



# Preservation of muscle mass as a strategy to reduce the toxic effects of cancer chemotherapy on body composition

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## Purpose of review

Cancer patients undergoing chemotherapy often experience very debilitating side effects, including unintentional weight loss, nausea, and vomiting. Changes in body composition, specifically lean body mass (LBM), are known to have important implications for anticancer drug toxicity and cancer prognosis. Currently, chemotherapy dosing is based on calculation of body surface area, although this approximation does not take into consideration the variability in lean and adipose tissue mass.

## Recent findings

Patients with depletion of muscle mass present higher chemotherapy-related toxicity, whereas patients with larger amounts of LBM show fewer toxicities and better outcomes. Commonly used chemotherapy regimens promote changes in body composition, primarily by affecting skeletal muscle, as well as fat and bone mass. Experimental evidence has shown that pro-atrophy mechanisms, abnormal mitochondrial metabolism, and reduced protein anabolism are primarily implicated in muscle depletion. Muscle-targeted pro-anabolic strategies have proven successful in preserving lean tissue in the occurrence of cancer or following chemotherapy.

## Summary

Muscle wasting often occurs as a consequence of anticancer treatments and is indicative of worse outcomes and poor quality of life in cancer patients. Accurate assessment of body composition and preservation of muscle mass may reduce chemotherapy toxicity and improve the overall survival.

## Keywords

body composition, cachexia, chemotherapy, skeletal muscle

## INTRODUCTION

Despite significant progress in the development of novel cancer treatments, chemotherapy is often utilized for most tumors irrespective of its associated toxicities [1]. It is now clear that chemotherapy plays a direct role in the loss of muscle mass and muscle strength in cancer patients (often referred to as 'cachexia'), a condition that can persist for months to years following remission [2–9]. Notably, patients suffering from cachexia-related symptoms are often unable to complete treatment regimens and may require delays in treatment, dose limitation, or discontinuation of therapy [10,11]. Several studies have been conducted with the goal of identifying strategies to minimize or prevent cancer therapy toxicities [12]. This review will highlight the mechanistic effects of cancer treatments on body composition and provide potential strategies proposed to limit chemotherapy-related toxicities in cancer patients, including ways to preserve lean body mass (LBM).

## CHEMOTHERAPY NEGATIVELY IMPACTS PHYSICAL FUNCTION BY CAUSING IMPAIRED MUSCLE FUNCTION

Chemotherapeutic agents act primarily by antagonizing essential mechanisms of cell division. These antiproliferative and cytotoxic drugs have a high

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## KEY POINTS

- Anticancer treatments severely affect body composition, primarily by causing muscle depletion, as well as loss of adipose tissues and bone mass.
- Muscle wasting following administration of chemotherapy strongly affects the quality of life, leading to fatigue and reduced physical function, and predicts poor survival among cancer patients.
- Accurate assessment of body composition and preservation of skeletal muscle mass represent powerful tools to reduce chemotherapy toxicity.

biological activity that lead to ablation of cancer cells, but at the same time are responsible for dramatic toxicities in the host body. Among these side effects, nausea, vomiting, diarrhea, anorexia, body weight changes, and anemia are the most relevant [13]. Notably, muscle weakness and fatigue are some of the most common and distressing symptoms associated with cancer and chemotherapy [14,15], and it is estimated that over 70% of patients receiving cancer treatments will present symptoms associated with these conditions [16,17,18<sup>22</sup>,19,20]. Because of this, chemotherapy-dependent effects on body composition and on musculoskeletal function have recently become subject of interest [3]. Indeed, muscle dysfunction in cancer patients may affect the overall quality of life, including productivity and physical functioning, and this may be further intensified following chemotherapy [21–27]. In this regard, it has been shown that administration of chemotherapy promotes depletion of skeletal muscle mass in patients affected with advanced tumors, including lung, breast, colorectal, prostate, and nonsmall-cell lung (NSCLC) cancers, and this condition negatively impacts physical function by causing impaired muscle strength (such as slower chair-rise time and reduced hand-grip force), as well as joint dysfunction [2–4,18<sup>22</sup>,28<sup>23</sup>,29]. Unfortunately, no treatments are currently available to relieve such conditions.

