Cachectic muscle wasting in acute myeloid leukaemia: a sleeping giant with dire clinical consequences

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Abstract

Acute myeloid leukaemia (AML) is a haematological malignancy with poor survival odds, particularly in the older (>65 years) population, in whom it is most prevalent. Treatment consists of induction and consolidation chemotherapy to remit the cancer followed by potentially curative haematopoietic cell transplantation. These intense treatments are debilitating and increase the risk of mortality. Patient stratification is used to mitigate this risk and considers a variety of factors, including body mass, to determine whether a patient is suitable for any or all treatment options. Skeletal muscle mass, the primary constituent of the body lean mass, may be a better predictor of patient suitability for, and outcomes of, AML treatment. Yet skeletal muscle is compromised by a variety of factors associated with AML and its clinical treatment consistent with cachexia, a life-threatening body wasting syndrome. Cachectic muscle wasting is associated with both cancer and anticancer chemotherapy. Although not traditionally associated with haematological cancers, cachexia is observed in AML and can have dire consequences. In this review, we discuss the importance of addressing skeletal muscle mass and cachexia within the AML clinical landscape in view of improving survivability of this disease.

Keywords   Acute myeloid leukaemia; Skeletal muscle; Cachexia; Chemotherapy; Cancer; Myopathy; Risk stratification

Introduction

The most common acute leukaemia in adults, acute myeloid leukaemia (AML), is a malignant disorder of haematopoietic stem cells resulting in impaired production of the myeloid blood cell lineage.[1] AML is initially treated with intense chemotherapy induction regimens, followed by haematopoietic cell transplantation (HCT) to achieve complete remission (CR). While these strategies have had some success in younger cohorts, their clinical utility is constrained in older adults: the intensity and cytotoxicity of the chemotherapy used in the induction regimen and HCT conditioning programme enhances the risk of multi-organ toxicity, promoting morbidity and mortality.[2] This aspect reduces the curability of AML in older patients and directly contributes to the higher mortality

in >65-year-old patients.[2] Thus, it is important to pursue novel ideas to optimize current treatment and risk management strategies to improve outcomes for AML patients.

One emerging consideration in patient risk stratification for AML is skeletal muscle mass (MM). Skeletal muscle wasting and dysfunction (referred to herein as myopathy) is a consequence of many cancers and is an event synonymous with the induction of the body wasting syndrome, cachexia. Cancer-associated cachexia is considered to compound with sarcopenia, the age-related loss of MM and function,[3] and malnutrition[4] in older cancer patients resulting in dire mortality rates. Cachexia affects a staggering 50–80% of cancer patients, and up to 80% of those who manifest cachexia will die.[5] Recently, it has emerged that cachexia is synergistically driven by both cancer-related factors and anticancer

chemotherapy treatments.[6] Solid tumours, in particular, release many signalling factors that drive myopathy. Because cachexia is most prevalent in solid tumours associated with the gastrointestinal (GI) system (including accessory organs) and lungs, disruption of systemic nutrient delivery (i.e. amino acids and oxygen) may be a contributing factor to skeletal muscle wasting, albeit parenteral nutrition does little to attenuate cachexia.[6] However, in a clinical setting where patients are quickly treated for diagnosed cancers while cachexia is emerging, it is difficult to separate out the contribution made by cancer factors and anticancer treatment. Challenging the current dogma, the burgeoning field of chemotherapy-induced cachexia research indicates that chemotherapy both independently drives skeletal myopathy and exacerbates cancer-associated myopathy.[7] Thus, chemotherapy appears to have a more prominent role in cachexia than originally considered. For haematological cancers, such as AML where intense chemotherapy is the primary (or only) treatment modality, the scope for severe chemotherapy-induced cachexia is profound. This poses serious consequences for AML patients: skeletal MM has emerged as a prominent prognostic factor for survivability, not only in older adults but also for patients diagnosed at any age.[8,9] Unfortunately, there is currently little emphasis on the impact of skeletal muscle during patient risk stratification in AML, despite its potential as a factor to optimize clinical decision making and for therapeutic intervention.

This review will provide a current account of the evidence surrounding the impact of AML, and its treatments, on skeletal muscle and highlight the potential for skeletal muscle health to be clinically utilized in patient risk stratification and clinical decision making in AML.

Overview of the clinical landscape of acute myeloid leukaemia

Acute myeloid leukaemia is characterized by uncontrolled clonal expansion and differentiation arrest of haematopoietic stem cells, whereby the hyper-production of immature myeloid progenitors replaces homeostatic haematopoiesis.[1] Specifically, AML suppresses the production of essential blood cells from the myeloid lineage (e.g. erythrocytes, platelets, and granulocytes), leading to anaemia, haemorrhage, and infection, respectively.[1] AML has a 5 year overall survival (OS) of ~29%.[10] However, this statistic is negatively skewed by age with adults >65 years old having a 5 year OS of only ~8%.[10] These statistics are even more grim considering that (i) the median age of AML diagnosis is 68 years old[11]; (ii) AML incidence is three-fold higher in adults >65 years old[10]; and (iii) over the past decade, the prevalence of AML has increased proportionately with the ageing population.[12] This highlights age as a key prognostic indicator. In 2021,

there is expected to be 20 240 new AML cases and 11 400 associated deaths in the USA alone,[13] which projects AML to have the greatest mortality to incidence ratio of all blood cancers.[13] The average cost of AML treatment in the USA is ~$200 000 USD per chemotherapy induction regimen and ~$330 000 USD per HCT, which is attributed to extensive inpatient hospitalization.[14] These figures exclude the costs associated with multiple chemotherapy cycles and HCTs, and relapse. Thus, the true disease and economic burden on patients and subsidizing healthcare systems is substantial and will only increase with the ageing population. Because AML has a median survival time of 8.5 months in the USA,[11] the initial treatment period is crucial to successful treatment outcomes. This is particularly true because, despite several promising novel treatments for AML being trialled for younger patients, there has been a distinct lack of progression in treatments targeting the predominant and most at-risk older adult population.

Since the 1970s, AML has been clinically treated with conventional chemotherapy, primarily the '3 + 7' induction regimen, which involves 3 days of an anthracycline (daunorubicin, epirubicin, or idarubicin) concurrent with 7 days of the antimetabolite, cytarabine.[1] The '3 + 7' induction regimen can be repeated multiple times before achieving CR. Future treatment decision making is then dependent upon risk stratification, which considers a suite of prognostic factors for relapse post-induction (e.g. cytogenetics and molecular mutations; for extensive review, see Papaemmanuil *et al.*[15]). AML patients with favourable risk profiles typically receive further chemotherapy as a 'consolidation' treatment, such as high-dose cytarabine, to maintain CR and reduce the potential of minimal residual disease—a major cause of relapse in AML.[1] However, most AML patients present with intermediate or adverse risk profiles,[15] which requires allogeneic HCT, the only current curative strategy for AML.

Preparation for HCT is initiated through an intense conditioning programme, typically utilizing a chemoradiation strategy, such as cyclophosphamide, alongside high-dose busulfan or total body irradiation.[16] These induce myeloablation but are associated with severe toxicity and co-morbidity. Nevertheless, it is an essential constituent of HCT, which confers a significant survival advantage for eligible patients.[17] However, in older adults, the utilization of HCT is limited. Only 10% of AML patients >65 years old are prescribed with HCT due to the high risk of graft vs. host disease (GvHD) and transplant-related mortality.[18] Reduced-intensity conditioning programmes coupled with improved supportive care and more accurate HLA-type matching have increased the risk/reward ratio of HCT prescription in older AML patients somewhat.[18] While an increased risk of severe GvHD remains in this patient cohort, the benefits (i.e. reduced risk of relapse and increased OS) are profound.[19] Thus, it is imperative to investigate new strategies to increase AML patient eligibility for HCT to achieve a more sustainable CR. In particular, the

ongoing optimization of patient risk stratification is essential, which requires novel ideas to better guide current therapeutic strategies and decision making for AML.

The impact of body composition on successful acute myeloid leukaemia treatment: a novel target for risk stratification?

Research arising over the past decade may have disingenuously overlooked the screening potential of anthropometry parameters in AML risk stratification. This is likely due to the lack of consensus surrounding the prognostic value of crude body composition indicator, body mass index (BMI), at diagnosis.[20,21] The key issue is that BMI does not accurately measure adiposity nor MM,[22] allowing for an 'obesity paradox' in cancer patients where the relationship between BMI and mortality does not adhere to its typical J-curve.[23] Instead, patients classified as overweight or obese (BMI > 25 kg/m^2) often demonstrate better survivability.[24] An exception to this paradigm, younger AML patients (<65 years old) categorized as overweight or obese display worse OS and GvHD-free survival compared with patients with lower BMI scores (<25 kg/m^2).[25] However, these adverse prognostic findings are suggested to be partly dependent on dose-capping at a body surface area (BSA) of 2 m^2, which occurs in ~40% of obese cancer patients and is associated with reduced therapeutic efficacy of chemotherapeutic agents (CAs).[26] Optimal dose selection is integral in AML treatment decision making and is based on risk stratification to ensure therapeutic efficacy while limiting drug-related toxicity (DRT) and non-disease mortality.[27] To avoid the issues surrounding dose-capping, additional studies evaluated chemotherapy dosing based on actual body mass (BM) rather than BSA with mixed results.[28-30] This suggests that dose-selection strategies require a more accurate body composition normalization measure to overcome the 'obesity paradox' and mitigate DRT. Historically, dose selection, derived from the classic BSA formula,[31] was based on the theory that larger patients have a higher capacity for drug clearance and thus require higher doses to reach equivalent bioavailable drug concentrations compared with smaller patients.[32] However, the clinical utility of BSA in the context of CA dosing circumvented the developing understanding of individual drug pharmacokinetics: BSA normalization is unable to account for the variability in plasma drug concentrations and clearance,[33] highlighting a need for alternative dose-selection strategies. Lean BM (LBM), that is, the sum of body water, total body protein, carbohydrates, non-fat lipids, and soft tissue mineral,[22] is a promising alternative to BSA for chemotherapy dose-related decision making.[34] BSA

does not account for the large and unpredictable role of fat mass relative to BM and is poorly correlated with LBM in cancer patients,[35] while LBM can account for a significant portion of the variation in the clearance of CAs, for example, the anthracycline epirubicin.[36] Thus, increasing the accuracy of body composition assessment is a promising strategy to improve risk stratification processes and mitigate DRT while improving patient survivability in populations in whom changes to body composition are masked by total BM.

