



# Sarcopenia associated with chemotherapy and targeted agents for cancer therapy

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**Abstract:** Clinicians often believe that cachexia is caused by cancer and anorexia as a toxicity of chemotherapy or targeted anti-cancer agents. It is now recognized that chemotherapy and certain targeted agents cause sarcopenia which reduce physical function and quality of life. Pre-treatment sarcopenia predicts chemotherapy toxicity, reduced response, increased disability, poor anti-tumor response and survival. Though bioelectrical impedance and dual energy X-ray absorptiometry (DEXA) scans have been used in the past for body composition measurements, CT scan cuts at the level of the 3<sup>rd</sup> lumbar vertebral body with measurement of skeletal muscle and visceral and subcutaneous fat areas has become standard. Nonpharmacological approaches to reducing sarcopenia during chemotherapy includes resistance training and dietary counselling. Pharmacologic therapies include vitamin D replacement if depleted, omega-3 fatty acids, testosterone and selective androgen receptor modulators (SARMS) and ghrelin. A comprehensive multimodal and multiple drug approach is likely to be better than single modalities. However, this is yet to be proven. Finally, it is not known if intervening to prevent or reverse sarcopenia will have a clinical benefit in terms of better tolerance to cancer therapy, physical function, well-being, tumor response and survival. Reversing sarcopenia and improving objective outcomes should be the goal of therapy.

**Keywords:** Sarcopenia; chemotherapy; prognosis; response; treatment

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## Introduction

Weight is a common metric when evaluating a patient's health. Cachexia by definition involves involuntary weight loss. Body mass index (BMI) is weight adjusted for stature ( $\text{kg}/\text{m}^2$ ), is used often for health assessment and nutritional status. Body surface area has been used to measure metabolic mass for chemotherapy administration (1). However, weight and weight per stature does not accurately assess body composition. The proportion of lean body mass (LBM), skeletal muscle and visceral fat as well as subcutaneous fat vary significantly between individuals with the same BMI. The increase in obesity within society

may lead clinicians to misjudge the health of patients and grossly overestimate skeletal muscle mass. The appearance of classical cachexia has become much less apparent today. Patients may have critical skeletal muscle loss to a much greater extent than fat and remain overweight. Patients do not necessarily proportionally gain or lose fat and muscle at equal rates with a change in weight (2-4). This is also true for patients with cancer who may have widely varying skeletal muscle mass and fat mass as well as distribution of fat per weight which has a profound effect on tolerance to anti-tumor therapy, efficacy, drug limiting toxicities (DLT), progression free, and overall survival (5-10).

## Definition and measurement of sarcopenia

There are distinct differences when measuring sarcopenia in the elderly population and in cancer patients. The geriatrician focuses on function and disability, while the oncologist measures muscle mass and weight compared to a population standard. A recent sarcopenia definition in the geriatric literature is “a loss of muscle associated with loss of function” (11). Elderly individuals are screened by gait speed, the rate at which they can sit and stand several times or by hand grip strength or by a series of tests. Falling below population standards predicts frailty and mortality (12,13). However, there is a complex relationship between muscle mass, muscle loss and reduced function which is not linear. Muscle mass diminishes 0.5–1% per year beginning around the age of 40 which accelerates after the age of 65. Muscle strength diminishes 3–4% per year in men and 2.5–3% per year for women around the age of 75 (14–16).

Pre-sarcopenia can be defined as low muscle mass without loss of strength or physical disability or performance. Sarcopenia is defined as low muscle mass with either reduced muscle strength or reduced physical performance relative to population standards. Severe sarcopenia is defined as low muscle mass, reduced muscle strength and reduced physical performance relative to population standards. Dynapenia is age-associated loss of muscle strength not caused by neurologic or muscle diseases (17).

