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NON-THEMATIC REVIEW

How progressive cancer endangers the heart: an intriguing and underestimated problem

Simonetta Ausoni[1] · Sara Calamelli[2] · Salvatore Saccà[2] · Giuseppe Azzarello[3]

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Abstract
Since it came into being as a discipline, cardio-oncology has focused on the prevention and treatment of cardiotoxicity induced by antitumor chemotherapy and radiotherapy. Over time, it has been proved that even more detrimental is the direct effect generated by cancer cells that release pro-cachectic factors in the bloodstream. Secreted molecules target different organs at a distance, including the heart. Inflammatory and neuronal modulators released by the tumor bulk, either as free molecules or through exosomes, contribute to the pathogenesis of cardiac disease. Progressive cancer causes cachexia and severe cardiac muscle wasting accompanied by cardiomyocyte atrophy, tissue fibrosis, and several functional impairments up to heart failure. The molecular mechanisms responsible for such a cardiac muscle wasting have been partially elucidated in animal models, but minimally investigated in humans, although severe cardiac dysfunction exacerbates global cachexia and hampers efficient anti-cancer treatments. This review provides an overview of cancer-induced structural cardiac and functional damage, drawing on both clinical and scientific research. We start by looking at the pathophysiological mechanisms and evolving epidemiology and go on to discuss prevention, diagnosis, and a multimodal policy of intervention aimed at providing overall prognosis and global care for patients. Despite much interest in the cardiotoxicity of cancer therapies, the direct tumor effect on the heart remains poorly explored. There is still a lack of diagnostic criteria for the identification of the early stages of cardiac disease in cancer patients, while the possibilities that there are for effective prevention are largely underestimated. Research on innovative therapies has claimed considerable advances in preclinical studies, but none of the molecular targets suitable for clinical application has been approved for therapy. These issues are critically discussed here.

Keywords Cancer cachexia · Cardiac atrophy · Cardiac cachexia · Inflammation · Simultaneous care · Target therapy

1 Introduction

Cancer cachexia is a multifactorial and multilayered syndrome characterized by loss of at least 5% muscle mass—with or without loss of fat mass—fatigue and generalized weakness that cannot be reversed by nutritional intake alone [1–3]. Cachexia represents the direct cause of death for nearly one-third of cancer patients [4]. Prevalence is estimated to be as high as 87% in pancreatic and gastrointestinal cancer; up to 61% in patients with colon, lung, and prostate cancer and non-Hodgkin lymphoma; and around 40% in breast cancer, leukemias, and sarcomas [1, 5]. Patients with metastases develop cachexia more often than patients without metastases, suggesting that the capabilities of cancer to cause cachexia and to metastasize might be intrinsically linked. Thus, it appears that induction of cachexia is an inherent characteristic of the tumor and of patients' response [6, 7]. In line with this observation is the finding that mutation status may correlate with cachexia, as demonstrated for KRAS mutations in lung cancer patients with skeletal muscle wasting [6].

In 1968, Burch et al. [8] first reported the preliminary evidence of a possible causative link between cancer and cardiac dysfunction. He hypothesized that cardiac atrophy observed in

✉ Simonetta Ausoni
simonetta.ausoni@unipd.it

✉ Giuseppe Azzarello
giuseppe.azzarello@aulss3.veneto.it

[1] Department of Biomedical Sciences, University of Padua, Padova, Italy

[2] Department of Cardiology, Local Health Unit 3 Serenissima, Mirano Hospital, Mirano, Venice, Italy

[3] Department of Medical Oncology, Local Health Unit 3 Serenissima, Mirano Hospital, Mirano, Venice, Italy

necropsies of unselected men who had died from cancer could be attributed to the tumor itself. This preliminary observation has been confirmed over time: tumor progression can induce cardiac atrophy, fibrosis, and dysfunction, up to chronic heart failure (HF) [9]. This serious clinical syndrome associated with a poor prognosis and low quality of life has been referred to as "cardiac cachexia" [10]. More recently, the same terminology has been adopted for cancer-derived cardiac disease to describe "cardiac atrophy, remodeling and dysfunction associated with cancer" [11]. Since cardiac disease in cancer patients may be of varying degrees of severity, of which cardiac cachexia represents the end point, this review continues to use the terminology "cardiac atrophy" and "cardiac muscle wasting," while limiting the use of "cardiac cachexia" to those conditions with cancer-induced HF.

Cardiac atrophy and its functional consequences remain largely underestimated in cancer patients. Diagnostic criteria are still lacking and, in a large majority of oncologic units, the management of cancer patients does not even include cachexia or pre-cachexia as criteria for diagnostic cardiologic evaluation. There is however compelling evidence in chemo-naïve patients that shows that the detrimental effects to heart structure and function in cancer patients is not only due to iatrogenic cardiotoxicity, but also to the direct effect of molecules produced and released by the tumor and acting at a distance. The concomitant onset of cardiac disease is critical because heart dysfunction hinders optimal management of cancer treatment, especially where aggressive therapies are employed. A vicious circle may therefore develop where cachexia induces HF and HF exacerbates global cachexia [12–16].