## PROPER ASSESSMENT OF BODY COMPOSITION IS ESSENTIAL TO PREVENT CHEMOTHERAPY TOXICITY

Experimental and clinical findings suggest that body composition and, in particular, skeletal muscle mass play a pivotal role in the response to chemotherapy and in the prevention of its associated toxicities, as well as in ultimately predicting outcomes and survival of cancer patients. For instance, Du Bois and Du Bois [30] proposed a method to estimate pharmacokinetics and dosage of a drug by

determining the body surface area (BSA) as a relation between height and weight, according to the formula  $BSA (m^2) = ([height (cm^2) \times weight (kg)] / 3600)^{1/2}$ . Although not optimal, this method is still widely used, especially for dosing of drugs characterized by a low therapeutic index, as in the case of chemotherapeutics, and several modifications were suggested to generate a better approximation of the BSA [31,32].

There remains, however, a potential limitation associated with this dosing method in that it does not take into account the considerable variation in BSA because of changes in fat mass. Indeed, it has been previously demonstrated that the assessment of BSA can overestimate or underestimate the correct drug dosing. This is particularly true for anti-neoplastic agents, most of which have a narrow therapeutic window, thus leading to low efficacy in case of underdosing or severe side effects in case of overdosing [33]. Along the same line, Chatelut *et al.* [34] provided evidence that the clearance of different chemotherapeutic agents often poorly correlate with the BSA, thus casting doubt on the effectiveness of this parameter for the dosing of chemotherapy. Another study by Prado *et al.* [35] also showed that cancer patients presenting with identical BSA may regardless show high variability in LBM, primarily because of significant changes in adipose tissue mass. These findings suggest that accurate body composition assessment is linked to chemotherapy toxicity and survival. Therefore, wasting of skeletal muscle mass, by constituting a smaller volume of distribution for anticancer drugs, may also lead to inadvertent overdosing and exacerbated toxicity. This hypothesis was further supported by more recent evidence showing that patients with low amount of lean tissue at time of cancer diagnosis were also more susceptible to develop side effects following chemotherapy administration [36]. Additionally, the prevalence of dose-limiting toxicities was also shown in a cohort of advanced renal cell carcinoma patients presenting muscle depletion and low lean tissue mass with respect to patients not affected by these conditions [37].

In order to address the concerns related to the use of BSA for chemotherapy dosing, alternative methods have been proposed, including the assessment of the ideal body weight or the BMI (i.e. weight adjusted for stature, kg/m<sup>2</sup>). However, all these weight-based metrics do not take into account body mass composition and the relative proportions and distributions of lean, fat and bone mass in the human body [38,39]. As body composition in cancer patients may result highly variable in terms of muscle and fat mass, as well as of distribution of adipose tissue between abdominal and subcutaneous compartments, these

factors are likely critical to effectively establish chemotherapy dosing [40<sup>22</sup>,41]. This is of particular importance in patients with ‘sarcopenic obesity,’ a condition describing individuals that simultaneously present with high fat mass and low muscularity resulting in increased risk for adverse outcomes in the occurrence of cancer [42,43].

Enhanced treatment-associated toxicity and increased mortality in patients affected with different types of cancer have been shown to directly correlate with changes in body composition, primarily muscle mass, and there is also evidence that the amount of adipose tissue may represent a useful predictor of outcomes. Indeed, data generated in patients with metastatic colorectal cancer (mCRC) receiving bevacizumab suggested that low visceral adipose tissue correlates with shorter survival and overall negative outcomes [44]. Sarcopenia is also an indicator of poor outcomes and greater toxicity in patients with non-metastatic [45] and resectable stage I–III colorectal tumors [46], or in patients affected with mCRC and receiving palliative chemotherapy [47<sup>23</sup>]. Loss of skeletal muscle or changes in skeletal muscle density (SMD) following systemic chemotherapy treatments were associated with poor survival in patients affected with diffuse large B-cell lymphoma [48], as well as foregut [49] and ovarian [50] cancers. Analogously, in a study conducted on lung cancer patients, chemotherapy treatment preceded the detection of decreased muscle mass and increased adipose tissue. In this context, sarcopenia was correlated with reduced tolerance to chemotherapy treatment and thought to predict a worse prognosis [51].