Oncologists and investigators interested in sarcopenia associated with cancer have largely used anatomical measurements of skeletal muscle mass as the initial screen. This is done through the use of bioelectrical impedance, dual energy X-ray absorptiometry (DEXA), and CT scan by the composition at a single cut through the level of the L3 vertebral body (18–26). Bioelectrical impedance measures tissue resistance and capacitance but body composition is computed by equations derived from normal populations which are certainly less accurate than by direct measurement through CT scans. However, the phase angle which is a relationship of capacitance to resistance directly reflects muscle mass and cellular health (27,28). The advantages to bioelectrical impedance is that it is inexpensive, portable, can be repeated frequently and does not expose patients to radiation. DEXA scans measure appendicular muscle but are cumbersome and expose patients to radiation. Patients undergoing chemotherapy or targeted therapy are often restaged after a few cycles of therapy or periodically. The images can be used to measure tumor response, skeletal muscle mass, as well as visceral and subcutaneous fat mass.

CT scan body composition uses Hounsfield units (–29 to 150) to measure skeletal muscle area at a single L3 cross sectional area (4). The L3 vertebral CT scan image includes 7 muscles; psoas, erector spinae, quadratus lumborum, transversus abdominis, external obliques, internal obliques, and rectus abdominis. Some studies used the cross section of the psoas alone (29). Abdominal and subcutaneous fat mass area can be quantified. Gender specific norms have been established. For males normal muscle mass is greater than or equal to 52.4 cm<sup>2</sup>/m<sup>2</sup> and for females 38.5 cm<sup>2</sup>/m<sup>2</sup>. This has been correlated with whole body skeletal muscle mass and externally validated using mortality (4,7,30). There are several software programs that used to perform these measurements; MIMICS TM (Materialise HQ, Leuven, Belgium), SliceOmatic TM (Tomovision, Magog, CA), NIH IMAGEJ TM (<http://IMAGEJgov/ij>).

## Causes of sarcopenia during chemotherapy and targeted therapy

There are four main causes of sarcopenia during chemotherapy; (I) impaired food intake with reduction in vitamin D; (II) omega 3 fatty acids and protein; (III) reduced physical activity secondary to fatigue; (IV) a direct effect of chemotherapy or targeted agents on muscle; (V) malabsorption secondary to mucositis or treatment related pancreatic insufficiency (31).

Cisplatin, irinotecan, doxorubicin, and etoposide cause direct muscle loss through activation of the transcription factor NF kappa B which upregulates ubiquitin and proteasomes, increases proteolysis and inflammatory cytokines (IL-1beta, IL6 and TNF alpha) which increases E3 ligases (atrogin-1) and increases ubiquitin protein binding for proteolysis (32). TNF alpha accelerates catabolism (protein loss, insulin resistance), muscle contractile dysfunction, and disrupts myogenesis leading to muscle weakness (33–35). Cisplatin downregulates protein kinase B (AKT)/mammalian target of rapamycin (mTOR)/leading to loss of myogenesis (36). Chemotherapy induces oxidative stress and increases reactive oxygen species (ROS) in muscle (36,37). Tumor growth factor (TGF) beta proteins are increased with chemotherapy which upregulates myostatin altering the balance of muscle metabolism toward catabolism (36,38,39). Combination chemotherapy causes mitochondrial damage which reduces cytochrome C needed for oxidative phosphorylation and peroxisome

proliferator-activated receptor gamma coactivator 1-alpha (PGC-1alpha), a protein transcriptional coactivator that regulates energy metabolism, mitochondrion biogenesis and muscle fiber type (40). Muscle wasting is associated with up-regulation of ERK1/2 and p38 MAPKs which impairs the AKT/mTor pathway leading to muscle atrophy (40). Chemotherapy causes reduction in muscle microvasculature through antiangiogenesis (41).

On the other hand, chemotherapy may counter cancer induced sarcopenia by reducing tumor burden. In a mouse model, 5FU reduced protein turnover by reducing one of the E3 ligases (atrogen-1) which would impair proteasome proteolysis. 5FU also increased muscle ribosomal activity and muscle metabolic capacity by increasing PGC-1alpha. Muscle autophagy is also reduced (42).

