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Review Article

The Relationship Between Sarcopenia and Cancer Chemotherapys

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Abstract: As an independent disease, characterized by progressive and generalized loss of skeletal muscle mass, quality and strength, Sarcopenia has become a research hotspot in recent years, and its position in cancer patients has been increasingly valued by clinicians. Clarifying the relationship between Sarcopenia and chemotherapeutics in the treatment of cancer patients will help to formulate interventions for Sarcopenia to improve the quality of life and prolong survival period of cancer patients. In order to understand the relationship between Sarcopenia and cancer chemotherapy, we review from the following aspects. How is Sarcopenia diagnosed in cancer patients? How to evaluate Sarcopenia in cancer patients? What is the incidence of Sarcopenia in cancer patients? What is the relationship between the changes in body composition and the dose of chemotherapy in cancer patients? Whether there is a relationship between Sarcopenia and chemotherapy-related toxicity in cancer patients? Its role in leading to chemotherapy toxicity and its effect on the prognosis and survival in cancer patients. Whether chemotherapeutic drugs have an effect on the development of Sarcopenia in cancer patients, or whether certain types of chemotherapy drugs will affect Sarcopenia? Finally, the review also aims to describe interventions for Sarcopenia and their impact on the outcome of treatment for cancer patients.

Keywords: Sarcopenia, Cancer Chemotherapy, Toxicity, Prognosis

1. Introduction

Sarcopenia is a syndrome characterized by the progressive and generalized loss of skeletal muscle mass, quality and strength. Sarcopenia is an important feature of cancer cachexia, which seriously affects quality of life and reduces the survival time of patients. In cancer patients, several major factors lead to sarcopenia, including high energy consumption, anorexia, inflammation, and metabolic imbalance. Some researchers have found that sarcopenia was closely related to chemotherapy for cancers such as gastrointestinal tumors [1-2], pulmonary tumors [3-4], breast cancer [5], ovarian cancer [6], and lymphoma [7-9].

The role of sarcopenia in cancer patients is receiving increasing attention. In Europe, the incidence of sarcopenia in the population of cancer patients is approximately 30-40% [10-13], while the incidence is higher in Asia [14]. The importance of sarcopenia is related to the following two factors. Sarcopenia is a major cause of poor tolerance of chemotherapy in tumor patients. Some patients have normal nutrition even when assessed according to international standards, yet they still suffer from sarcopenia. In fact, weight reduction does not truly reflect changes in body composition or muscle tissue. Studies have shown that 41% of patients lose more than 5% of their muscle tissue when they lose 5% of their weight [15].

To better understand the pattern of sarcopenia in cancer patients, it is necessary to clarify the relationship between

sarcopenia and chemotherapeutics in the treatment of cancer patients; this will help to formulate interventions for sarcopenia to improve quality of life and prolong the survival period for cancer patients. At present, through a large number of basic and clinical studies conducted abroad in recent years, the possible pathogenesis of sarcopenia, pathogenesis factors related to sarcopenia, and related intervention methods have been proposed. However, there is less research in China. Here, we review the relationship between sarcopenia and cancer chemotherapy.

2. Diagnosis of Sarcopenia

Sarcopenia is derived from the Greek words sarx (muscle) and penia (drain). The European Working Group on Sarcopenia (EWGSOP) in 2010 and The International Working Group for the study of Sarcopenia (IWGS) in 2011 defined sarcopenia as progressive and extensive skeletal muscle mass loss and muscle weakness; therefore, the diagnosis of sarcopenia includes three major elements: muscle mass loss, muscle weakness, and muscle dysfunction [16]. Baumgarner et al. [17] proposed the muscle volume index, calculated by dividing the muscle volume of the limbs, as measured by dual-energy X-ray absorptiometry (DEXA), by the square of the height. Sarcopenia was defined as a muscle volume index lower than 2 standard deviations below the mean muscle volume index for healthy young people of the same race and sex. However, when most scholars conduct sarcopenia research in cancer patients, CT is often used to take the L3 spine as a bone marker for cross-sectional image analysis because the cross-sectional area of this level of muscle is positively related to the muscle volume of the entire body [18]. At present, there are two methods for the diagnosis of sarcopenia using the L3 skeletal muscle index. One defines the skeletal muscle index based on sex only, and the other defines the skeletal muscle index by combining sex and body mass index (BMI) [19]. The benefits of CT imaging are its high resolution power, the three-dimensional reconstruction of muscle tissue, and the measurement of muscle density. DEXA cannot accurately distinguish muscle tissue as CT can. In addition, DEXA is limited by weight and size. When the height or width of the patient is not within the range of the DEXA scanning area, it is difficult for DEXA to accurately measure the patient. Bioimpedance analysis (BIA) is suitable for longitudinal studies, but the patients' hydration and recent daily activities have a greater impact on the results. Therefore, the tools required for diagnosis vary from person to person. It is worth mentioning that most scholars only use muscle mass to directly diagnose sarcopenia in cancer patients, and few scholars combine muscle strength and muscle function to diagnose sarcopenia. Studies have found that the diagnosis of sarcopenia by combining muscle strength and muscle function after the comprehensive evaluation of cancer patients can more comprehensively and accurately assess the prognosis of these patients and the correlation of sarcopenia and chemotherapy [20]. Therefore, in addition to the application of CT scan assessments, the assessment of muscle strength and muscle function in cancer patients is expected to allow a more comprehensive study of the role of sarcopenia in tumorigenesis and development in future studies.