Body composition assessments are an emerging frontier of personalized medicine and risk stratification in the oncological setting.[4] They are particularly important in the at-risk older adult AML cohort, a population also at high risk for sarcopenia, which is poorly correlated with BMI classification.[37] However, BMI does have some prognostic value in the geriatric AML patient population: lower BMI scores in older adults (>60 years old) are associated with reduced OS and GvHD-free survival and are exacerbated in patients classified as underweight (BMI < 18.5 kg/m^2) compared with normal weight (BMI 18.5–25 kg/m^2).[38] These data do not break the constraints surrounding current risk stratification practice, with underweight geriatric populations routinely flagged as high risk for DRT in geriatric assessments, for example, Karnofsky Performance Scale, evaluating suitability to receive intense chemotherapy.[39] A complementary body composition assessment modality is the skeletal muscle index (SMI), the gold standard for detecting changes in skeletal MM ascertained using computed tomography (CT) scans to quantitate total abdominal muscle area corrected for height (cm^2/m^2) at the third lumbar (L3) level.[40] Recently, reference ranges of the total abdominal muscle area were published, with cut-off points determining low MM to range between 36.54–45.2 and 30.21–36.05 cm^2/m^2 in healthy individuals and 36–43.2 and 29–34.9 cm^2/m^2 in cancer patients, for men and women, respectively.[41] For cancer patients, and consistent with the 'obesity paradox', a similar 'BMI paradox' exists: low MM, that is, myopenia (any age) or sarcopenia (specifically in older age), can be hidden in patients classified as normal or overweight (BMI 18.5–29.9 kg/m^2), and low MM alongside high adiposity, that is, sarcopenic obesity, can be hidden in patients classified as obese (BMI > 30 kg/m^2).[42] Accordingly, Martin *et al.* stratified myopenia cut-off values in lung and GIT cancer patients through accounting for BM-related variance, with criteria proposed: <41 cm^2/m^2 for women; <43 cm^2/m^2 (BMI < 25 kg/m^2) and <53 cm^2/m^2 (BMI ≥ 25 kg/m^2) for men.[43] While these cut-off values for CT-derived SMI and BMI in cancer-specific subpopulations are the most refined to date, there is further investigation required to cultivate tertile cut-off ranges that are more sensitive to the changes in BMI and CT-derived SMI typically observed in large and diverse population-based multicentre trials. Future research should also pursue the refinement of these myopenia/sarcopenia and sarcopenic obesity cut-off ranges specific to the cancer type and especially for AML.

Despite being commonly undetected because of the clinical reliance on BMI, myopenia and sarcopenia at the time of cancer diagnosis are associated with increased risk of DRT from, and consequently poor adherence to, anticancer treatment.[42,44] This instigates a vicious wasting cycle because chemotherapy exacerbates myopenia, thus potentiating the risk of mortality.[45] While sarcopenia is central to these findings, it is known that this condition is typically present alongside other co-morbidities, with recent data suggesting there is a nine-fold increase in the likelihood to have a Charlson Co-morbidity Index >2 in sarcopenic individuals.[46] These co-morbidities include low nutrition status, diabetes, cardiovascular disease, kidney disease, and liver disease, which may all contribute to poorer treatment outcomes and survivability in AML.[47] There are less empirical data available regarding the connection between myopenia and co-morbidities, predominately due to the lack of consensus of a definition of skeletal muscle wasting that accounts for conditions across all ages, not just the older population.[48] Specific to AML, myopenia and sarcopenia pre-diagnosis are prognostic of poorer survivability.[8,9] However, the outlook for the older AML cohort is particularly devastating: the 3 year OS for sarcopenic patients is 0% compared with 49% for non-sarcopenic patients.[8] Interestingly, sarcopenia, characterized solely by low SMI, was associated with reduced muscle function in AML patients[49] despite the poor correlation of SMI with functional measurements,[50] leading to more questions rather than answers. These findings highlight the importance of skeletal MM at diagnosis and provoke questions regarding the potential interplay between myopenia/sarcopenia and fellow wasting condition, cachexia, at other important stages of AML treatment such as before and after HCT, which could have serious implications for AML patients of any age.

Cancer-associated cachexia is defined as the loss of BM alongside the depletion of skeletal MM with, or without, loss of fat mass.[51] Cachexia is clinically characterized by (i) weight loss of >5% over a 6 month period; (ii) BMI < 20 kg/m^2 and body weight loss of 2%; or (iii) an appendicular SMI consistent with sarcopenia and weight loss >2% over the past 6 months.[51] Importantly, skeletal MM loss is purported as the quintessential prognostic factor in cachexia, particularly when conceding the impact of the 'obesity paradox'.[43] Indeed, Roeland et al. highlighted that monitoring BM changes may not be sensitive enough to capture cachexia-induced skeletal MM loss.[52] The diagnosis of cachexia is a dynamic continuum of staging from pre-cachexia to cachexia to refractory cachexia, and progression through each stage is associated with increased morbidity and mortality risk.[51] Cachexia comprises multifactorial underlying systemic issues, including anorexia, chronic inflammation, and altered energy metabolism.[6] Collectively, these factors perturb the nutritional status of cachectic patients. This is acknowledged within the definition of cachexia, that is, that BM loss cannot be fully reversed by conventional nutritional support.[51] Fur-

ther, cachectic muscle wasting is accompanied by progressive dysfunction, which reduces exercise tolerance, physical performance, ambulatory capacity, and ability to undertake activities of daily living, which reduce patient quality of life (QoL). Cachexia is not typically considered as part of risk stratification in AML nor other haematological malignancies, despite its prevalence in these cancers and the deleterious impact it has in other cancers.[6] Although confirmatory data from multicentre studies with larger sample sizes are required, Keng et al. suggest that AML patients experience a median BM loss of ~6% from diagnosis to CR attainment, which is consistent with the definition of cachexia.[53] Moreover, the loss of BM from AML diagnosis to the commencement of HCT is associated with reduced OS and GvHD-free survival.[54] These findings build on emerging evidence that lower BMI scores before HCT are associated with increased risk of relapse and mortality,[55] where the degree of wasting corresponds with the risk of negative treatment outcomes.[56] Further, and perhaps more importantly, pre-HCT abdominal CT scans measuring myopenia/sarcopenia-defined MM loss have been identified as a powerful prognostic factor in determining non-relapse mortality after HCT.[57] However, neither skeletal muscle nor BM loss during treatment is considered as a risk factor for HCT eligibility. Remarkably, only a pre-HCT BMI score >35 is included in the HCT co-morbidity index,[58] which typically identifies a morbidly obese patient.[23] It is also important to consider pre-HCT BM loss for risk stratification purposes. Weight loss history before HCT is a significant predictor of patient deconditioning,[59] and superfluous weight loss after HCT increases non-relapse mortality risk.[60] Thus, developing screening strategies for indicators of patient susceptibility for BM (particularly lean mass) loss during treatment would enrich risk stratification guidelines at multiple treatment stages (i.e. during induction, consolidation, and/or HCT; Figure 1). Further, understanding the factors that contribute to cachexia induction in the AML setting is essential for identifying strategies to mitigate the influence of cachexia on poor treatment outcomes.

