring body composition are radiologic assessments by means of CT, MRI and dual X-ray absorptiometry. However, despite their high sensitivity and accuracy, these methods are expensive, require trained personnel, partly expose patients to radiation and may not be included as routine measures into therapeutic regimens [31]. Questionnaire surveys and functional tests are less time-consuming alternatives that can easily be implemented into clinical practice and may result in adapting treatment strategies and in including supportive therapies to prevent sarcopenia.

Prevention of sarcopenia in cancer patients

As a preventive measure, resistance and aerobic exercise training were reported to increase quality of life by reversing a sarcopenic state and by reducing fatigue symptoms in breast cancer patients receiving neoadjuvant chemotherapy [33]. Prostate cancer patients undergoing androgen deprivation therapy (ADT) had a significant benefit from exercise programs, which were able to preserve and improve muscle strength upon initial losses [34]. Since malnutrition is a common incidence in cancer patients, there is growing evidence that nutritional support may be beneficial for improving muscle mass and strength. The intake of branched-chained amino acids, ω-3 fatty acids or high performance nutrition, for instance, was shown to have positive effects on quality of life, metabolism, energy balance and survival [35].

Although underlying molecular mechanisms for sarcopenia development are not fully understood, previous studies suggested malfunctioning mitochondria, autophagy and other factors to be associated with muscle atrophy [36]. In search for pharmacological interventions, multiple antibodies targeting and inhibiting myostatin, a negative regulator of muscle mass, are currently being explored in clinical trials.

Conclusion

Geriatric assessments, nutritional counseling and monitoring of muscle health before and during therapy are of high clinical significance and should be part of the routine management of elderly cancer patients. However, clinical data, criteria and cut-offs characterizing cancer-related geriatric sarcopenia are sparse and no consensus about definitions exists to date. We hence highlight a need for clinical trials focusing on sarcopenia in elderly cancer patients, due to its high prevalence and potential negative consequences on therapy outcomes, mortality, quality of life and physical mobility.

Funding Open access funding provided by Medical University of Vienna.

Conflict of interest M. Marhold, T. Topakian, and M. Unseld declare that they have no competing interests.

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