3. Sarcopenia Evaluation Methods

The EWGSOP recommends a comprehensive assessment of sarcopenia from three aspects: muscle mass, muscle strength and muscle function. In tumor patients, sarcopenia can be diagnosed by a DEXA-calculated appendicular lean soft tissue (ALST) lower than 7.26 kg/m2 for men and 5.45 kg/m2 for women [17]. Although the definition of sarcopenia mainly depends on DEXA, most of the current studies often use CT to diagnose and follow sarcopenia in tumor patients. In tumor patients with sarcopenia, CT can not only observe changes in muscle, adipose tissue and the tumor itself but also find the tumor site and its changes. In this way, CT can provide a large amount of timely information on anthropometrics and tumor-related measurements during the evaluation and treatment of tumor patients. According to different research purposes, the C3, T4, L3 or L5 spine can be used as a bone marker to measure the skeletal muscle of the corresponding CT plane. However, at present, L3 is usually used as a bone marker to measure the skeletal muscle volume at the L3 level (males ≤52.4 cm2/m2, females ≤38.5 cm2/m2) to diagnose sarcopenia in tumor patients [18]. Studies have also found that the skeletal muscle volume at the L3 level can reflect the skeletal muscle volume of the whole body [21].

When a CT scan is used to evaluate muscle mass, the skeletal muscle radiation density (mean Heinz unit) of the measured cross-sectional area can also be obtained. Low skeletal muscle radiation density is related to increased fat deposition, which is more common in obese and diabetic patients, and decreased physical activity. To date, there is no internationally accepted threshold for the diagnosis of sarcopenia. The potential correlation of skeletal muscle density with tumor prognosis has become a research area of interest for many scholars. An increasing number of studies have found that the radiation density of skeletal muscle has adverse effects on the prognosis of many tumors, such as some solid tumors [19], non-small cell carcinomas [22], malignant melanomas [23], metastatic renal cell carcinomas [24], pancreatic cancer or terminal cholangiocarcinoma [25] and follicular lymphoma [26]. Large-scale studies of non-small cell carcinomas have shown that skeletal muscle radiation density is an independent prognostic factor for overall survival, but overall survival cannot be predicted based on muscle mass calculated from the horizontal cross section of the lumbar spine [22]. Studies on elderly cancer patients have shown that skeletal muscle density was more closely related to physiological functions than skeletal muscle mass calculated by conventional CT scans. Therefore, the application of skeletal muscle density is more helpful in assessing the patients at risk of impaired function and providing evidence for formulating individualized treatment plans for cancer patients [19-26].

4. Incidence of Sarcopenia

Muscle development is generally affected by factors such as race, sex, age, and obesity. At present, there is no universal threshold for defining muscle loss. Muscles in the human body generally decrease after approximately 40 years of age. Muscles decrease at an average annual rate of 0.8% before 70 years old [27] and 2.5-4% after 70 years old [28-29]. Because tumors often develop in adults, sarcopenia is also more common in cancer populations. Because there is no universal diagnostic standard for sarcopenia worldwide, and because the thresholds used to assess muscle mass loss are not completely uniform, the incidence rates reported in the literature are different. Overall, the incidence of sarcopenia in tumor patients is approximately 21-71%. The overall incidence of sarcopenia varies among different tumor types. Even within the same tumor type, the incidence of sarcopenia is different among patients with different stages of disease. Some studies have reported that the incidence of sarcopenia is the highest in pancreatic cancer, lung cancer and bladder cancer. In some tumors, such as pancreatic cancer and breast cancer, the incidence of sarcopenia in patients advanced cancer was higher than that in patients with early cancer. During the treatment of cancer patients, the incidence of sarcopenia may increase due to various factors. To enable a comparative analysis of the results of various studies, it is necessary to formulate common diagnostic criteria and common assessment methods for sarcopenia in the future.