An opportunity to waste: exploring the multifactorial contributors to skeletal myopathy in acute myeloid leukaemia

Encompassing ~40% of total BM, skeletal muscle is essential for locomotion, mastication, swallowing, and breathing, highlighting its necessity for undertaking activities of daily living and preserving QoL.[61] Skeletal MM is controlled through balancing protein synthesis and degradation (i.e. muscle turnover) and can be influenced by many hypertrophic and atrophic factors.[62] Skeletal muscle also regulates basal metabolic rate. It is both a 'sink' for blood glucose disposal (stored as glycogen) and a reservoir for amino acids: both can be me-

Proposed muscle-related risk stratification criteria
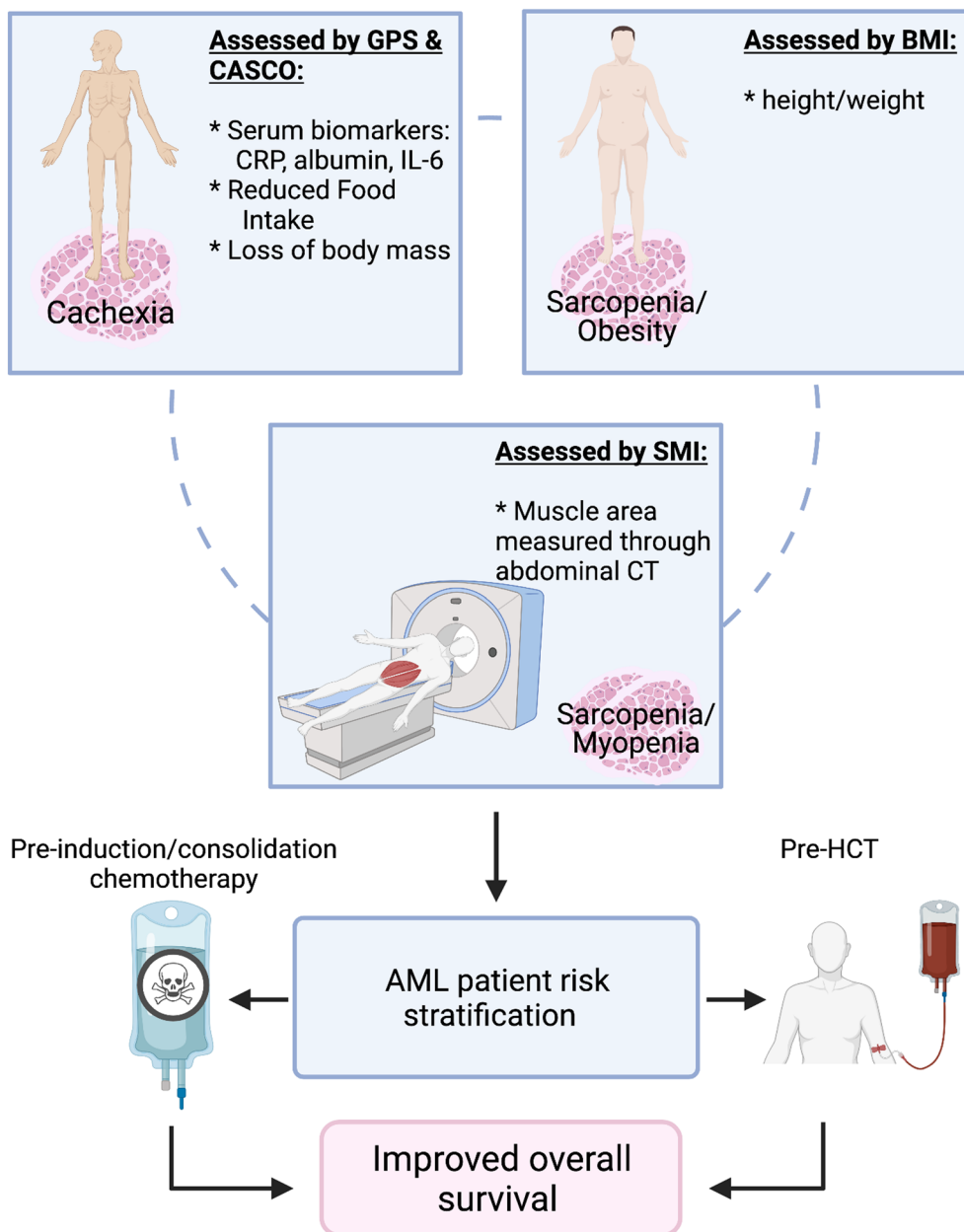
Figure 1 Proposed muscle-related risk stratification criteria in acute myeloid leukaemia (AML). Improved risk stratification criteria for AML could consider, measure, and utilize skeletal muscle mass because muscle loss is correlated with higher morbidity and mortality rates. Patients could be stratified through the identification of (i) cachexia by the CAchexia SCOre (CASCO), which utilizes pro-inflammatory status [measured by interleukin-6 (IL-6)], and the Glasgow prognostic score (GPS), which measures serum C-reactive protein (CRP) and albumin; (ii) sarcopenia/obesity by the body mass index (BMI) using the rudimentary measures of patient height and weight; or (iii) myopenia/sarcopenia by the skeletal muscle index (SMI), the gold standard assessment of skeletal muscle mass by abdominal computed tomography (CT). This could occur before, during, and after AML treatment to determine acceptable chemotherapy exposure (e.g. type of anthracycline, dose, and number of consolidation cycles) and eligibility for haematopoietic cell transplantation (HCT) and increase overall survival.

tabolized for energy production and are important signals for muscle growth.[61,63] While these stores are maintained by regulatory homeostatic processes, under severe metabolic stress caused by wasting conditions like cachexia, muscle protein can become depleted through catabolism. Consequently, metabolism is dysregulated, contributing to debilitating dysfunction. Discovering the underlying mechanisms that drive skeletal myopathy in cancer cachexia has received attention, predominantly through studies in rodent models or human patients with solid tumours.[64] A host of potential

drivers of the cachectic condition have been illuminated (summarized in *Figure* 2). However, there is limited understanding concerning the contributing factors that drive muscle cachexia in haematological malignancies, such as AML.

Chemotherapy-induced myopathy

Over the past decade, the impact of CAs on skeletal muscle has become increasingly evident as recently reviewed by us.[7] The anthracycline class of CAs have been at the forefront of this research, primarily using doxorubicin, an analogue of daunorubicin/epirubicin/idarubicin used interchangeably in the '3 + 7' AML induction regimen. Anthracyclines are widely known to induce cardiomyopathy,[65] a key risk factor associated with their limited clinical utility in AML treatment.[66] It is also well documented that doxorubicin induces skeletal myopathy as observed in cell culture, rodent models, and humans, with the mechanisms extensively investigated.[7] Briefly, it has been shown that doxorubicin (i) promotes mitochondrial toxicity through hijacking complex I redox cycling and (ii) amplifies reactive oxygen species production. Together, these can impair mitochondrial respiration and cause oxidative stress/damage.[67] Oxidative stress promotes skeletal muscle catabolism by up-regulating proteolytic pathways that degrade myofibrillar proteins including myosin and actin, resulting in contractile apparatus dysfunction.[67] Daunorubicin also reduces myosin and actin expression and disrupts sarcomeric organization in C2C12 myotubes.[68] While these data highlight the deleterious impact of certain anthracyclines on the quality and quantity of skeletal muscle, further studies are required to contextualize their impact in AML treatment because daunorubicin, epirubicin, and idarubicin differ in their chemical structure and may exert different degrees of toxicity on the muscular system.
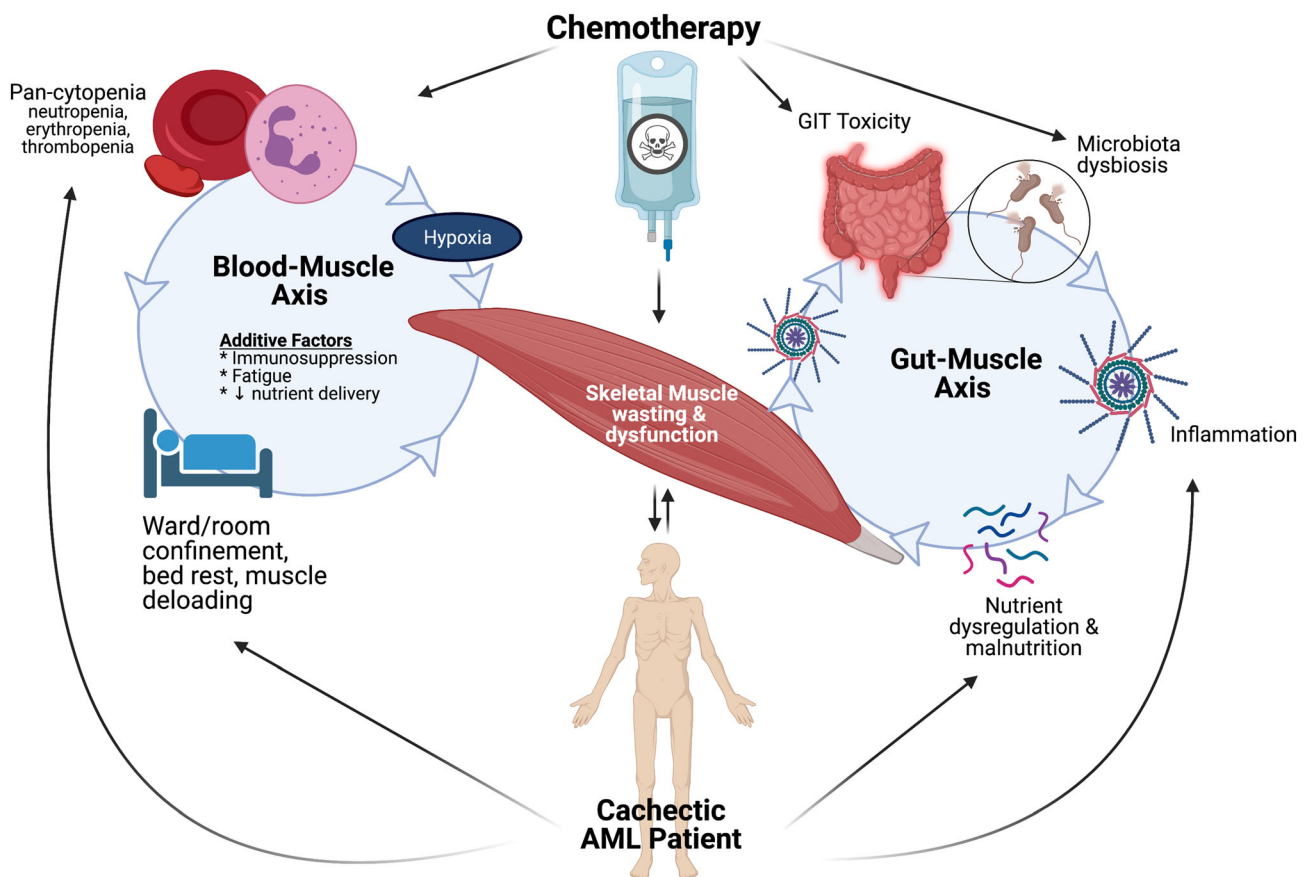
Figure 2 Potential drivers of muscle mass loss in acute myeloid leukaemia (AML). Chemotherapy administration has been shown to directly induce skeletal muscle wasting and dysfunction. This can be exacerbated by the effect of chemotherapy on the gastrointestinal tract (GIT), which dysregulates motility and microbiota composition and compromises the intestinal barrier. Collectively, these symptoms reduce nutrient absorption and nutrient status signalling through the microbiome and increase the risk of infection and passage of inflammatory mediators. Furthermore, chemotherapy extirpates blood cells causing hypoxia and supressing the immune response. Consequently, patients are incapacitated, because of both fatigue and risk of infection, respectively. Ultimately, processes that maintain muscle mass and function are compromised, and muscle damage and wasting is potentiated. The outcome is cachexia, which further drives muscle wasting and dysfunction through dysregulated signalling, malnutrition, and muscle deloading.