This paper provides an overview of the mechanisms that induce cardiac atrophy, focusing on inflammation, neuroendocrine routes, and regulation of cardiomyocyte proteostasis. We go on to discuss the latest epidemiological evidence of cancer-derived cardiac atrophy and dysfunction and its clinical implications in the management of cancer. We emphasize a "multimodal policy of intervention" aimed at identifying pre-cachectic stages for early supporting therapies to mitigate the risk of myocardial dysfunction or reduce the risk of cardiotoxicity. Clinical cases from our cardio-oncology unit are also drawn on to provide further evidence that cancer-induced cardiac muscle progressive dysfunction urges appropriate diagnosis and treatment in synergic cardio-oncology units. Finally, we discuss conventional treatments and the new therapeutic options, with an emphasis on candidate molecules suitable for future therapeutic approaches.

Although open to a broad audience, this review is specifically aimed at cardio-oncology teams, with the hope of keeping alive the debate to considered contributions and of encouraging greater synergy in clinical research.

2 Cancer cachexia and cardiac atrophy: insights from animal models

Cancer-induced cachexia has been largely investigated in the laboratory through the injection of rodents with cancer cell lines that rapidly generate malignant tumors within 4–8 weeks from inoculation [17]. Well-characterized models are Colon 26 adenocarcinoma (hereafter referred as C26), Lewis lung carcinoma, Multiple intestinal neoplasia in adenomatous polyposis coli (ApcMin/+), and to a lesser extent MAC 16 adenocarcinoma (MAC16), Walker 256 carcinosarcoma (Walker 256), Yoshida hepatoma AH130 (YAH-130), and Ehrlich Ascites Carcinoma [18]. The major advantage of these models is that they allow investigating the molecular and cellular mechanisms of cachexia in the absence of any iatrogenic contamination effect and that they help addressing issues that could not be investigated otherwise, such as the different outcome attributed to the microenvironment where tumor cells are inoculated [19]. On the other hand, substantial evidence indicated that none of these models fully reproduces the complexity of human disease, and do not entirely recapitulate the cardiac remodeling observed in human cardiac cachexia. For instance, the majority of studies on cancer cachexia have not been conducted in a metastatic context, although cachexia in patients parallels with progressive and advanced metastatic disease. New cancer cachexia models are evolving to better recapitulate features relevant to human cancer. These include genetically engineered mouse models, orthotopic transplantation (grafting the tumor in the organ of its origin), and models with metastasis occurrence [20].

Cardiac muscle wasting is a common feature in experimental cancer cachexia, although with some variability due to the properties of injected cancer cells, the mode and site of cell administration, gender differences, and time course of tumor development. Histological examination of the heart typically shows reduced wall thickness, reduced cardiomyocyte cross-sectional area, and a variable degree of fibrosis and inflammatory infiltrate (Fig. 1) [18]. Myofibril misalignment, reduced contractile protein content, and mitochondrial abnormalities are also present, reflecting decreased fatty acid oxidation, bioenergetic unbalance, and oxidative stress [21–23]. Echocardiographic measurements show functional deterioration, with decreased left ventricular posterior wall thickness, reduced ejection fraction, and fractional shortening [22, 24].

Unlike skeletal muscle wasting, which has been studied in a variety of pathological conditions, including denervation, diabetes, degenerative diseases, and chronic inflammation and sepsis, cardiac atrophy and the underlying mechanisms have been poorly explored, presumably because this state is physiologically less relevant than cardiac hypertrophy and affects a limited number of pathological conditions. It is therefore no surprise to find that much of our knowledge on cardiac atrophy is extrapolated from studies on skeletal muscle.

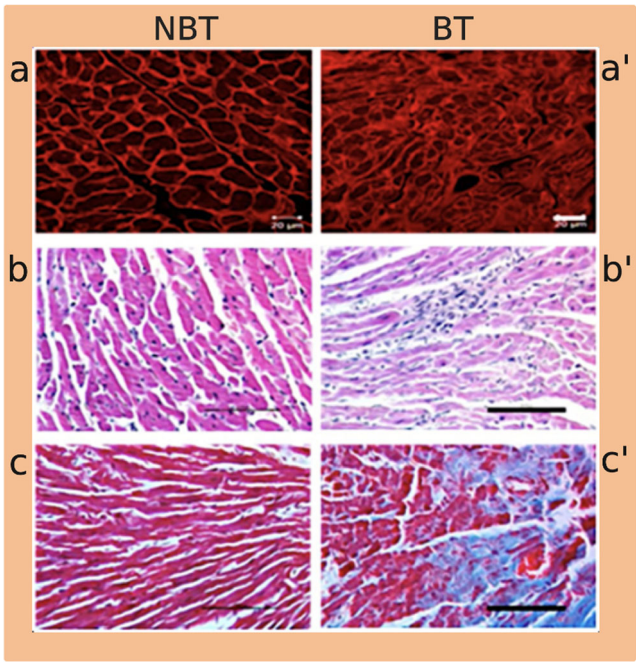

Fig. 1 Tumor induces cardiac atrophy, fibrosis, and remodeling. Histopathological analysis of heart sections shows atrophy, fibrosis, and degenerative changes in a mouse model of Ehrlich Ascites Carcinoma subcutaneous tumor. Heart sections of non-tumor-bearing (NTB) and tumor-bearing (TB) mice were stained with wheat germ agglutinin (a and a′) to measure cardiomyocyte size and hematoxylin eosin (b and b′) and Masson's trichrome staining (c and c′) to detect inflammatory infiltrate and fibrosis. Scale bars in a and a′ = 20 μm (adapted from [18]; image encompassed under the Creative Commons license (http://creativecommons.org/licences/by/4.0/)

Proteomic analyses have, though, shown that protein expression in cachectic skeletal and cardiac muscle varies considerably and so a note of caution should be introduced when applying to the heart any conclusions reached in relation to skeletal muscle.