### Outcomes associated with sarcopenia and sarcopenia obesity during cancer therapy

In a retrospective study of patients receiving neoadjuvant chemotherapy (NAC) for urothelial cancer, 14% had sarcopenia at the beginning of treatment as measured by CT scan body composition and 20% by bioelectrical impedance. There was no correlation between the presence of sarcopenia and a prognostic nutritional index using albumin and lymphocyte blood levels. After 3 cycles of NAC, skeletal mass decreased while fat mass increased suggesting that cisplatin NAC causes sarcopenic obesity (42).

Several studies of foregut origin malignancies found a pre-treatment sarcopenia prevalence of 26–47% which increased after chemotherapy. Pre-NAC sarcopenia and the development of sarcopenia during chemotherapy correlated with an increased risk for neutropenic fever, a greater degree of dose-limiting toxicity (DLT), reduced successful surgical resections, and a shorter survival (43–45). A large study (n=225) of patients receiving NAC or palliative systemic chemotherapy also demonstrated a high prevalence of sarcopenia (40%) prior to treatment. In addition, close to half of patients had myosteatosis and 62% had cancer cachexia (involuntary weight loss of 5% or more over 6 months). Those on NAC lost 6.6 cm<sup>2</sup> of skeletal muscle by CT scan body composition. Those on palliative chemotherapy lost on average 3.9% of the skeletal muscle mass by 100 days. Reduced muscle mass of >6% predicted reduced survival with a hazard ratio (HR) of 2.7 (46). In this study a high number of nutritionally vulnerable patients, with demonstrated abnormal body composition on CT analysis were misclassified by nutritional indices. The

authors cautioned when categorizing the nutritional risk of oncology patients using nutritional tools only (47).

Two studies involving the elderly undergoing chemotherapy have conflicting findings. A smaller study (n=103) involved patients with a mean age of 70. The authors found that hand grip strength predicted survival whereas CT scan body composition including the measurement of myosteatosis did not predict for drug toxicity or survival (48). An earlier study involved patients (n=131 with a median age of 72 years). Pre-sarcopenia was present in 48%, sarcopenia in 18.5% and severe sarcopenia in 7.7%. Severe sarcopenia was associated with loss of physical independence after chemotherapy with a HR of 5.95. Skeletal muscle mass in this study correlated with strength but not tests of physical function (49).

In a study which sequentially measured skeletal muscle mass through repeated CT scans during palliative chemotherapy for lung cancer, the mean reduction in skeletal muscle mass over time was 1.4 kg. Most who had objective response to chemotherapy had stable to improved muscle mass. Maintaining or gaining muscle mass predicted survival (10.7 *vs.* 5.8 months) (50). A second study in a similar group of patients used the phase angle as a measure of skeletal muscle mass. A phase angle less than 5.8 predicted a poor survival (HR 3.0) by multivariable analysis (18).

Even in patients undergoing a curative therapy, sarcopenia had clinical significance. In a group of patients undergoing curative treatment for large B-cell lymphomas, sarcopenia predicted a poorer 2-year survival (46% *vs.* 86%) with a HR of 3.22 for mortality (51). Patient who have pre-treatment sarcopenia undergoing curative resection for colorectal cancer have a shorter recurrence free survival and overall survival with a HR of 2.18 and 2.27 respectively (52). Post-surgical anastomotic leak occurred more frequently in sarcopenic patients (53).

These are only a few of the studies which have demonstrated the adverse effects of sarcopenia on the course of cancer. Sarcopenia predicts reduced survival in multiple cancers. Not only does sarcopenia predict reduced overall survival, but also increases a number of risks including postoperative infections, the need for inpatient rehabilitation, recurrent hospitalizations, hospital length of stay (54–58), respiratory and surgical complications, intensive care unit admissions, and days of enteral nutrition because of delays in gastric emptying (53,59–75).