It is important to acknowledge that not all CAs exert comparable effects on skeletal muscle nor have they all been evaluated, indicating a significant knowledge gap. In AML, there is limited understanding of the effect of cytarabine, the other constituent of the '3 + 7' chemotherapy induction regimen, on skeletal muscle. Amrute-Nayak *et al.* is the only study of note to investigate this, and no impact of cytarabine was reported.[68] However, the authors did not justify dose selection, and given that CAs elicit skeletal myopathy in a dose-dependent manner,[7] dose-escalation studies would be beneficial. Cytarabine is an antimetabolite like 5-fluorouracil, an established potent activator of cell stress signalling factor, mitogen-associated protein kinase (MAPK).[69] During oxidative stress, MAPK activation, particularly p38 MAPK, promotes pro-inflammatory cytokine activity through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling.[70] 5-Fluorouracil-based chemotherapy regimens induce skeletal myopathy through p38 and ERK1/2 MAPK activation and impair mitochondrial dynamics.[71] Thus, it is likely that stress signalling and myopathy would occur with clinically compatible dosing of cytarabine-based regimens, particularly when multiple induction cycles and consolidation therapy are utilized.

Chemotherapy is also conventionally utilized as a treatment strategy in HCT conditioning programmes, which typically include the non-specific alkylating agents cyclophosphamide and busulfan. While there are no data regarding the impact of busulfan on skeletal muscle, there are several studies documenting the effect of cyclophosphamide. Cyclophosphamide promotes a negative nitrogen balance, impairs protein metabolism, causes skeletal muscle disorganization, and induces mitochondrial dysfunction: these manifest as exercise intolerance and reduce both MM and BM.[72,73] Cyclophosphamide also promotes inflammation through increased transcription of NF-κB and subsequent production of pro-inflammatory cytokines, which are prominent mediators of skeletal muscle atrophy.[74] NF-κB activation is central to the myopathy caused by both chemotherapy and cancer.[5,7] Identifying the underlying mechanisms of cyclophosphamide-induced skeletal myopathy requires future exploration as does the impact of emerging CAs for AML treatment, such as multi-targeted kinase inhibitors, which are known to elicit significant off-target effects that can induce cardiac and skeletal myopathies.[75] It is imperative that further research concerning both current and novel drug candidates is conducted to elucidate their relative contribution to cachexia and myopathy induction. Hopefully, this will occur without delay as opposed to the historical paucity of action.

Myelogenous cytopenia-related factors

Inextricably, the aim of therapeutic strategies against AML is to nullify non-functional leukaemic progenitors that have re-

placed normal myeloid progenitors and inadvertently depleted the blood cells from the myeloid lineage. Paradoxically, chemotherapy induces pan cytopenia leaving the haematological system severely challenged. This is epitomized by the effect of chemotherapy on neutrophils, granulocytes of myeloid lineage. Neutropenia (abnormally low neutrophil count) is a risk factor implicated in the high rates of mortality associated with AML. Neutrophils are master regulators of innate immunity,[76] and their depletion renders patients immunocompromised and susceptible to opportunistic infections. Febrile neutropenia is a common complication in haematological malignancies, and it accounts for ~11% of patient mortality.[77] While there are prophylactic drugs to treat arising infections, neutropenia, unlike other forms of cytopenia, cannot be improved through blood transfusions. Moreover, standard neutropenia treatment with granulocyte colony-stimulating factor has only modest efficacy in AML: while it can reduce neutrophil recovery time, it does not reduce the risk of infections nor improve survivability.[78] Neutropenic AML patients are confined to wards as a protective environmental prophylactic antibiotic measure.[79] More severe confinement occurs in patients with vancomycin-resistant enterococci, an otherwise commonplace colonizer of gut flora, to prevent the spread of infection (and risk of mortality) to other AML patients.[80] While necessary, these strategies are to the muscular system's detriment: patient inactivity and bed rest promote muscle de-loading and drive muscle wasting.[81] This is further complicated by the prevalence of erythropenia, which results in poor tissue oxygenation (i.e. hypoxia), particularly of skeletal muscles. Hypoxia exacerbates inactivity-related muscle wasting and contributes to muscle fatigue,[82] which is reported to be the most stressful side effect experienced by cancer (and AML) patients as it incapacitates, reducing QoL.[83] While further research is required to interrogate the protective role of physical activity against skeletal myopathy and physiological fatigue in AML, exercise has been shown to ameliorate the induction of central fatigue and depression.[84]

Systemic myeloid-related cytopenia induced by AML and chemotherapy treatment, especially neutropenia and erythropenia, can also directly impact skeletal muscle tissue and drive myopathy. Neutrophils are critical for skeletal muscle remodelling through stimulating monocyte chemotaxis, and subsequently macrophage recruitment, early events in the response to myotrauma.[85] In the clinical AML setting, myotrauma may result from (i) cellular injury (e.g. oxidative stress and proteolytic system activation) caused by cancer secretions, chemotherapy, and other drugs utilized in standard clinical care and (ii) transient re-loading after moderate–long periods of de-loading. Unfortunately, there is limited understanding of the effect of cancer-related neutropenia on skeletal myopathy, although it is hypothesized that neutropenia blunts the muscle repair response following damage.[85] Interestingly, monocytes, also derived from the myeloid lineage,

may play a larger role in skeletal muscle damage and repair processes compared with neutrophils, because they regulate the recruitment and function of macrophages. Monocytes are involved in the transition of pro-inflammatory M1-like macrophages, which remove damaged tissue, to anti-inflammatory and pro-fibrotic M2-like macrophages, which mediate extracellular matrix remodelling and skeletal muscle regeneration.[85] Recently, it has been demonstrated that chemotherapy reduces the number of skeletal muscle M1-like macrophages and M1–M2-like transitional macrophages but has no effect on M2-like macrophages.[86] These data highlight that dysregulation of the skeletal muscle immune microenvironment may contribute to AML and treatment-related skeletal myopathy and could be a target for prevention/reversal of cachexia.

Erythropenia results in systemic tissue hypoxia, which is clinically managed through blood transfusions until endogenous erythropoiesis recovers. The impact of acute and chronic hypoxia on skeletal muscles in a cachectic environment is relatively uncharacterized. Indeed, erythropenia-mediated hypoxia causes debilitating physiological fatigue in which a claudication-like loss of muscle sensation has been reported.[87] Systemic hypoxia can stimulate molecular adaptations within skeletal muscle through the oxygen-sensitive target, hypoxia inducible factor-1α (HIF-1α).[87] During acute muscle hypoxia, such as that following intense exercise, HIF-1α is transiently activated, stimulating an adaptive stress response that clears unhealthy mitochondria and promotes healthy mitochondria biogenesis to mediate recovery.[88] Conversely, persistent HIF-1α activation in response to chronic hypoxia impairs bioenergetic efficiency.[88] Chronic hypoxia is associated with skeletal muscle atrophy and is considered to occur in a fibre type-dependent manner. Oxidative muscle fibres appear to be more sensitive to hypoxia because their metabolism is dependent on oxygen delivery.[88] It is an obvious problem for AML patients and is also observed in cancer cachexia, likely as an adaptive stress response to limit oxidative damage or due to tumour-specific factors.[89] Chronic hypoxia also supresses mammalian target of rapamycin, mTORC1, a master regulator of protein synthesis and therefore MM, via up-regulation of *regulated in development and DNA damage 1* (REDD1).[88] Interestingly, the gene REDD1 is a key transcriptional target of chemotherapy-induced myopathy.[7]