3 Systemic induction of cardiac atrophy: the role of inflammation

Mechanistically, one prominent scenario describes the onset of cancer cachexia (Fig. 2). The primary tumor and cells of the microenvironment generate a "secretome" that releases pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, and IFN-γ), chemokines, and soluble factors into the bloodstream and that directly elicit catabolic responses in various target organs, including in skeletal muscle, adipose tissue, in the brain, and in the heart [25–27]. As disease progresses, the primary tumor and the target organs contribute to generate a chronically perturbed inflammatory milieu driving global cachexia [28, 29]. Not only soluble molecules but also tumor-derived nanovesicles (exosomes) continuously deliver a variety of molecules, including DNA, proteins, and different RNAs to recipient tissues. The molecular profile of exosomes reflects the original cell types and represents a snapshot of each tumor in the so-called liquid biopsies (biological fluids of cancer-affected patients) [30]. Depending upon their cargo, exosomes mediate tumor progression, invasiveness, and immune escape, but they can also change metabolic and functional properties of those target organs where they are internalized [31, 32]. In C26 colon carcinoma, exosomes containing heat-shock proteins 70 and 90 (hsp70 and hsp90) have been found to cause muscle catabolism and wasting through the activation of the Toll-like receptor 4 and the inflammatory p38-MAPK signaling pathway in muscle fibers [33]. Similarly, microRNAs (miRNAs) and circularRNAs (circRNAs) specific for human gastric tumors and transported by exosomes have been found to induce white adipose tissue browning, a hallmark of systemic inflammation [34]. To the best of our knowledge, no evidence has been provided so far linking specific biomarkers of tumor-derived exosomes to cardiac atrophy and wasting.

The central nervous system (CNS) plays a major role in the onset of systemic cancer-induced inflammation and catabolic response. In the hypothalamus, signals of pro-inflammatory cytokines are amplified and activate three major downstream axes. The *first* resides in the feeding centers, namely the paraventricular (PVN) and arcuate nuclei (ARC). Here, neurons express cytokine receptors [35] and are therefore extremely sensitive to the inflammatory state. The ARC contains two types of neurons with opposed actions on energy balance, the pro-opiomelanocortin system (POMC) that secrete anorexigenic melanocortin neuropeptides, and adjacent neurons expressing the agouti-related protein (AgRP), and the orexigenic peptide Y (NPY). In cancer patients, metabolism is diverted largely towards catabolic stimuli [36, 37], possibly because pro-inflammatory cytokines shift the balance towards anorexigenic neuropeptide production [38]. The *second* is the hypothalamic-pituitary-adrenal axis. Administration of IL-1β in experimental cancer cachexia rapidly induces skeletal muscle atrophy through the release of glucocorticoids. This effect is inhibited by the glucocorticoid receptors and by adrenectomy [37]. Glucocorticoids induce insulin resistance, inhibit the anabolic response, and activate the ubiquitin-proteasome system (UPS) and autophagy [39]. Increased levels of hormones released by the adrenal gland (cortisol) and the medulla (epinephrine and norepinephrine) have been reported in patients affected by cardiac cachexia associated with HF [40]. The *third* catabolic response involved in cancer cachexia resides in the hypothalamus-gut axis. The fundus region of the stomach releases ghrelin, a orexigenic neuropeptide that stimulates hunger and food intake [41], increases anabolic responses, inhibits protein degradation, and has anti-inflammatory properties [42]. Surprisingly, plasma ghrelin concentrations are elevated in cancer patients although they do not show increased appetite. Elevated ghrelin may signify a compensatory mechanism in response to weight loss, negative energy balance, reduced appetite, and inflammation [43].