As expected, a retrospective analysis of advanced nonsquamous NSCLC patients who received platinum-based therapy in combination with bevacizumab demonstrated that weight gain during or after treatment is a reliable indicator of clinical benefit and improved survival [52]. In a retrospective study including 193 patients affected with unresectable pancreatic cancer showing significant loss of adipose tissue following administration of neoadjuvant treatment, gain in muscle mass was associated with increased chance of resectability and better outcomes [53<sup>24</sup>]. Together these findings indicate that proper assessment of body composition is an important factor to consider for the prevention of chemotherapy toxicity.

### **ANTI-CANCER DRUGS ARE ASSOCIATED WITH MUSCULOSKELETAL DYSFUNCTIONS**

Preclinical investigations support a relationship between chemotherapy treatment and the loss of body weight, constituting both LBM and adipose

tissue (i.e. cachexia) occurring in the majority of cancer patients. Le Bricon and colleagues were among the first to provide evidence of a link between the administration of chemotherapeutics [such as cyclophosphamide, 5-fluorouracil (5-FU), cisplatin, or methotrexate] and abnormal nitrogen balance in the muscle of tumor-bearing rats leading to significant loss of skeletal muscle mass. Notably, these drug-associated toxicities were exacerbated in the cancer hosts, despite the fact that tumor proliferation was effectively counteracted [54].

Further, several investigators provided the first mechanistic explanation for the loss of muscle mass observed in tumor hosts exposed to chemotherapeutics. On the basis of these findings, anticancer drugs (including cisplatin, irinotecan, Adriamycin, and etoposide) were shown to cause muscle wasting directly via activation of the NF- $\kappa$ B pathway and independently of the commonly implicated ubiquitin-proteasome system, or indirectly via production of pro-inflammatory cytokines, such as IL-1 $\beta$ , IL-6, and TNF, or by inducing oxidative stress and tissue injury [55–57]. Other independent investigations also proposed that the molecular mechanisms accounting for the loss of muscle size and strength in animals bearing cancer and/or exposed to chemotherapy were correlated with activation of pro-inflammatory pathways, down-regulation of anabolism and exacerbation of muscle proteolysis [58].

In the attempt to identify some of the mechanisms responsible for the development of cachexia following exposure to chemotherapy, we recently investigated the role of some of the anticancer agents utilized for the treatment of colorectal and other solid tumors, namely FOLFIRI (5-FU, leucovorin, irinotecan) and FOLFOX (5-FU, leucovorin, oxaliplatin) [9]. The administration of these widely used chemotherapy regimens to healthy mice was able to reproduce some of the alterations typical of cancer cachexia, including body weight loss, adipose tissue, skeletal muscle wasting, and weakness. Our evidence showed that the chemotherapy treatment was responsible for hyperactivation of the ERK1/2 signaling pathway, previously involved in the pathogenesis of cachexia [59], as well as for structural changes in the sarcomeres and for dramatic muscle mitochondrial depletion. Chemotherapy also led to abnormal oxidative metabolism and to an oxidative-to-glycolytic shift in fiber type composition [9].