### Myosteatosis

Excessive levels of inter- and intra-muscular adipose tissue

and intramyocellular lipids adversely impacts metabolism and force generation with clinically relevant outcomes (76,77). Myosteatosis increases with aging, regardless of changes in body weight, which is more prevalent in diabetics and reflects insulin resistance, impaired secretion of adipokines and altered skeletal muscle blood flow (78,79). Myosteatosis of thigh muscles as measured by reduced Hounsfield units, is associated with an increased risk of hip fracture in the elderly and with reduced muscle strength, physical performance, and muscle mass (80). As discussed later, muscle depletion is associated with low plasma eicosapentaenoic (EPA) and docosahexaenoic (DHA) in cancer and supplementation with omega-3 fatty acids has been shown to ameliorate muscle loss and myosteatosis in clinical studies (81). In multiple studies, low attenuation of muscle on CT scans has been associated with reduced cancer survival with a HR of 1.36 to 2.5 (8,77,82-86).

### Sarcopenic obesity

As mentioned previously, cisplatin has been associated with sarcopenic obesity. In a series of patients with lung cancer undergoing chemotherapy, after 4 months of chemotherapy, patients exhibited sarcopenia with decreased muscle and increased visceral adiposity relative to subcutaneous fat mass. This was not adequately mirrored by BMI and weight loss (87). In addition, cyclophosphamide, doxorubicin, vincristine and prednisone, used to treat non-Hodgkin's lymphoma, has been associated with increased fat mass with stable LBM. Weight gain during chemotherapy, with an unfavorable change in body composition, misleads treating physicians to attribute weight gain as a sign of regaining health (88).

Sarcopenic obesity has an independent adverse effect on clinical outcomes. In a retrospective study of patients with pancreatic cancer, overall and recurrence-free survival rates in patients with a high visceral to subcutaneous fat ratio were significantly lower than those in patients with low ratio. Survival and relapse free survival rates of patients with sarcopenic visceral obesity were significantly lower compared with those without sarcopenic obesity. The ratio of visceral to subcutaneous fat was an independent risk factor for mortality with a HR of 1.58 suggesting that visceral fat mass plays a role in clinical outcomes (89). In a series of patients with pancreatic cancer, 18 had sarcopenic obesity, 44 had obesity without sarcopenia and 62 had sarcopenia alone. Obese sarcopenia was an independent risk predictor for mortality with a HR of 2.07. Multiple

additional studies have demonstrated adverse cancer-related outcomes for those with sarcopenic obesity (1,6,7,42,90-98).

One question that arises when reviewing these studies is how much the increase in fat mass plays a role in predicting adverse outcomes relative to sarcopenia alone. A second question is whether it is the overall increase in fat mass or its relative distribution between subcutaneous versus visceral compartments (in addition to reduced skeletal muscle mass) that is the important clinical feature that defines sarcopenic obesity. It has been suggested that chemotherapy dosing paradigms should differ between the obese without sarcopenia and the sarcopenic obese. Chemotherapy doses perhaps should be limited to a 2 m<sup>2</sup> BSA in the sarcopenic obese due to the increased risk for chemotherapy related toxicity (1).

### Sarcopenia and targeted therapies

Certain targeted agents are associated with sarcopenia and the cancer outcomes of targeted therapy can be influenced by sarcopenia. The comparison was made between chemotherapy and targeted agents as to the prevalence of sarcopenia on therapy. Most patients were on epidermal growth factor receptor tyrosine kinase inhibitors. Sarcopenia was measured by CT scan body composition. Chemotherapy produced greater muscle loss relative to targeted agents. There was also greater variation in skeletal muscle loss or gains with chemotherapy. The authors attributed this to less anorexia with targeted agents as well as differences in toxicity (99).

Three classes of targeted agents have been shown to improve skeletal muscle mass: poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors and the mitogen-activated protein (MEK) inhibitor, selumetinib. PARP activation causes muscle mass loss and muscle dysfunction in animal models (100,101). Inhibitors of PARP reduce muscle oxidative stress, reduces muscle catabolism, enhances muscle metabolism and improves mitochondrion function and biogenesis (100,102-106). PARP inhibitors improve exercise capacity by boosting mitochondrion respiratory capacity in mice (103).