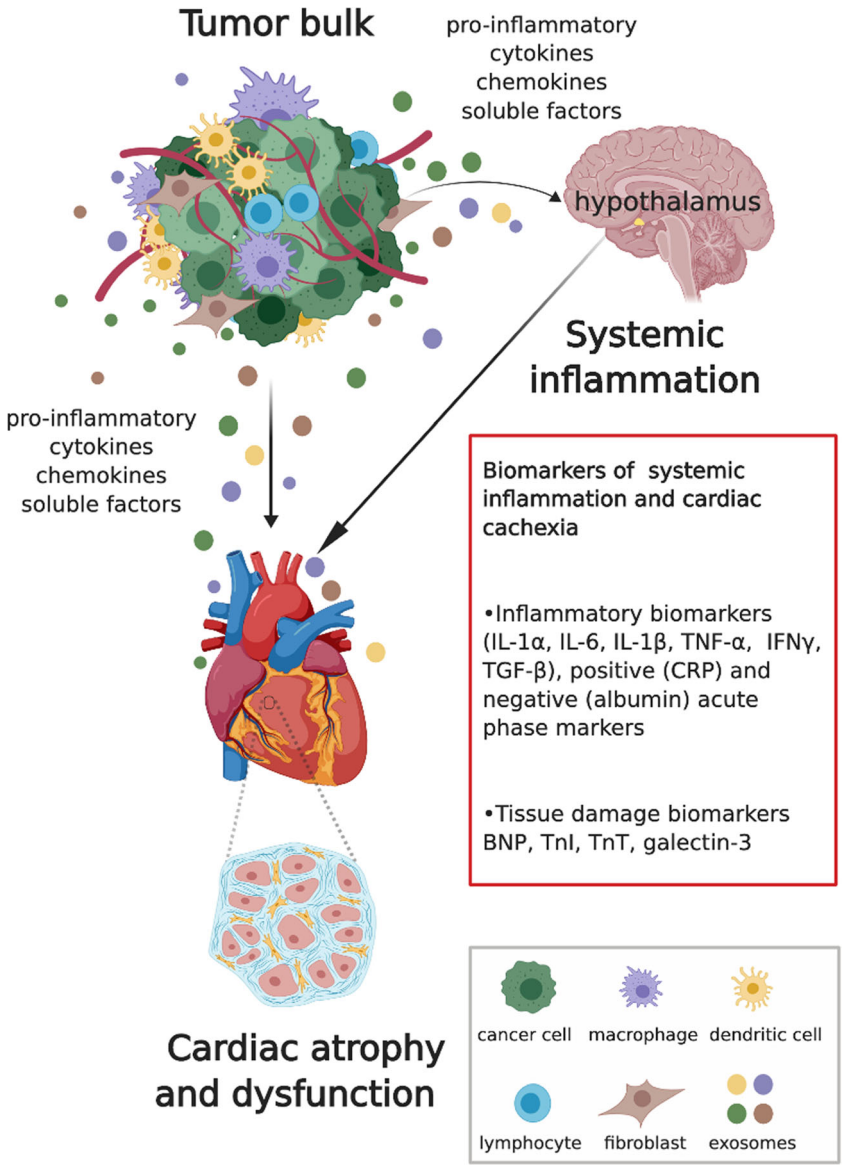

Fig. 2 The tumor bulk affects cardiac structure and function through the release of pro-inflammatory and pro-cachectic mediators. Systemic inflammation is a major driver in cancer-induced cardiac muscle wasting. Cytokines and other pro-cachectic factors are released by the tumor bulk into the bloodstream and reach different organs at a distance. Inflammation is potentiated in the hypothalamus, which sustains additional cytokine production. Systemic inflammation and tumor-derived catabolic factors cause cardiac atrophy and dysfunction. Pro-inflammatory cytokines, acute phase proteins, and proteins released during cardiac tissue damage are suitable markers for early diagnosis. Abbreviations: TNF-α, tumor necrosis factor-α; IL-1α, interleuchin-1α; IL-1β, interleuchin-1β; IL-6, interleuchin-6; IFNγ, interferon-γ; CRP, C-reactive protein; TGF-β, transforming growth factor-β; BNP, brain natriuretic peptide; TnI, Troponin I, TnT, Troponin T (Artwork has been created with Biorender.com)

Interestingly, from a therapeutic perspective, chronic administration of ghrelin ameliorates cardiac performance and attenuates cardiac cachexia, both in animal models of HF [44] and in patients [42] with chronic HF, providing a rationale for further use of ghrelin and ghrelin receptor agonists in large-scale clinical studies.

4 Pro-inflammatory pathways in cancer-derived cardiac atrophy

In the myocardium, pro-inflammatory cytokines and tumor-derived catabolic factors interact with their receptors on cardiomyocytes and activate a variety of signaling pathways responsible for increased protein degradation and autophagy (Fig. 3). Understanding how each molecule and downstream signaling pathways affect physiological and pathological peculiar response in cardiomyocytes is crucial for the development of new therapies against cardiac cachexia. Chronic inhibition of pro-inflammatory signals may indeed counteract global cachexia, but also generate unintended side effects resulting in functional impairment.

Cytokines and NF-KB signaling pathway Oliff et al. [45] first demonstrated that high levels of circulating tumor necrosis factor-α (TNF-α) were detectable in experimental cancer, and the administration of antibodies blocking the TNF-α pathway resulted in weight gain and increased appetite in tumor-bearing animals [46]. Promising preclinical data prompted the testing of anti-TNF treatment in cancer patients, but clinical results were largely discouraging (see below). More recently, a TNF-α family member, the TWEAK (TNF-α-like weak