5. Sarcopenia and Chemotherapy Resistance

A large number of studies have shown that patients with sarcopenia are susceptible to excessive toxicity when receiving cancer treatment, which has forced their physicians to reduce the dose of chemotherapy or reduce the number of chemotherapy cycles. Excessive toxicity ranged from 1.6 to 13 points, depending on the drug used in the different studies. The reason that patients with sarcopenia are prone to excessive toxicity is mainly due to the fact that the height and weight (body surface area, BSA) of the patient are considered when formulating the dose of chemotherapy drugs in the clinic, but the proportion of fat is not considered. In some patients, although their BMI indicates obesity, they have already suffered from sarcopenia, a condition known as obese sarcopenia, which is especially easy to ignore in tumor patients and is also related to the toxic effects of chemotherapy drugs [30-31]. A century ago, the calculation of BSA was first proposed by Du Bois by dividing the body into eight parts, calculating the surface area according to the length and volume of each part, and then summing the surface area of each part to obtain the BSA of the whole body [32]. Because some physiological constants are more closely related to BSA than other anthropometric parameters, the application value of the BSA calculation method proposed by Du Bois is limited. In addition, Prado et al. found that nonfat tissue representing the distribution volume of cytotoxic chemotherapy agents had little relationship to BSA in obese patients, and the individual variation in the effective distribution volume of chemotherapy agents per unit of body surface area increased by a factor of three [33]. In subsequent studies, Prado et al found that lean soft tissue (LST) and aspartate aminotransferase accounted for 1/3 of epirubicin clearance, suggesting that LST is related to the pharmacokinetics of epirubicin. Therefore, in the evaluation of patients, if only based on BSA, without considering LST, the dosage will be overestimated, and the patients will be prone to excessive toxicity [34]. Therefore, future studies should clarify the changes in body composition and their effects on the dose of chemotherapy to help physicians formulate individualized and tolerable chemotherapy doses for their tumor patients.

6. Sarcopenia and Toxicity of Chemotherapy Drugs

Most cancer patients respond poorly to chemotherapy drugs if sarcopenia is present. Breast cancer patients with sarcopenia respond poorly to capecitabine, paclitaxel, docetaxel, or albumin-bound paclitaxel [35-36]. Moreover, judging by dose-limiting toxicity, patients with sarcopenia were more likely to develop high-level toxicity reactions when treated with capecitabine than those without sarcopenia [37]. A cross-sectional study showed an increased incidence (approximately 67%) of chemotherapy-induced grade 3/4 toxicities in patients with stage III colon cancer who have small baseline muscle volume when treated with adjuvant chemotherapy (oxaliplatin, 5-fluorouracil, and formyl tetrahydrofolate). After adjusting for age, sex, hormone levels and glomerular filtration rate, the results were similar [38]. Among patients with metastatic colon cancer, only sarcopenia was found to be most closely associated with toxicities, which occurred in approximately 38% of patients [39]. Patients with sarcopenia are more likely to experience chemotherapeutic toxicity when receiving platinum-based chemotherapy because platinum-based chemotherapy is mainly distributed in fat-free tissues such as kidneys, liver, pancreas and muscle tissues. Sarcopenia is an independent predictor of chemotherapy dose-limiting toxicity in patients with locally advanced head and neck cancer. A routine CT scan of the head and neck to assess skeletal muscle mass (SMM) before treatment may predict the risk of chemotherapy dose-limiting toxicity (CDLT) occurrence, providing a basis for formulating diagnosis and treatment strategies [40]. Tumor patients with sarcopenia have an increased probability of toxic reactions during chemotherapy, which in turn leads to a reduction in the dose of chemotherapeutic drugs. The inability of patients to receive sufficient doses of chemotherapy is also an important cause of poor outcomes [41].

The results of studies on sarcopenia and tumor-associated toxicity in esophageal cancer patients are divergent. To determine whether there is a relationship between sarcopenia and chemotherapy-related toxicity in esophageal cancer patients, the next step is to expand the sample size.

Interestingly, the studies that found a relationship between sarcopenia and chemotherapeutic toxicity stratified by CT measurement of the psoas index at the time of diagnosis of sarcopenia, while those studies that concluded that sarcopenia was not related to chemotherapeutic toxicity stratified by BIA at the time of diagnosis of sarcopenia. Therefore, the selection methods were different, and the research results were also different. It is suggested that the same methods are adopted when studying the relationship between sarcopenia and chemotherapy-related toxicity to better find the predictors of chemotherapy-related toxicity and provide a basis for the individual treatment and comprehensive evaluation of patients [42].