Selumetinib was studied in BALB/C mice implanted with C26 adenocarcinoma. Selumetinib reduced E3 ligases which are important to proteasome proteolysis. Selumetinib also enhanced the AKT/mTor pathway (107). Selumetinib increased muscle mass and weight in 80% of patients treated for biliary cancers and produced an objective response in 12% suggesting that the anabolic benefits are independent

of anti-cancer activity (108,109).

Imatinib mesylate inhibits signaling from tyrosine kinase receptors, including PDGFR alpha, and has been used to treat CML. PDGFR alpha is expressed in muscle mesenchymal progenitors, when stimulated induces muscle fibrosis (110). Imatinib reverses the sarcopenia associated with gastrointestinal stromal tumors (GIST) (111).

There are targeted agents which have been either associated with sarcopenia or have outcomes are adversely influenced by sarcopenia. Sorafenib has the greatest evidence for inducing sarcopenia. Sorafenib activates the proteasome and calcium dependent proteolysis pathways (112). Sorafenib causes progressive loss of skeletal muscle mass over time, unrelated to cancer (113). On the other hand, pre-existing sarcopenia on sorafenib is associated with disease limiting toxicity (DLT) and a shortened survival (114-116). Sorafenib responses are diminished in individuals with sarcopenic obesity with increased visceral fat (117,118). However, there is a single study that suggests increased visceral fat in patients on endothelial growth factor-targeted therapy portends a better outlook and prognosis (119). Patients with sarcopenia have a significantly inferior progression free survival and overall survival compared to non-sarcopenic patients [PFS: 7.6 vs. 18.2 months (120)]. Sunitinib therapy in sarcopenic patients is associated with DLT with a 4-fold increased risk in grade 3 and vascular toxicities (121). Dose limiting toxicity is seen in half of patients at 6 months who are sarcopenic prior to starting sunitinib therapy. Those with sarcopenia and reduced fat mass have a 90% chance of experiencing DLT and an increased number of treatment related toxicities (5 vs. 2) (122).

Inhibitors of the mTor pathway have been associated with sarcopenia. The use of mTOR inhibitors significantly decreases skeletal muscle area and LBM but has no effect on adipose tissue or body weight (123). Skeletal muscle mass is an independent prognostic factor for patients with metastatic renal cell cancer treated with everolimus (21.9 vs. 10 months for those with the highest to lowest L3 muscle cross section area) (124).

## Treatment of sarcopenia

### *Reversibility and multimodality therapy*

Patients with cancer have anabolic capacity. Sarcopenia can be reversed in older aged individuals, those that are deconditioned, and in those with multiple comorbidities (125). Serial studies have demonstrated that muscle protein synthesis can be

stimulated in these individuals (126,127). However, it is likely that reversibility will depend on multimodality approaches. Pharmacologic trials have frequently been carried out without regard to adequate nutrition intake within the trial design. Failure to reverse sarcopenia may not be related to failure to generate anabolism but inadequate calorie intake (128,129).

### *Diet*

Patients with cancer are often catabolic and the need for protein intake may not be adequately predicted by their BMI. At least 35% of patients with cancer have inadequate protein intake (less than 1 g/kg body weight per day) (19). Protein intake should be 1.2–1.5 g/kg per day for those with acute or chronic diseases (130,131). Leucine rich supplements have been shown to maintain or build muscle mass (132,133). Leucine was found has beneficial effects on body weight, BMI, and LBM in older persons prone to sarcopenia, but does not improve muscle strength (134). Healthy elderly men can take in 500 mg/kg per day without an increase in ammonia. A more conservative approach would be an intake of 351 mg/kg per day (135).