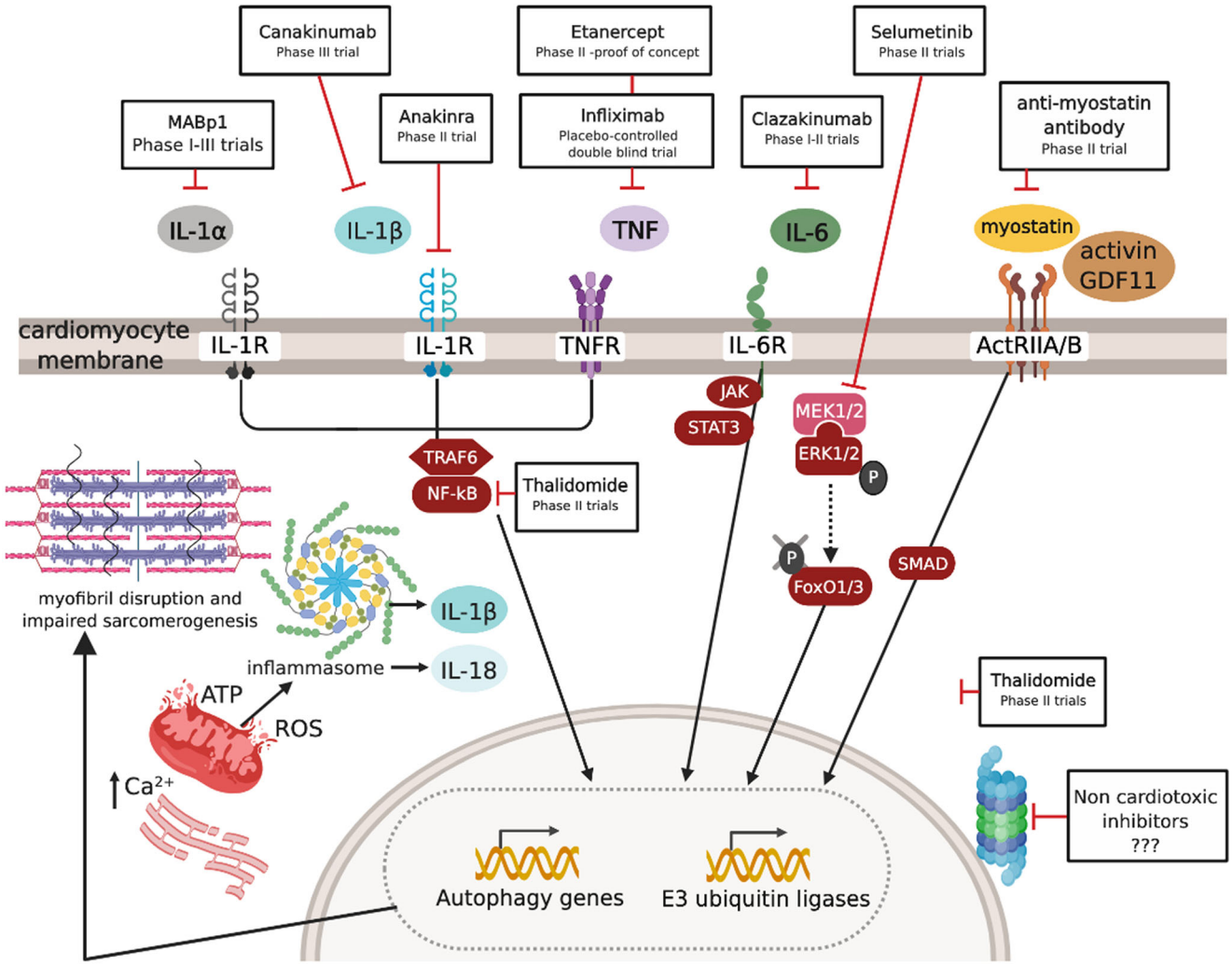

Fig. 3 Pro-inflammatory, catabolic pathways, and therapeutic targets for cardiac cachexia. Two major steps can be identified in the molecular mechanisms leading to cardiomyocyte atrophy and dysfunction. In the first, pro-inflammatory cytokines and circulating catabolic factors signal through their respective receptors and activate multiple signaling pathways, including TRAF6/NF-kB, JAK/STAT3, MEK1/2-ERK1/2-FoxOs, and SMAD. In the second, activated factors, directly or indirectly, upregulate transcription of E3 ubiquitin ligases and autophagy genes, leading to myofibril disruption and atrophy. Mitochondrial dysfunction causes massive release of ROS and ATP and activates the inflammasome, which in turn produces IL-1β and IL-18. The endoplasmic reticulum stress response increases cytosolic Ca^{2+}, thus compromising further sarcomeric stability. Cytokines, soluble factors, and their cognate receptors are major targets of innovative therapies. The figure includes only drugs selected for controlled clinical trials. MABp1 blocks IL-1α, canakinumab blocks 1L-1β, anakinra inhibits IL-1β receptor, etanercept and infliximab both block TNF, clazakinumab blocks IL-6, and selumetinib inhibits MEK1/2-dependent ERK1/2 phosphorylation and thus inactivates Foxo-mediated catabolic response. Thalidomide suppresses pro-inflammatory response and TGF-β/SMAD signaling. TGF-β family members control cardiomyocyte catabolism by interacting with the corresponding ActRIIA and ActRIIB receptors. Only anti-myostatin antibody, for which a controlled clinical study has been published, is included. Proteasome inhibitors (bortezomib and new-generation anti-proteasome drugs) are not shown, because of their proved toxicity. Abbreviations: TNF-α, tumor necrosis factor-α; IL-1α, interleuchin-1α; IL-1β, interleuchin-1β; IL-6, interleuchin-6; GDF11, growth and differentiation factor 11; TRAF6, tumor necrosis factor receptor associated factor 6; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; STAT3, signal transducer and activator of transcription 3; MEK1/2, MAPK kinase 1/2; ERK1/2, extracellular signal–regulated kinases ½, FoxoO 1/3, Forkhead transcription factors 1 and 3. (Artwork has been created with Biorender.com)

inducer of apoptosis) protein, has been found to cause cachexia [47] and blocking of its Fn14 receptor with monoclonal antibodies rescued cachectic phenotype in C26 mice [48]. These findings raised new interest in TNF cytokine family members as potential pharmacological targets of cachexia.