Malnutrition and metabolic dysregulation

Historical interpretations of BM wasting in cancer were previously attributed to impaired nutritional status.[90] Presently, malnutrition remains a key hallmark of cachexia, arising from reduced food intake due to loss of appetite.[6] During nutrient stress, skeletal muscle undergoes catabolism to unlock stored amino acids for energy production and is magnified during extended periods of hospitalization.[91] In haematological cancers, ~30% of patients are malnourished.[92] However, there is dissensus on the incidence of malnutrition in AML. It is estimated that ~15–30% of patients receiving induction chemotherapy, or those in the post-remission phase, present with malnutrition, which is associated with longer hospital stays and increased level of minimal residual disease, GI toxicity, and risk of mortality.[93,94] Unsurprisingly, patients who are malnourished prior to HCT are at increased risk of adverse treatment outcomes.[95] Subsequently, the European Society for Clinical Nutrition and Metabolism established guidelines for malnutrition risk screening and recommendations for intervention, albeit these are poorly adhered to in AML clinical care management.[96] This may be due to the scarcity of information pertinent to AML. Parenteral feeding has been touted as preferential over enteral feeding due to common oncological challenges (i.e. GI toxicities, tube feeding complications, and absorption difficulties[95]). Conversely, European Society for Clinical Nutrition and Metabolism guidelines recommend enteral feeding due to the lower risk of complications from infections in immunocompromised patients undergoing intense chemotherapy or HCT conditioning programmes.[97] This highlights a requirement for more extensive clinical investigations to aid clinical care management and decision making through improved risk stratification processes. Delineating AML patients that are wasting due to malnutrition vs. cachexia is imperative because not all malnourished patients are cachectic and thus can respond to nutritional interventions.[98] In contrast, all cachectic patients are invariably malnourished but typically insensitive to nutrition interventions.[98]

The underlying drivers of malnutrition in AML are poorly understood, but are purported to be driven by chemotherapy-associated toxicities, particularly GIT-related side effects.[99] GIT toxicity is typically attributed to mucositis,[99] which perturbs food intake behaviours and impairs GIT nutrient absorption. This can exacerbate malnutrition especially in the presence of enteric neuropathy, which is provoked by chemotherapy treatment and results in dysregulated peristalsis, reduced gut motility, and delayed bolus transit time.[100] Mucositis can also induce complications through neutropenia-related blood infections arising from intestinal barrier damage. This has been observed following AML chemotherapy induction regimens.[101] The intestinal barrier also confines the microbiota, a key regulator of GIT homeostasis and integrity: its composition and function is affected by intestinal inflammation, as seen in mucositis, and directly through chemotherapy-mediated cytotoxicity.[99] It has recently been shown that reduced microbial diversity, that is, dysbiosis, predicts the risk of infection in AML patients.[102] Dysbiosis has also emerged as a prognostic factor for mortality in haematological cancer patients undergoing HCT, with increased microbiota diversity associated with higher OS.[103] Pertinent to skeletal muscle, microbiota

diversity has a positive role on physical function and skeletal MM maintenance.[104] It is also salient in sarcopenia-related skeletal myopathy.[105] Thus, in AML where poor prognosis is significantly increased in older adults, it would be interesting to investigate the impact of sarcopenia alongside chemotherapy on microbiota diversity and how this interplay relates to the induction and progression of cachexia.

Metabolic dysregulation is intimately intertwined with malnutrition in cancer cachexia, where a negative energy balance is reflective of disproportionate energy consumption vs. production.[106] In this context, cancer cell metabolism usurps systemic metabolism, driving the increase in basal metabolic rate.[106] Cancer cells create metabolic symbiotic relationships with the host whereby systemic glucose metabolism is enhanced to support cell survival and proliferation.[107] This paradigm has been observed in AML patients, with systemic glucose metabolism progressively enhanced in patients stratified by cytogenetic risk.[108] Further, AML patients with adverse risk profiles have higher circulating glycolytic metabolites (lactate and pyruvate).[108] Dysregulation of glucose metabolism negatively affects energy substrate-rich tissue, such as skeletal muscle, through the proteolytic release of amino acids that are utilized for hepatic gluconeogenesis, and adipose tissue, through the lipolytic release of free fatty acids to be utilized for glycolysis via β-oxidation.[106] This is further complicated by insulin resistance, an event that can be potentiated by both AML and chemotherapy.[108,109] Insulin resistance suppresses the phosphatidylinositol 3-kinase and protein kinase B signalling pathways and, subsequently, the transcription of downstream effector forkhead box O. These, in turn, enhance the expression of classic proteolytic factors, E3 ubiquitin ligases, muscle RING-finger protein-1, and atrogin-1, a common signalling cascade associated with skeletal muscle atrophy.[110] In response to reduced insulin-mediated glucose uptake, skeletal muscle increases the uptake of lipid intermediates, diacylglycerol and ceramide, as a compensatory mechanism to reduce the energy deficit.[111] However, this mechanism inadvertently promotes intramuscular lipid deposition, that is, myosteatosis, a common feature of primary myopathies that incite progressive muscle dysfunction.[112] It is important to note that dysregulated metabolism is only one of the contributing factors driving myosteatosis: defective leptin signalling, increased intramuscular pro-adipogenic progenitor cells, and reduced regenerative potential are also suggested potentiators.[112] Interestingly, these mechanisms are pervasive in the cachectic phenotype[113] and are associated with poor survivability in a multitude of cancers.[114]

Disturbing the inflammatory milieu

Although cachexia induction is a multifactorial phenomenon, it is consistently underpinned by elevated systemic inflammation mediated by an increased pro-inflammatory to anti-inflammatory cytokine ratio.[6] The central nervous system is a crucial regulatory target of cachexia induction and progression through its role in the recognition of inflammatory cytokines as signallers of the acute illness response.[115] Subsequently, the central nervous system can evoke systemic catabolism through hypothalamic–pituitary–adrenal axis activation, which contributes to fatigue, malnutrition, and BM and MM loss.[6] The utility of pro-inflammatory biochemical markers has emerged through specific diagnostic tools, including the (i) Glasgow prognostic score (GPS), which utilizes C-reactive protein and albumin to diagnose cachexia[116] and, and (ii) CAchexia SCOre (CASCO), which incorporates the pro-inflammatory cytokine interleukin-6 in its criteria panel for quantitative staging of cancer patients across the cachexia continuum.[117] While these strategies are a positive step towards improved cachexia identification, especially because it is typically under-diagnosed, one disadvantage of these approaches is that the inflammatory milieu is heterogeneously modulated by different types of cancer and typically involves complex and specific interactions between the cancer and host.[118] Solid tumour cancers release mediators (i.e. a secretome), including pro-inflammatory cytokines, which promote systemic inflammation and induce cachexia.[118] In haematological malignancies like AML, the role of the secretome on cachexia induction has been largely ignored despite evidence suggesting that inflammatory mediators promote AML disease progression.[119] Freire *et al.* were the first to demonstrate the AML secretome releases cachexia-inducible factors (CIFs) that contribute to cachexia induction and are associated with an increased risk of mortality.[118] Because AML is a heterogeneous disease with multiple subtypes, it would be imperative to stratify the datasets surrounding CIFs by cytogenetic mutations to identify translational pipelines specific to AML. Future investigations in this area will enrich the academic utility of the Freire *et al.*, paper, which exhaustively predicted ~613 dysregulated genes from the AML secretome.[118] There is limitless potential for future studies stemming from this data given that the AML-specific cachexia field is largely untouched.

Future studies investigating AML-derived CIFs will also have the potential to aid development of screening strategies for AML-specific cachexia risk stratification using biomarkers. Current biomarkers are overtly non-specific to cancer type and do not delineate the general ratio between pro-inflammatory and anti-inflammatory cytokines.[64] However, biomarker strategies for cachexia screening may still be useful in haematological malignancies such as AML, given their current lack of utility. Clinical trials are now required to evaluate their efficacy, alongside investigating other emerging biomarkers that can identify both MM loss and changes to the inflammatory cytokine ratio.[120]

Perspectives and conclusions

Historically, cachexia, and its clinical repercussions, has been overlooked in haematological malignancies, like AML, focussing instead on solid tumour cancers that present with more profound body and muscle wasting.[6] Nevertheless, AML research is typically partisan towards risk stratification associated with patient cytogenetics: this has been relatively successful, particularly in the AML subtype, acute promyelocytic leukaemia, through the identification of a novel gene therapy, which proffers improved survivability.[121] Despite the clinical utility of risk stratification based on cytogenetics, patients in each cytogenetic risk group remain prognostically heterogeneous.[18] Thus, further stratification strategies are required. These could include (i) scoring criterion related to skeletal muscle health such as CT-derived SMI or (ii) cachexia diagnostic tools, GPS, and CASCO, to better inform clinical decision making and improve patient survivability. While serum biomarker scoring systems like GPS and CASCO are relatively easy to implement and interpret within the clinical AML setting during routine pretreatment blood work-up, CT-derived SMI quantitation is labour intensive, requires interpretive expertise, and is not routinely performed for AML work-up. Emerging automated technologies, such as deep learning artificial intelligence, will facilitate implementation and integration of CT-derived SMI into clinical AML care.[122] The use of novel AML-derived CIFs[118] as personalized biomarkers for cachexia risk stratification is also not outside the realm of possibility given that AML is already a frontier for personalized medicine.