Beta-hydroxy beta-methyl butyrate (HMB) supplements have been used to build muscle mass. HMB enhances sarcoplasmic reticulum thus improves to peak contraction force *in vitro* (136). HMB improves the proliferation of muscle stem cells in fast twitch muscles in mice which increases muscle mass (137). So it is rational to think that HMB might increase muscle mass and function. In a randomized trial involving individuals over the age of 65, HMB improved strength and muscle quality independent of resistance exercises (138). Seven randomized trials involving 287 patients found that patients gain muscle mass without improved function or strength (139). There is no study that the authors could find which addressed the use of HMB during chemotherapy. Studies are needed to address the specific effectiveness of HMB in attenuating muscle wasting in various muscle-wasting disorders (140).

Besides improving protein intake overall and the types of protein consumed, the amount of simple carbohydrates should be reduced with the emphasis on whole foods rather than processed foods and high fiber intake (141-143). One caveat though is that patients who develop dysgeusia on chemotherapy might not find protein palatable (144,145). Dronabinol reduces the chemosensory changes that occur on chemotherapy and allows patients to increase protein intake (146).

### *Vitamin D*

We recommend checking vitamin D levels and replacing vitamin D if low which has a low risk and potential benefits (133,147). Prolonged deficiency is reported to produce both muscle loss and weakness (147-149). The muscle losses are particularly severe for type II muscle which are prevented by maintaining levels 25 hydroxyvitamin D >20 ng/mL (149,150). In addition, to low 25 hydroxyvitamin D, high parathyroid hormone levels (PTH) levels ( $\geq 4.0$  pmol/L) are associated with an increased risk for sarcopenia (151). Replacement of vitamin-D increases muscle fiber size and lowers extremity proximal muscle strength (152,153). Vitamin D deficiency is defined as a 25 hydroxyvitamin D3 level of <20 ng/mL, insufficient when 21–29 ng/mL. The prevalence of vitamin D deficiency is 36–47% during the winter in the general population and is likely to be higher in patients with cancer who have insufficient intake and insufficient light exposure (154).

Vitamin D (1 alpha, 25 dihydroxyvitamin D3) binds to vitamin-D receptors (VDR) which are transported to the nucleus where they interact with 9-cis-retinoid acid receptors and form a heterodimer. The heterodimer modulates the FOXO subfamily which is responsible for myoblast maturation. The end result is downregulation of myostatin (155). Besides atrophy of type II muscle fibers, vitamin D deficiency is associated with myosteosis and loss of satellite cells necessary for muscle regeneration (156-158).

### *Omega 3 fatty acids*

Myosteosis and sarcopenia have been associated with low plasma levels of omega-3 fatty acids (OMF). And conversely, supplementation of diets with OMF ameliorate sarcopenia and reverse myosteosis in clinical studies (81,159).

OMF improves muscle mass by several different mechanisms. OMF increases mTor ribosomal activity through phosphorylation and inhibits mTOR translocation into lysosomes (160,161). Muscle anabolic responses to insulin and amino acid infusion are greater in the presence of OMF (162). Another mechanism involves increases in uncoupling protein-2 by mitochondrion which reduces reactive oxygen species and down-regulates proteasome proteolysis (163,164).

A series of small studies have been done where omega-3 fatty acid supplementation has been given during chemotherapy. A dose finding study found that 6 g of OMF per day was the maximum tolerable dose. OMF improved appetite and fatigue. Participants in this study had advanced