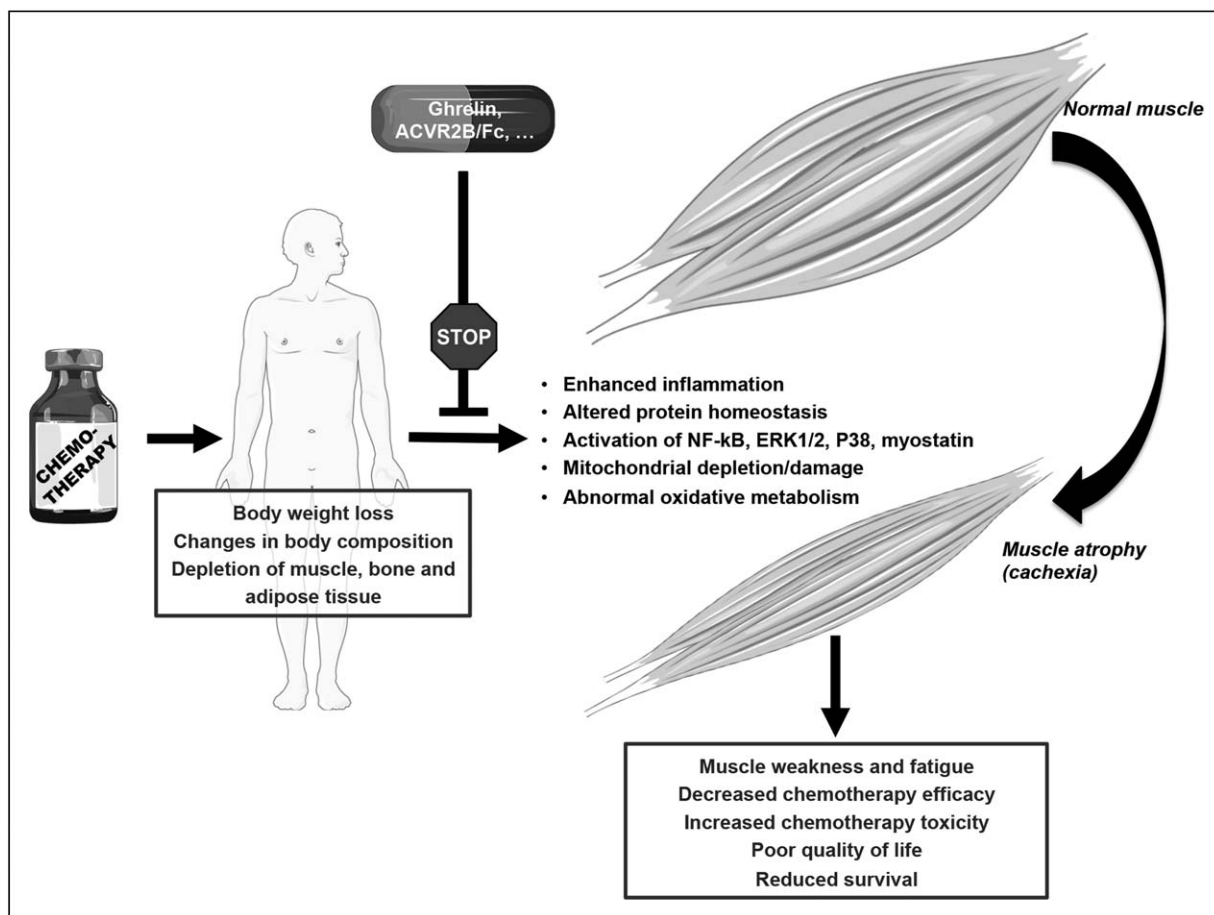
Interestingly, these findings were in line with previously published data, suggesting that cancer and chemotherapy may promote the appearance of a cachectic phenotype by activating similar mechanisms [60]. Our observations were also subsequently validated by our comprehensive proteomic profiling aimed at comparing cachexia in a setting of cancer

or following chemotherapy [61]. Importantly, trabecular bone tissue was also significantly affected by chemotherapy treatments. For instance, doxorubicin and, in particular, FOLFIRI were recently shown to promote dramatic loss of bone [62,63], whereas aromatase inhibitors, usually prescribed as the standard of care in the therapy of postmenopausal breast cancer, were shown to promote osteolysis by activating osteoclast-mediated bone resorption and to exacerbate muscle weakness in animals bearing estrogen-receptor negative breast cancers [64]. Altogether, these findings suggest that administration of compounds with cytotoxic and antiproliferative properties promote muscle and bone derangements by activating a wide range of mechanisms.