A variety of cancer cells and cells of the tumor microenvironment produce IL-6. Circulating levels of IL-6 increase significantly in experimental models of tumorigenesis and in cancer patients [22, 49] and monoclonal antibodies targeting IL-6 reduced muscle wasting in nude mice injected with either melanoma cells or prostate tumor cells [50]. Studies in post-ischemic heart and perfusion injury indicate that in the short term, IL-6 preserves the heart from acute damage, while in the long term, it becomes detrimental [51, 52]. Thus, IL-6 remains

a promising therapeutic strategy for attenuating cachexia progression with many types of cancer, but further progress will require a better understanding of direct and indirect IL-6 acute and chronic cardiac-specific effects.

The pro-inflammatory cytokine IL-1 (both in its IL-1α and IL-1β variants) is strongly released by the tumor bulk, and IL-1β circulating levels in cancer patients are the worst prognostic factor [53]. In the heart, exposure to both IL-1α and IL-1β is intimately associated with development of cardiac injury and IL-1 signaling contributes to the development of dilated cardiomyopathy [54]. IL-1β induces systolic dysfunction and treatment with IL-1β inhibitors and therapeutic strategies that reduce inflammasome activation improves heart function [55], making IL-1β an attractive molecule for the treatment of cardiovascular diseases mediated by a chronic inflammatory state [56].

NF-kB signaling pathway stands at the crossroad of a variety of pro-inflammatory responses; thus, it is no surprise that inhibiting the NF-kB pathway has attracted considerable attention as a therapeutic option against cancer cachexia. Two molecules, the natural phytoalexin resveratrol [57, 58] and the natural flavonoid luteolin [59], were found to inhibit skeletal and cardiac atrophy in C26 tumor-bearing mice and in Lewis lung cancer mouse model. Other NF-kB inhibitors have been designed and are under preclinical validation, but a major limitation to targeting NF-kB remains cardiotoxicity, due to the dual cardioprotective and detrimental effect of this transcription factor on the heart, depending upon acute or chronic exposure [52].

In the NF-kB route, the tumor necrosis factor receptor-associated factor 6 (TRAF6) has attracted considerable attention as a possible therapeutic target, both for cancer and for cancer-derived cardiac muscle wasting. TRAF6 is an adaptor protein that connects upstream-activated Toll-like receptors with downstream NF-kB pathway. TRAF6-deficient mice are resistant to muscle loss induced by cancer, denervation, and starvation [60, 61], and patients affected by gastric cancer have increased circulating levels of TRAF6 [62]. TRAF6 displays also peculiar effects on the heart. Upregulation of TRAF6 is implicated in the pathogenesis of cardiac hypertrophy, myocardial infarction, myocarditis, sepsis-related cardiomyopathy, and HF. TRAF6 function has been associated with activation of the bromodomain and extra-terminal (BET) family of proteins [63] a new class of proteins that associate with chromatin and regulate gene transcription. A selective bromodomain inhibitor, JQ1, suppresses pathological remodeling in experimental cardiac hypertrophy [63] and suppresses the TRAF6/NF-κB signaling in a rat model of acute infarction [64]. Thus, TRAF6 inhibition, either with BET antagonists or other compounds, can become a new therapeutic option, having the dual property to inhibit the pro-inflammatory response and to attenuate cardiac damage.

Inflammasome and cardiokines A number of damage-associated molecular patterns (DAMPS) produced inside the cells activate the inflammasome, a molecular platform that triggers maturation of pro-inflammatory cytokines IL-1β and IL-18 [65, 66]. Multiple studies suggest that mitochondrial loss of integrity and the release of ATP, mitochondrial DNA, and reactive oxygen species (ROS) activate the nucleotide-binding oligomerization domain-like receptors with pyrin domain (NLRP3) inflammasome in cardiomyocytes [67]. In response to damage, the heart starts releasing a large variety of proteins, called cardiokines. These are cytokines, growth factors, and neurohormones, including TNF-α, IL-1β, IL-6, IL-18, myostatin, activin A, neuregulin, and A- and B-natriuretic peptide [68]. Thus, during progressive cancer disease, the heart contributes to sustain inflammation by releasing pro-cachectic factors, similar to adipose tissue and skeletal muscle. The roles of inflammasome and cardiokines in cancer cachexia are currently poorly explored.