While the identification of cachexia in AML is an exciting opportunity for risk stratification, it also represents a detrimental co-morbidity that requires therapeutic intervention. Thus, strategies that protect skeletal muscle health could play a key role in mitigating AML-related and treatment-related toxicities, with the central goal of improving patient eligibility for HCT. Given the heterogeneity of potential contributing factors to skeletal myopathy induction in the AML setting, multifactorial strategies will likely be required for efficacy. The Multimodal-Exercise, Nutrition and Anti-inflammatory medication for Cachexia (MENAC) Phase III trial has shown promise in treating cachexia arising from other cancer types.[123] Indeed, more research is required surrounding novel strategies to promote ambulation and load bearing during extended periods of hospitalization, particularly those that acknowledge the environmental challenges of ward and/or room confinement experienced by AML patients. However, before multifaceted interventions like the MENAC trial can be translated into the AML setting, it is imperative to consider the T.A.R.G.E.T. approach, which highlights the need to initially pursue strategies that promote teaching, awareness, and recognition of the effect of AML and its treatments on skeletal muscle to further establish this emerging field.[124]

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Conflict of interest

None declared.

References

1. Short NJ, Rytting ME, Cortes JE. Acute myeloid leukaemia. *Lancet* 2018;**392**: 593–606.
2. Almeida AM, Ramos F. Acute myeloid leukemia in the older adults. *Leuk Res Rep* 2016;**6**:1–7.
3. Batsis JA, Villareal DT. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. *Nat Rev Endocrinol* 2018;**14**:513–537.
4. Hilmi M, Jouinot A, Burns R, Pigneur F, Mounier R, Gondin J, et al. Body composition and sarcopenia: the next-generation of personalized oncology and pharmacology? *Pharmacol Ther* 2019;**196**:135–159.
5. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cancer cachexia: understanding the molecular basis. *Nat Rev Cancer* 2014;**14**:754–762.
6. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. *Nat Rev Dis Primers* 2018;**4**:17105.
7. Campelj DG, Goodman CA, Rybalka E. Chemotherapy-induced myopathy: the dark side of the cachexia sphere. *Cancer* 2021;**13**:3615.
8. Nakamura N, Ninomiya S, Matsumoto T, Nakamura H, Kitagawa J, Shiraki M, et al. Prognostic impact of skeletal muscle assessed by computed tomography in patients with acute myeloid leukemia. *Ann Hematol* 2019;**98**:351–359.
9. Jung J, Lee E, Shim H, Park JH, Eom HS, Lee H. Prediction of clinical outcomes through assessment of sarcopenia and adipopenia using computed tomography in adult patients with acute myeloid leukemia. *Int J Hematol* 2021;**114**:44–52.
10. National Cancer Institute. Cancer stat facts: leukemia—acute myeloid leukemia (AML). National Institutes of Health. 2017. https://seer.cancer.gov/statfacts/html/amyl.html. Accessed 22/03/2021.
11. Shallis RM, Wang R, Davidoff A, Ma X, Zeidan AM. Epidemiology of acute myeloid leukemia: recent progress and enduring challenges. *Blood Rev* 2019;**36**:70–87.
12. Hao T, Li-Talley M, Buck A, Chen W. An emerging trend of rapid increase of leukemia but not all cancers in the aging population in the United States. *Sci Rep* 2019;**9**:12070.
13. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin* 2021;**71**:7–33.
14. Pandya BJ, Chen C-C, Medeiros BC, McGuiness CB, Wilson SD, Walsh EH,

et al. Economic and clinical burden of acute myeloid leukemia episodes of care in the United States: a retrospective analysis of a commercial payer database. *J Manag Care Spec Pharm* 2020;**26**: 849–859.

15. Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med* 2016;**374**:2209–2221.

16. Gupta V, Lazarus HM, Keating A. Myeloablative conditioning regimens for AML allografts: 30 years later. *Bone Marrow Transplant* 2003;**32**:969–978.

17. Gupta V, Tallman MS, Weisdorf DJ. Allogeneic hematopoietic cell transplantation for adults with acute myeloid leukemia: myths, controversies, and unknowns. *Blood* 2011;**117**:2307–2318.

18. Yanada M. Allogeneic hematopoietic cell transplantation for acute myeloid leukemia during first complete remission: a clinical perspective. *Int J Hematol* 2015;**101**:243–254.

19. Muffly L, Pasquini MC, Martens M, Brazauskas R, Zhu X, Adekola K, et al. Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States. *Blood* 2017;**130**:1156–1164.

20. Lee HJ, Licht AS, Hyland AJ, Ford LA, Sait SN, Block AW, et al. Is obesity a prognostic factor for acute myeloid leukemia outcome? *Ann Hematol* 2012;**91**:359–365.

21. Li S, Chen L, Jin W, Ma X, Ma Y, Dong F, et al. Influence of body mass index on incidence and prognosis of acute myeloid leukemia and acute promyelocytic leukemia: a meta-analysis. *Sci Rep* 2017;**7**: 17998.

22. Prado CM, Heymsfield SB. Lean tissue imaging: a new era for nutritional assessment and intervention. *JPEN J Parenter Enteral Nutr* 2014;**38**:940–953.

23. Cheng FW, Gao X, Mitchell DC, Wood C, Still CD, Rolston D, et al. Body mass index and all-cause mortality among older adults. *Obesity* 2016;**24**:2232–2239.

24. Caan BJ, Meyerhardt JA, Kroenke CH, Alexeeff S, Xiao J, Weltzien E, et al. Explaining the obesity paradox: the association between body composition and colorectal cancer survival (C-SCANS Study). *Cancer Epidemiol Biomarkers Prev* 2017;**26**:1008–1015.

25. Crysandt M, Kramer M, Ehninger G, Bornhäuser M, Berdel WE, Serve H, et al. A high BMI is a risk factor in younger patients with *de novo* acute myelogenous leukemia. *Eur J Haematol* 2016;**97**: 17–24.

26. Griggs JJ, Mangu PB, Anderson H, Balaban EP, Dignam JJ, Hryniuk WM, et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2012;**30**: 1553–1561.

27. Estey EH. Acute myeloid leukemia: 2021 update on risk-stratification and management. *Am J Hematol* 2020;**95**:1368–1398.

28. Medeiros BC, Othus M, Estey EH, Fang M, Appelbaum FR. Impact of body-mass index on the outcome of adult patients with acute myeloid leukemia. *Haematologica* 2012;**97**:1401–1404.

29. Wenzell CM, Gallagher EM, Earl M, Yeh JY, Kusick KN, Advani AS, et al. Outcomes in obese and overweight acute myeloid leukemia patients receiving chemotherapy dosed according to actual body weight. *Am J Hematol* 2013;**88**:906–909.

30. Cahu X, Carré M, Recher C, Pigneux A, Hunault-Berger M, Vey N, et al. Impact of body-surface area on patients' outcome in younger adults with acute myeloid leukemia. *Eur J Haematol* 2017;**98**: 443–449.

31. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition* 1989;**5**:303–311, discussion 12-3.

32. Pinkel D. The use of body surface area as a criterion of drug dosage in cancer chemotherapy. *Cancer Res* 1958;**18**: 853–856.

33. Felici A, Verweij J, Sparreboom A. Dosing strategies for anticancer drugs: the good, the bad and body-surface area. *Eur J Cancer* 2002;**38**:1677–1684.

34. Morgan DJ, Bray KM. Lean body mass as a predictor of drug dosage. Implications for drug therapy. *Clin Pharmacokinet* 1994; **26**:292–307.

35. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 2008;**9**:629–635.

36. Prado CM, Lima IS, Baracos VE, Bies RR, McCargar LJ, Reiman T, et al. An exploratory study of body composition as a determinant of epirubicin pharmacokinetics and toxicity. *Cancer Chemother Pharmacol* 2011;**67**:93–101.

37. Kirk B, Zanker J, Bani Hassan E, Bird S, Brennan-Olsen S, Duque G. Sarcopenia Definitions and Outcomes Consortium (SDOC) criteria are strongly associated with malnutrition, depression, falls, and fractures in high-risk older persons. *J Am Med Dir Assoc* 2021;**22**:741–745.

38. Harada K, Doki N, Hagino T, Miyawaki S, Ohtake S, Kiyoi H, et al. Underweight status at diagnosis is associated with poorer outcomes in adult patients with acute myeloid leukemia: a retrospective study of JALSG AML 201. *Ann Hematol* 2018;**97**: 73–81.

39. Klepin HD. Geriatric perspective: how to assess fitness for chemotherapy in acute myeloid leukemia. *Hematology Am Soc Hematol Educ Program* 2014;**2014**:8–13.

40. Rier HN, Jager A, Sleijfer S, Maier AB, Levin M-D. The prevalence and prognostic value of low muscle mass in cancer patients: a review of the literature. *Oncologist* 2016;**21**:1396–1409.

41. Walowski CO, Braun W, Maisch MJ, Jensen B, Peine S, Norman K, et al. Reference values for skeletal muscle mass—current concepts and methodological considerations. *Nutrients* 2020;**12**:755.

42. Caan BJ, Cespedes Feliciano EM, Kroenke CH. The importance of body composition in explaining the overweight paradox in cancer—counterpoint. *Cancer Res* 2018; **78**:1906–1912.

43. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 2013;**31**:1539–1547.

44. Baracos VE, Arribas L. Sarcopenic obesity: hidden muscle wasting and its impact for survival and complications of cancer therapy. *Ann Oncol* 2018;**29**:ii1–ii9.

45. Bozzetti F. Forcing the vicious circle: sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. *Ann Oncol* 2017;**28**: 2107–2118.

46. Moorthi RN, Liu Z, El-Azab SA, Lembcke LR, Miller MR, Broyles AA, et al. Sarcopenia, frailty and cachexia patients detected in a multisystem electronic health record database. *BMC Musculoskelet Disord* 2020;**21**:508.

47. Østgård LS, Nørgaard JM, Sengeløv H, Severinsen M, Friis LS, Marcher CW, et al. Comorbidity and performance status in acute myeloid leukemia patients: a nation-wide population-based cohort study. *Leukemia* 2015;**29**:548–555.

48. Fearon K, Evans WJ, Anker SD. Myopenia —a new universal term for muscle wasting. *J Cachexia Sarcopenia Muscle* 2011;**2**:1–3.

49. Fukushima T, Nakano J, Ishii S, Natsuzako A, Sato S, Sakamoto J, et al. Factors associated with muscle function in patients with hematologic malignancies undergoing chemotherapy. *Support Care Cancer* 2020;**28**:1433–1439.

50. Williams GR, Deal AM, Muss HB, Weinberg MS, Sanoff HK, Nyrop KA, et al. Skeletal muscle measures and physical function in older adults with cancer: sarcopenia or myopenia? *Oncotarget* 2017;**8**:33658–33665.

51. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;**12**:489–495.

52. Roeland EJ, Ma JD, Nelson SH, Seibert T, Heavey S, Revta C, et al. Weight loss versus muscle loss: re-evaluating inclusion criteria for future cancer cachexia interventional trials. *Support Care Cancer* 2017;**25**:365–369.

53. Keng MK, Sidana S, Mukherjee S, Elson P, Seastone DJ, Nazha A, et al. The degree and effect of weight loss in acute myeloid leukemia patients receiving induction and post-remission chemotherapy. *Blood* 2013;**122**:3889.

54. Ando T, Fujisawa S, Teshigawara H, Ogusa E, Ishii Y, Miyashita K, et al. Impact of treatment-related weight changes from diagnosis to hematopoietic stem-cell transplantation on clinical outcome of

acute myeloid leukemia. *Int J Hematol* 2019;**109**:673–683.

55. Fuji S, Takano K, Mori T, Eto T, Taniguchi S, Ohashi K, et al. Impact of pretransplant body mass index on the clinical outcome after allogeneic hematopoietic SCT. *Bone Marrow Transplant* 2014;**49**: 1505–1512.

56. Tamaki M, Nakasone H, Nakamura Y, Kawamura M, Kawamura S, Takeshita J, et al. Body weight loss before allogeneic hematopoietic stem cell transplantation predicts survival outcomes in acute leukemia patients. *Cell Ther Transplant* 2021;**27**:340–e1.

57. Armenian SH, Xiao M, Berano Teh J, Lee B, Chang HA, Mascarenhas K, et al. Impact of sarcopenia on adverse outcomes after allogeneic hematopoietic cell transplantation. *J Natl Cancer Inst* 2019;**111**: 837–844.

58. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood* 2005;**106**:2912–2919.

59. Anderson LJ, Yin C, Burciaga R, Lee J, Crabtree S, Migula D, et al. Assessing cachexia acutely after autologous stem cell transplant. *Cancers (Basel)* 2019;**11**:1300.

60. Fuji S, Mori T, Khattry N, Cheng J, Do YR, Yakushijin K, et al. Severe weight loss in 3 months after allogeneic hematopoietic SCT was associated with an increased risk of subsequent non-relapse mortality. *Bone Marrow Transplant* 2015;**50**: 100–105.

61. Wolfe RR. The underappreciated role of muscle in health and disease. *Am J Clin Nutr* 2006;**84**:475–482.

62. Schiaffino S, Dyar KA, Ciciliot S, Blaauw B, Sandri M. Mechanisms regulating skeletal muscle growth and atrophy. *FEBS J* 2013; **280**:4294–4314.

63. Philp A, Hargreaves M, Baar K. More than a store: regulatory roles for glycogen in skeletal muscle adaptation to exercise. *Am J Physiol Endocrinol Metab* 2012;**302**: E1343–E1351.

64. Berardi E, Madaro L, Lozanoska-Ochser B, Adamo S, Thorrez L, Bouche M, et al. A pound of flesh: what cachexia is and what it is not. *Diagnostics* 2021;**11**:116.

65. Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. *N Engl J Med* 1998;**339**: 900–905.

66. Neuendorff NR, Loh KP, Mims AS, Christofyllakis K, Soo WK, Bölükbasi B, et al. Anthracycline-related cardiotoxicity in older patients with acute myeloid leukemia: a Young SIOG review paper. *Blood Adv* 2020;**4**:762–775.

67. Min K, Kwon OS, Smuder AJ, Wiggs MP, Sollanek KJ, Christou DD, et al. Increased mitochondrial emission of reactive oxygen species and calpain activation are required for doxorubicin-induced cardiac and skeletal muscle myopathy. *J Physiol* 2015;**593**:2017–2036.

68. Amrute-Nayak M, Pegoli G, Holler T, Lopez-Davila AJ, Lanzuolo C, Nayak A. Chemotherapy triggers cachexia by deregulating synergetic function of histone-modifying enzymes. *J Cachexia Sarcopenia Muscle* 2021;**12**:159–176.

69. Elsea CR, Roberts DA, Druker BJ, Wood LJ. Inhibition of p38 MAPK suppresses inflammatory cytokine induction by etoposide, 5-fluorouracil, and doxorubicin without affecting tumoricidal activity. *PLoS ONE* 2008;**3**:e2355.

70. Kefaloyianni E, Gaitanaki C, Beis I. ERK1/2 and p38-MAPK signalling pathways, through MSK1, are involved in NF-κB transactivation during oxidative stress in skeletal myoblasts. *Cell Signal* 2006;**18**: 2238–2251.

71. Barreto R, Waning DL, Gao H, Liu Y, Zimmers TA, Bonetto A. Chemotherapy-related cachexia is associated with mitochondrial depletion and the activation of ERK1/2 and p38 MAPKs. *Oncotarget* 2016;**7**:43442–43460.

72. Le Bricon T, Gugins S, Cynober L, Baracos VE. Negative impact of cancer chemotherapy on protein metabolism in healthy and tumor-bearing rats. *Metabolism* 1995;**44**: 1340–1348.

73. Crouch M-L, Knowels G, Stuppard R, Ericson NG, Bielas JH, Marcinek DJ, et al. Cyclophosphamide leads to persistent deficits in physical performance and in vivo mitochondria function in a mouse model of chemotherapy late effects. *PLoS ONE* 2017;**12**:e0181086.

74. Li H, Malhotra S, Kumar A. Nuclear factor-kappa B signaling in skeletal muscle atrophy. *J Mol Med (Berl)* 2008;**86**: 1113–1126.

75. Huot JR, Essex AL, Gutierrez M, Barreto R, Wang M, Waning DL, et al. Chronic treatment with multi-kinase inhibitors causes differential toxicities on skeletal and cardiac muscles. *Cancers (Basel)* 2019;**11**: 571.

76. Malech HL, Deleo FR, Quinn MT. The role of neutrophils in the immune system: an overview. *Methods Mol Biol* 2014;**1124**: 3–10.

77. De Naurois J, Novitzky-Basso I, Gill M, Marti FM, Cullen M, Roila F. Management of febrile neutropenia: ESMO clinical practice guidelines. *Ann Oncol* 2010;**21**: v252–v256.

78. Peseski AM, McClean M, Green SD, Beeler C, Konig H. Management of fever and neutropenia in the adult patient with acute myeloid leukemia. *Expert Rev Anti Infect Ther* 2021;**19**:359–378.

79. Bodey GP, Freireich EJ. Influence of high-efficiency particulate air filtration on mortality and fungal infection: a rebuttal. *J Infect Dis* 2006;**194**:1621–1622.

80. Kirkizlar TA, Akalin H, Kirkizlar O, Ozkalemkas F, Ozkocaman V, Kazak E, et al. Vancomycin-resistant enterococci infection and predisposing factors for infection and mortality in patients with acute leukaemia and febrile neutropenia. *Leuk Res* 2020;**99**:106463.

81. Gao Y, Arfat Y, Wang H, Goswami N. Muscle atrophy induced by mechanical unloading: mechanisms and potential countermeasures. *Front Physiol* 2018;**9**: 235.

82. Debevec T, Ganse B, Mittag U, Eiken O, Mekjavic IB, Rittweger J. Hypoxia aggravates inactivity-related muscle wasting. *Front Physiol* 2018;**9**:494.

83. Gilreath JA, Rodgers GM. How I treat cancer-associated anemia. *Blood* 2020; **136**:801–813.

84. Knips L, Bergenthal N, Streckmann F, Monsef I, Elter T, Skoetz N. Aerobic physical exercise for adult patients with haematological malignancies. *Cochrane Database Syst Rev* 2019;**1**:Cd009075.