lung cancer and a systemic immune-metabolic syndrome (chronic systemic inflammatory syndrome) (165). A group of patients who were receiving palliative chemotherapy for visceral breast cancer metastases were randomized between the OMF docosahexaenoic acid (DHA) 1.8 g daily or placebo. Chemotherapy responses occurred in 88% of those on DHA versus 44% of those treated with anthracycline-based chemotherapy alone. Those with the highest plasma DHA levels had a significantly longer survival (34 *vs.* 18 months) and less chemotherapy toxicity (166). A trial of patients undergoing palliative chemotherapy for lung cancer (n=92) randomized patients (n=112) between the omega-3 fatty acid eicosapentaenoic acid (EPA) and an isocaloric diet. All patients received paclitaxel and cisplatin/carboplatin chemotherapy. EPA randomized patients followed a standardized menu and two containers (237 mL each) per day of ProSure<sup>®</sup> (Abbott Nutrition, Columbus, Ohio, USA). Calorie and protein consumption in the control group decreased during the two cycles of treatment (P=0.08 and P=0.04 respectively), while in the experimental group dietary intake of calories and protein were maintained. The EPA group had increased energy, protein, carbohydrate and fat intake when including oral supplement compared with control group. The EPA group had an increased global health status while the control group did not. LBM decreased in the control group but increased in the EPA group by the second cycle of chemotherapy. There were no differences in tumor response or survival (167).

In a small randomized trial (n=40), 2.2 g of EPA during chemotherapy for lung cancer resulted in less muscle and weight loss and less myosteosis than patients who were not supplemented (168). Sixty-nine percent of patients in the EPA group gained or maintained muscle mass while only 29% of patients in the control group did. Fat mass was unchanged between groups. A second study by the same group found that 2.5 gms of EPA daily improved response rate and clinical benefit of chemotherapy for lung cancer. Eighty percent of those on EPA had a clinical benefit to chemotherapy versus 42% of those in the control group. The trial was small with only 46 patients and thus was under powered. Survival at 1 year was 60% for those receiving the supplement versus 39% of those on standard care though this was not significantly different (P=0.15) (159).

There are multiple randomized trials demonstrating benefits to EPA and DHA supplementation during chemotherapy but trial populations were small and most were phase II designs. Large randomized trials will be needed to confirm these promising findings.

### *Testosterone*

Men with cancer often have low testosterone levels which could lead to sarcopenia. Women may benefit from testosterone during chemotherapy in attempts to maintain muscle mass. A small randomized trial (n=24) of patients with cervical and head and neck cancer used testosterone enanthate 100 mg weekly for 7 weeks during therapy. Appendicular skeletal muscle mass was maintained and body weight increased on average by 1.3 kg. Quality of life improved but physical well-being, strength and performance were not improved (169).

### *Selective androgen receptor modulators (SARMS)*

Androgens promote growth hormone release, stimulate appetite, increase LBM and regulate energy homeostasis but also increase the risk for cardiovascular disease, depression, aggression and sleep disordered breathing (170). SARMS have been developed to take advantage of the anabolic effects of androgen receptor agonists while avoiding the adverse effects of androgen on prostate, heart, and liver (171,172). Selectivity occurs through different interactions with the androgen receptor leading to distinctly different receptor conformation, and interactions with coactivators and corepressors resulting in differences in recruitment of nongenomic signaling and gene regulation (173,174). SARMS have been used in both genders to improve bone health and increase LBM, countering osteoporosis, sarcopenia and cachexia (175,176).

Enobosarm is a hyper-myo-anabolic SARM with high oral bioavailability and preclinical safety. It is not subject to peripheral aromatase or 5-alpha reductase metabolism and thus is not converted to an estrogenic or androgenic metabolite (177). In a phase 2 study patients with cancer who were treated with enobosarm had improvement in LBM and stair climbing power. There was no reduction in free testosterone levels (129). However, two phase III trials involving patients receiving chemotherapy for lung cancer found that enobosarm improved LBM but failed to improve stair climbing power which was a co-primary outcome of the study (178,179).

### *Ghrelin*

Ghrelin is a growth hormone secretagogue receptor agonist which increases appetite by up-regulating neuropeptide Y and agouti-related protein in the

hypothalamus (180). Ghrelin also has skeletal muscle anabolic effects even though muscle lacks growth hormone secretagogue receptors (36). Experimentally ghrelin reverses the adverse effects of cisplatin and cancer on skeletal muscle. Cisplatin and tumor down-regulate the AKT pathway, MyoD and myogenin while up-regulating E3 ligases responsible for proteasome proteolysis. In addition, cisplatin up-regulates myostatin. Ghrelin reverses this (36). In animals, cisplatin causes muscle necrosis with associated inflammatory cell infiltrates which is prevented by ghrelin. In animals ghrelin not only prevents sarcopenia but improves muscle strength (181).