7. Sarcopenia and Tumor Chemotherapy Prognosis/Survival

We aimed to systematically study the impact of sarcopenia on tumor prognosis and survival. In the European consensus on the definition of sarcopenia, several levels of sarcopenia were identified, i.e., presarcopenia (solitary low-muscle mass), sarcopenia (low-muscle mass + low-muscle strength or slow-walking speed) and severe sarcopenia (low-muscle mass + both low-muscle strength and slow-walking speed). In exploring the relationship of sarcopenia with the clinical outcomes of tumors, it was found that severe sarcopenia was closely related to clinical outcomes [43]. Meta-analysis showed that sarcopenia was an adverse prognostic factor not only for cancer-specific survival but also for cumulative cancer survival. Colorectal cancer, liver cancer, kidney cancer and esophageal gastric cancer patients with sarcopenia had an increased risk of death (risk ratios of 2.2, 2.1, 1.7 and 1.5, respectively) [44]. Since sarcopenia is closely related to the adverse outcomes of tumor patients and can be an important predictor of tumor prognosis, methods to identify sarcopenia early are necessary to develop a reasonable comprehensive intervention model for tumor patients to improve their quality of life and survival rate. Kitagawa M et al. found that CRP, the n-6/n-3 ratio and the AA/EPA ratio in blood were positively correlated with sarcopenia in patients with advanced gastrointestinal tumors. The detection of CRP, the n-6/n-3 ratio and the AA/EPA ratio in the blood before and after surgery or chemotherapy can better predict sarcopenia, thus allowing for the provision of early nutritional support and helping to improve the prognosis of patients [45].

8. Effects of Chemotherapy Drugs on Sarcopenia

There is no consensus on the development of sarcopenia during chemotherapy. Rutten IJ et al. [46] observed that skeletal muscle (SM) was an important factor in overall survival (OS) during neoadjuvant chemotherapy in patients with advanced ovarian cancer. During neoadjuvant chemotherapy, patients with advanced ovarian cancer who could maintain or increase skeletal muscle mass had a higher overall survival rate than those with reduced skeletal muscle mass, which means a better prognosis. In addition, a decrease in SM during chemotherapy has also observed in other tumor patients [47], but the relationship between the decrease in SM and OS varied according to different studies or different types of tumors. For example, in patients with esophageal cancer, the decrease in SM during chemotherapy had no effect on OS. During the period of neoadjuvant chemotherapy in patients with pancreatic cancer, SM and visceral adipose tissue (VAT) decreased, but only the decrease in VAT was associated with OS [48]. In breast cancer patients, few patients develop sarcopenia after 4-6 cycles of adjuvant chemotherapy. Whether chemotherapeutic drugs have an effect on the development of sarcopenia or whether certain types of chemotherapy drugs will affect sarcopenia remain to be further studied. In the use of chemotherapy drugs, monitoring the changes in the indicators of sarcopenia is recommended to provide help for follow-up treatment [49].

9. Sarcopenia Interventions

In the clinical treatment of sarcopenia, two aspects are generally considered. One is that the treatment strategy for muscle loss must be confirmed by randomized controlled trials (RCTs). The other is that the patient's status and adherence to treatment should be considered. In fact, the prerequisite for any treatment to achieve the desired results in improving muscle mass is that the patient has a normal nutritional intake. Therefore, when treating sarcopenia, anti-inflammatory drugs that can promote both catabolism and anabolism, such as ɯ-3 fatty acids, should be used. If the above method is not effective, enteral or parenteral nutrition can be used. This not only ensures sufficient nutrition but also artificially regulates the nutrition supply to ensure better synthesis of muscle proteins. Under normal nutritional conditions, muscle training is very beneficial for maintaining or increasing muscle mass. However, when taking nutritional support therapy and exercising, the patient's tolerance must be taken into consideration so that the patient does not feel excessive fatigue. The detailed analysis of various treatments in the intervention of sarcopenia is not the main purpose of this review. In short, the current first-line treatment for sarcopenia is still nutritional support therapy based on ɯ-3 fatty acids. Other drugs, such as Amoralin and multimodal therapy, have also been studied in RCTs but have not yet been used in clinical practice [52].

10. Conclusion

Deteriorating nutritional status and sarcopenia not only affect patients' compliance with chemotherapy but also reduce patients' response to chemotherapy. To have a better prognosis for cancer patients, oncologists should comprehensively evaluate patients. Especially during the onset of tumor treatment, a systematic assessment of sarcopenia should be made, and timely intervention measures according to the assessment situation and changes in the condition should be

made to improve the quality of life and prognosis of cancer patients.

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