TGF-β family members The contribution of TGF-β family members in cancer cachexia has been a matter of intense investigation and controversy. TGF-β family members include 33 proteins that bind to their membrane receptors and propagate the signal *via* SMAD proteins' phosphorylation, their translocation to the nucleus, and the activation of transcription [69]. In addition to the canonical SMAD-mediated signaling pathway, TGF-β family members can activate non-canonical pathways, relying on ERK and p38/MAPK. TGF-β family members produce a variety of different effects in the heart, including apoptosis, fibrosis, and autophagy. Relevant for cardiac muscle wasting is the capacity of TGF-β family members activins, myostatin, and the growth and differentiation factor 11 (GDF11) to stimulate catabolism and induce cachexia. By interacting with the activin type II receptors A and B (ActRIIA and ActRIIB), these factors initiate a signaling cascade that culminates in the activation of E3 ubiquitin protein ligases. Overexpression of GDF11 in mice activates atrogin and MuRF1 and causes whole-body wasting, loss of ventricular muscle wall thickness, decreased cardiomyocyte size and impaired cardiac function [70]. Administration of synthetic compounds blocking ActRII completely abolishes skeletal and cardiac cachexia and dramatically prolongs survival in experimental cancer [71]. The combination of the soluble myostatin receptor ActRIIB and formoterol, a potent β2-adrenoceptor selective agonist, also reverses muscle wasting, prolongs survival, and reduces the number of metastasis in experimental cancer cachexia [72], providing a rationale for targeting this catabolic pathway to attenuate cardiac muscle wasting. High levels of activin A and myostatin [70, 73] have been detected in experimental models and in patients affected by various tumors, including breast cancer [74] and lung adenocarcinoma [75]. Of note, Roh et al. [76] demonstrated that activin/ActRII signaling increases in HF, raising the possibility that systemic

delivery of ActRII antagonists also counteract cardiac cachexia.

5 Pathways of protein degradation in cancer-derived cardiac atrophy

Cancer-induced cardiac atrophy is characterized by sustained catabolic response, with an imbalance between protein synthesis and degradation. The ubiquitin-proteasome system (UPS) and the autophagy-lysosome process mainly control the catabolic response. We briefly discuss here general concepts on UPS and autophagy, with a focus on their role in the pathogenesis of cardiac atrophy, and the interplay with inflammation. For a comprehensive review on UPS and autophagy, which is outside the scope of this contribution, readers are referred to [77–83].

UPS and autophagy UPS-mediated degradation consists of an ATP-dependent ubiquitination of target proteins followed by their degradation in the 26S proteasome and release of free and reusable Ub. Protein polyubiquitination is catalyzed by ubiquitin-activating (E1), -conjugating (E2), and -ligase (E3) enzymes and is counterbalanced by protein deubiquitination and activation of deubiquitinating enzymes (DUBs) [83]. Hundreds of different ubiquitin ligases have been discovered and about 60 E3 ligases have an assigned cardiac function [84]. In cardiomyocytes, the most relevant E3 ligases are Atrogin-1; the three members of the tripartite motif-containing (TRIM) proteins MuRF1, MuRF2, MuRF3; and Smurf1 [85, 86]. Collectively, these E3 ligases control 80–90% of proteins turnover, including short-lived, native, misfolded, or damaged proteins in the cell. Other TRIM family members have been identified in cardiomyocytes and are receiving great attention for their differential expression in various pathophysiological processes, such as HF (TRIM8 and TRIM21) and cardiac hypertrophy (TRIM32) [84]. It will be interesting to investigate expression of TRIMs in different models of cardiac atrophy, including those of cancer cachexia.

Autophagy mostly degrades long-lived proteins that likely reside in the membrane of cellular organelles or generate aberrant protein aggregates, thus assuring continuous renewal of subcellular components and the recycling of metabolic substrates. Three forms of autophagy have been described in mammalian cells: chaperone-mediated autophagy, microautophagy, and macroautophagy (currently termed autophagy), with macroautophagy being the most prevalent in the heart and also extensively investigated. Autophagy is initiated from an isolation membrane emerging from the endoplasmic reticulum through activation of the Unc-51-like kinase (ULK) complex [87]. This initial stem elongates up to the formation of a double-membrane vesicle (autophagosome), a process regulated by other autophagy-related genes (ATG) and related proteins. Within the autophagosome, specific cargo is sequestered. In the final step, the autophagosome fuses with the lysosome to form an autolysosome, a process controlled by syntaxin 17 and SNAREs proteins [88]. Within the lysosome, the cargo undergoes an acid hydrolase-dependent degradation, followed by release of amino acids and lipids for reuse. The Forkhead transcription factors (FoxOs) are critical to autophagy. Active dephosphorylated FoxOs upregulate ATGs and other genes of the autophagic pathway [89], and transgenic mice overexpressing FoxO3 present reversible atrophy and decreased heart weight of 25% [90].

UPS and autophagy in cardiac atrophy Tight regulation of UPS and autophagy is essential for cardiomyocytes, which are terminally differentiated cells that mostly survive for the entire life of a human being and require sophisticate “quality control” systems to avoid irreversible damage [85, 91]. Perturbation of UPS and autophagy contributes to cardiovascular disease. Inhibition of these mechanisms results in proteotoxicity, but sustained activation can also shift from adaptive and cardioprotective to maladaptive and detrimental, depending on the timing, the magnitude, and the specific stress conditions [91]. The relative contribution of UPS and autophagy in cancer-derived cardiac atrophy remains controversial. Using C26 female mice, Cosper and Leinwand found increased autophagy and abundant autophagosomes in cardiomyocytes, but no UPS activation ([49]. In experimental hepatoma, Musolino et al. demonstrated that megestrol acetate, a synthetic derivative of progesterone, reduces atrophy through a marked downregulation of autophagy [92].