Anamorelin, a growth hormone secretagogue receptor agonist, has been used in several chemotherapy trials to decrease sarcopenia and improve muscle strength. In these studies patients had advanced lung cancer and cachexia. Appendicular muscle was measured by DEXA scans and muscle strength by hand grip. Similar to enobosarm, anamorelin improved muscle mass but not the functional co-primary functional outcome, hand grip strength (182-184).

### *Resistance training*

Some type of resistance training should be recommended. Resistance training increases type II muscle, improves strength, and directs protein intake toward muscle production. Resistance training forestalls age-related changes in mobility, improves gait speed, balance, and reduces fall risk in the elderly (185). There are differences in physiologic effects between aerobic and resistance training. Aerobic training alters mitochondrial and cytosolic enzyme activities, resistance exercise training increases contractile protein mass (186). It may be reasonable, therefore, to consider cross training between aerobic and resistance exercises. However, resistance training appears to be the most important element to an exercise program for patients undergoing therapy for their cancer. Early-stage breast cancer patients on adjuvant chemotherapy have a high risk of sarcopenia and dynapenia. Resistance training is superior to aerobic training in reversing both sarcopenia and dynapenia (187). Breast cancer patients undergoing hormone therapy have increased fat mass by 6 months, resistance training significantly increases LBM and fat free body mass (188). Resistance training decreases sarcopenia, reduces body fat, improves muscle strength and quality of life in hypogonadal prostate cancer patients, but not physical function (189).

### Combination therapy

Combinations of medications or combinations of medications with resistance training has been reported. OMF supplementation of 2–4 g/day has been combined with resistance training. Both muscle strength and mass improved (190–193). These studies have almost exclusively been done in geriatric populations. The combination overcomes anabolic resistance that occurs in older individuals (194). A combination of vitamin D supplementation and a metabolite of leucine, calcium  $\beta$ -hydroxy  $\beta$ -methyl butyrate (CaHMB), improves muscle strength, grip and gait speed in randomized trials. It was most effective in patients with mild to moderate sarcopenia but not severe sarcopenia (195). This finding suggests that prevention approaches or early interventions are likely to be more successful. Vitamin D supplementation and whey protein rich in leucine increases appendicular skeletal muscle mass. Benefits are best seen in those with higher serum vitamin D levels (196). Whey protein should not be the only protein source. A combination of HMB, whey protein, vitamin D and exercise has improved muscle mass and strength in the elderly. Lasting impact will depend on baseline nutritional status, severity of sarcopenia prior to the intervention, and adherence to the intervention (197). In a small underpowered study of patients with lung cancer the combination of OMF and a cyclooxygenase inhibitor improved body weight, muscle strength and reduced C-reactive protein. The combination was better than OMF alone (165).

### Summary

Sarcopenia is present at the beginning of chemotherapy in a subgroup of patients, and worsens or develops during neoadjuvant chemotherapy or palliative chemotherapy. Clinical outcomes are adversely influenced by the presence of sarcopenia prior to treatment or with the development of sarcopenia during therapy. Certain targeted agents cause sarcopenia while others may prevent or reverse sarcopenia. To treat and prevent sarcopenia, patients need adequate protein intake and resistance exercises. Patients should be screened for vitamin-D deficiency and vitamin-D should be replaced if deficient or insufficient. OMF 2–6 g/day should be considered as a supplement since toxicity is low and there are potential benefits. Large randomized trials are needed to validate the findings from small studies. Both anamorelin and enobosarm are unlikely to be approved

to treat or prevent sarcopenia in cancer since neither one improved function. Combinations of protein supplements, OMF, HMB and exercise are promising but largely untested in cancer.

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### Footnote

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