85. VanderVeen BN, Murphy EA, Carson JA. The impact of immune cells on the skeletal muscle microenvironment during cancer cachexia. *Front Physiol* 2020;**11**: 1037.

86. VanderVeen BN, Sougiannis AT, Velazquez KT, Carson JA, Fan D, Murphy EA. The acute effects of 5 fluorouracil on skeletal muscle resident and infiltrating immune cells in mice. *Front Physiol* 2020;**11**:1585.

87. Wang GL, Semenza GL. General involvement of hypoxia-inducible factor 1 in transcriptional response to hypoxia. *Proc Natl Acad Sci U S A* 1993;**90**:4304–4308.

88. Favier FB, Britto FA, Freyssenet DG, Bigard XA, Benoit H. HIF-1-driven skeletal muscle adaptations to chronic hypoxia: molecular insights into muscle physiology. *Cell Mol Life Sci* 2015;**72**:4681–4696.

89. Devine RD, Bicer S, Reiser PJ, Wold LE. Increased hypoxia-inducible factor-1α in striated muscle of tumor-bearing mice. *Am J Physiol Heart Circ Physiol* 2017;**312**: H1154–H1162.

90. Ryan AM, Power DG, Daly L, Cushen SJ, Ní Bhuachalla Ē, Prado CM. Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. *Proc Nutr Soc* 2016;**75**: 199–211.

91. Landi F, Camprubi-Robles M, Bear DE, Cederholm T, Malafarina V, Welch AA, et al. Muscle loss: the new malnutrition challenge in clinical practice. *Clin Nutr* 2019;**38**:2113–2120.

92. Pressoir M, Desné S, Berchery D, Rossignol G, Poiree B, Meslier M, et al. Prevalence, risk factors and clinical implications of malnutrition in French Comprehensive Cancer Centres. *Br J Cancer* 2010; **102**:966–971.

93. Deluche E, Girault S, Jesus P, Monzat S, Turlure P, Leobon S, et al. Assessment of the nutritional status of adult patients with acute myeloid leukemia during induction chemotherapy. *Nutrition* 2017; **41**:120–125.

94. Esfahani A, Ghoreishi Z, Abedi Miran M, Sanaat Z, Ostadrahimi A, Eivazi Ziaei J, et al. Nutritional assessment of patients with acute leukemia during induction chemotherapy: association with hospital outcomes. *Leuk Lymphoma* 2014;**55**: 1743–1750.

95. Baumgartner A, Bargetzi A, Zueger N, Bargetzi M, Medinger M, Bounoure L, et al. Revisiting nutritional support for allogeneic hematologic stem cell transplan-

tation—a systematic review. *Bone Marrow Transplant* 2017;**52**:506–513.

96. van Lieshout R, Tick LW, de Laat D, Custers S, Dekker IM, Douma MD, et al. Adherence to guidelines on nutrition support during intensive treatment of acute myeloid leukemia patients: a nationwide comparison. *Clin Nutr ESPEN* 2020;**39**: 242–250.

97. Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, et al. ESPEN practical guideline: Clinical Nutrition in cancer. *Clin Nutr* 2021;**40**: 2898–2913.

98. Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin Nutr* 2010;**29**:154–159.

99. Bajic JE, Johnston IN, Howarth GS, Hutchinson MR. From the bottom-up: chemotherapy and gut-brain axis dysregulation. *Front Behav Neurosci* 2018;**12**:104.

100. McQuade RM, Al Thaalibi M, Nurgali K. Impact of chemotherapy-induced enteric nervous system toxicity on gastrointestinal mucositis. *Curr Opin Support Palliat Care* 2020;**14**:293–300.

101. Hueso T, Ekpe K, Mayeur C, Gatse A, Joncquel-Chevallier Curt M, Gricourt G, et al. Impact and consequences of intensive chemotherapy on intestinal barrier and microbiota in acute myeloid leukemia: the role of mucosal strengthening. *Gut Microbes* 2020;**12**:1800897.

102. Galloway-Peña JR, Smith DP, Sahasrabhojane P, Ajami NJ, Wadsworth WD, Daver NG, et al. The role of the gastrointestinal microbiome in infectious complications during induction chemotherapy for acute myeloid leukemia. *Cancer* 2016;**122**:2186–2196.

103. Peled JU, Gomes ALC, Devlin SM, Littmann ER, Taur Y, Sung AD, et al. Microbiota as predictor of mortality in allogeneic hematopoietic-cell transplantation. *N Engl J Med* 2020;**382**:822–834.

104. Lustgarten MS. The role of the gut microbiome on skeletal muscle mass and physical function: 2019 update. *Front Physiol* 2019;**10**:1435.

105. Grosicki GJ, Fielding RA, Lustgarten MS. Gut microbiota contribute to age-related changes in skeletal muscle size, composition, and function: biological basis for a gut-muscle axis. *Calcif Tissue Int* 2018; **102**:433–442.

106. Fonseca GW, Farkas J, Dora E, von Haehling S, Lainscak M. Cancer cachexia and related metabolic dysfunction. *Int J Mol Sci* 2020;**21**:2321.

107. Morrot A, da Fonseca LM, Salustiano EJ, Gentile LB, Conde L, Filardy AA, et al. Metabolic symbiosis and immunomodulation: how tumor cell-derived lactate may disturb innate and adaptive immune responses. *Front Oncol* 2018;**8**:81.

108. Chen W-L, Wang J-H, Zhao A-H, Xu X, Wang Y-H, Chen T-L, et al. A distinct glucose metabolism signature of acute myeloid leukemia with prognostic value. *Blood* 2014;**124**:1645–1654.

109. de Lima Junior EA, Yamashita AS, Pimentel GD, De Sousa LG, Santos RV, Gonçalves CL, et al. Doxorubicin caused severe hyperglycaemia and insulin resistance, mediated by inhibition in AMPk signalling in skeletal muscle. *J Cachexia Sarcopenia Muscle* 2016;**7**:615–625.

110. Honors MA, Kinzig KP. The role of insulin resistance in the development of muscle wasting during cancer cachexia. *J Cachexia Sarcopenia Muscle* 2012;**3**:5–11.

111. Sylow L, Tokarz VL, Richter EA, Klip A. The many actions of insulin in skeletal muscle, the paramount tissue determining glycemia. *Cell Metab* 2021;**33**:758–780.

112. Correa-de-Araujo R, Addison O, Miljkovic I, Goodpaster BH, Bergman BC, Clark RV, et al. Myosteatosis in the context of skeletal muscle function deficit: an interdisciplinary workshop at the National Institute on Aging. *Front Physiol* 2020;**11**: 963.

113. Martin A, Freyssenet D. Phenotypic features of cancer cachexia-related loss of skeletal muscle mass and function: lessons from human and animal studies. *J Cachexia Sarcopenia Muscle* 2021;**12**: 252–273.

114. Aleixo GFP, Shachar SS, Nyrop KA, Muss HB, Malpica L, Williams GR. Myosteatosis and prognosis in cancer: systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2020;**145**:102839.

115. Burfeind KG, Michaelis KA, Marks DL. The central role of hypothalamic inflammation in the acute illness response and cachexia. *Semin Cell Dev Biol* 2016;**54**: 42–52.

116. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. *Cancer Treat Rev* 2013;**39**: 534–540.

117. Argilés JM, Betancourt A, Guàrdia-Olmos J, Peró-Cebollero M, López-Soriano FJ, Madeddu C, et al. Validation of the CAchexia SCOre (CASCO). Staging cancer patients: the use of miniCASCO as a simplified tool. *Front Physiol* 2017;**8**:92.

118. Freire PP, Fernandez GJ, de Moraes D, Cury SS, Dal Pai-Silva M, Dos Reis PP, et al. The expression landscape of cachexia-inducing factors in human cancers. *J Cachexia Sarcopenia Muscle* 2020; **11**:947–961.

119. Craver BM, El Alaoui K, Scherber RM, Fleischman AG. The critical role of inflammation in the pathogenesis and progression of myeloid malignancies. *Cancer* 2018;**10**:104.

120. Bruggeman AR, Kamal AH, LeBlanc TW, Ma JD, Baracos VE, Roeland EJ. Cancer cachexia: beyond weight loss. *J Oncol Pract* 2016;**12**:1163–1171.

121. Lo-Coco F, Avvisati G, Vignetti M, Thiede C, Orlando SM, Iacobelli S, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. *N Engl J Med* 2013;**369**:111–121.

122. Wang NC, Zhang P, Tapper EB, Saini S, Wang SC, Su GL. Automated measurements of muscle mass using deep learning can predict clinical outcomes in patients with liver disease. *Am J Gastroenterol* 2020;**115**:1210–1216.

123. Solheim TS, Laird BJA, Balstad TR, Bye A, Stene G, Baracos V, et al. Cancer cachexia: rationale for the MENAC (Multimodal—Exercise, Nutrition and Anti-inflammatory medication for Cachexia) trial. *BMJ Support Palliat Care* 2018;**8**:258–265.

124. Muscaritoli M, Molfino A, Lucia S, Rossi Fanelli F. Cachexia: a preventable comorbidity of cancer. A T.A.R.G.E.T. approach. *Crit Rev Oncol Hematol* 2015; **94**:251–259.

125. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2019. *J Cachexia Sarcopenia Muscle* 2019;**10**:1143–1145.