### PRESERVATION OF MUSCLE MASS AS A TOOL TO COUNTERACT CHEMOTHERAPY TOXICITY

Experimental and clinical data support the importance of the relationship between muscle mass and

the response to chemotherapy, thus also suggesting that preservation of muscle mass *per se* represents a novel strategy to ultimately prevent chemotherapy toxicity and improve quality of life with cancer. Agents targeting skeletal muscle anabolism have been tested with the goal of preserving muscle mass in the presence of cancer and following the treatment with chemotherapy drugs (Fig. 1). In 2008, Garcia *et al.* [65] proposed the treatment with ghrelin, a potent growth hormone secretagogue endowed with orexigenic and neuroprotective properties, as a method to counteract cisplatin-associated loss of body and muscle weight. The molecular mechanisms involved in determining better muscle phenotype and improved survival in tumor hosts exposed to chemotherapy included down-regulation of inflammation and p38/C/EBP- $\beta$ /myostatin signaling, as well as activation of Akt and myogenic factors, such as myogenin, and myoD [58]. Another group showed that synthetic agonists of the ghrelin receptor counteract chemotherapy-induced toxicity by effectively preventing



**FIGURE 1.** Pro-anabolic strategies preserve muscle mass in association with chemotherapy. Counteraction of mechanisms usually responsible for derangements of skeletal muscle size and function contributes to reduce chemotherapy toxicity and to improve quality of life and survival in cancer patients.

calcium dysregulation and mitochondrial damage in skeletal muscle [66,67].

With others, we reported that ACVR2B/Fc potentially counteracts muscle wasting in combination with FOLFIRI [63<sup>¶</sup>], doxorubicin [62], or cisplatin [68<sup>¶</sup>]. ACVR2B/Fc is a soluble ACVR2B fusion protein and inhibitor of the activin 2B receptor signaling previously shown to preserve muscle mass and prolong better survival in tumor hosts [69]. Interestingly, our recent studies found that ACVR2B/Fc also exerts powerful protective effects related to the preservation of bone mass in animals chronically administered FOLFIRI in combination with ACVR2B/Fc. These findings further demonstrate that the preservation of muscle mass may provide a tool to counteract chemotherapy toxicity by identifying a potential strategy for the detection of early cancer-associated musculoskeletal deficits following cancer treatments [63<sup>¶</sup>].

## CONCLUSION

Changes in body composition, mainly resulting in depletion of skeletal muscle mass, have been linked to the use of anticancer drugs. On the basis of a growing number of experimental and clinical studies, there is now substantial agreement on the idea that the loss of lean mass represents an accurate prognostic factor for augmented treatment toxicity, worsened outcomes, and overall reduced survival in cancer patients. In an attempt to identify the molecular causes responsible for musculoskeletal disorders upon treatment with chemotherapy, several research groups have focused their attention on the in-vivo effects of commonly used chemotherapy regimens, including cisplatin, doxorubicin, FOLFIRI. These findings support that muscle size and function are primarily affected by activating signaling pathways that have been previously implicated in promoting muscle atrophy and that are driven by processes that impinge on mitochondrial metabolism and muscle protein homeostasis. A series of promising experimental data also suggests the use of muscle pro-anabolic strategies as powerful tools to spare lean tissue in a setting of cancer or chemotherapy (Fig. 1). However, additional studies are necessary to establish novel methods for the accurate assessment of body composition in patients with cancer, with the ultimate goal of monitoring the changes in fat, muscle, and bone tissue that follow the treatment with chemotherapy. Completion of this endeavor will ultimately allow performing simultaneous adjustment of drug dosing, thus also attaining reduction in musculoskeletal side effects in patients with cancer.

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## Conflicts of interest

There are no conflicts of interest.

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