Other models of cardiac atrophy highlight a central role of UPS in proteolysis. MuRF1 overexpression results in a thinner left ventricular wall, and genetic ablation of MuRF1 protects against glucocorticoid- and dexamethasone-induced cardiac atrophy, two findings that link inflammation to autophagy [93]. Finally, doxorubicin, a highly cardiotoxic chemotherapy drug, induces cardiac atrophy through complex mechanisms of proteolysis. These include activation of autophagy and upregulation of MuRF1 and its upstream regulator BNIP3 (BCL2 interacting protein3) [94]. These results suggest that activation of autophagy and UPS in cardiac atrophy is highly context-dependent. Clinical studies on cardiac atrophy consequent of left ventricular assist device placement showed an increase in MuRF1 expression and UPS-mediated protein degradation. Similarly, in heterotopic heart transplantation, where the heart undergoes unloading similar to that observed in left ventricular assist device [95], atrophy is accompanied by little activation of autophagy and significant upregulation of UPS. Finally, in cardiac atrophy induced by tail suspension, or by starvation, there is an increase in autophagy and atrophy is reversed by the administration of chloroquine, an autophagy inhibitor.

Inflammation and protein degradation in cardiac atrophy UPS and autophagy are activated by a variety of tumor-released pro-inflammatory molecules (Fig. 3). Sustained inflammation secondary to cardiac-restricted overexpression of TNF leads to proteasome dysfunction and impaired autophagic flux and causes abnormal proteotoxicity. TWEAK activates MuRF1, and MURF1 regulates protein turnover of contractile proteins, such as myosin heavy chain and cardiac troponin I [96]. Other pro-inflammatory molecules, such as IFN-γ, cause cardiac atrophy through UPS-induced specific degradation of sarcomeric proteins. Mitochondrial dysfunction and release of reactive oxygen species (ROS) and ATP contribute to promote proteolysis by oxidative modification of myofibril proteins and direct activation of NF-kB and NLRP3 inflammasome [97]. NLRP3 contributes to angiotensin II-induced skeletal muscle wasting *via* PPAR-γ, an effect attenuated by administration of the PPAR-γ agonist rosiglitazone [98]. Thus, it appears that modulating UPS and autophagy in response to cardiac atrophy requires further experimental studies to validate the concept of context-dependent regulation and to precisely identify those target molecules that reduce tissue wasting without affecting heart function.

6 Cancer-derived cardiac atrophy: clinical correlations and options for prevention and treatment

Is cancer-derived cardiac atrophy clinically relevant? To date, the experimental evidences supporting direct tumor-to-heart influence have not been extensively investigated in the clinical setting. Limited numbers of clinical observations may be due to the difficulties in completely distinguishing cancer-induced structural and functional changes from cardiotoxicity or previous cardiovascular diseases, and to the lack of indications for cardiological evaluation in cancer cachectic patients. We do however have robust clinical evidence that cancer is detrimental to the heart. A retrospective study analyzed cardiac muscle wasting in 177 patients who died of cancer. Patients showed heart weight loss, which was statistically significant in gastrointestinal, pancreatic, and pulmonary malignancies [99]. In another study, patients who died of cancer showed progressive cardiac muscle wasting, perivascular fibrosis, and extensive cardiac remodeling [100]. In a third longitudinal study, echocardiography was performed in 70 chemo-naïve patients with advanced non-small cell lung carcinoma eligible for chemotherapy. Results showed significant cardiac dysfunction in almost 13% of patients, with a close association of neoplastic cachexia with cardiac atrophy, measured by echocardiography as left ventricular mass (LVM) [101, 102].

All the clinical studies on cancer cachexia have been conducted on patients with advanced disease (locally advanced or recurrent/metastatic); thus, we cannot distinguish the prominent role played by the primary tumor *vs* the metastatic sites. However, given the prevalence of global cachexia in advanced cancer patients, it is reasonable to postulate a continuum, with a peak of cardiac muscle wasting during the metastatic phase. Shiono et al. [6] analyzed progressive weight loss in various stages of lung cancer and found that cachexia reached the significant 5% threshold only in stage IV patients. These observations led to the conclusion that the capabilities of lung cancer to metastasize and also induce cachexia might be linked intrinsically. In addition, KRAS-mutated tumors were more commonly associated with global cachexia.

From the clinical perspective, there are areas cardio-oncology teams can reflect upon. As a first recommendation, we would stress the importance of early diagnosis of neoplastic cachexia [103]. Identification of pre-cachectic stages (weight loss of >1.0 kg, but $<5\%$) [104] through regular evaluation of body weight, body mass index (BMI), or more sophisticate techniques, such as computerized axial tomography, in cancer patients is rare. Implementation of suitable support treatments is generally restricted to terminal stages of cachexia (refractory cachexia) when the probability of therapeutic success is very limited. In this regard, we present real life data from our Cardio-Oncology Unit as a reference point for consideration and self-criticism. We retrospectively analyzed 90 consecutive patients referred to our hospital for therapeutic planning in colon cancer and extrapolated 21 cases with an indication for cardiological evaluation. In no cases were cachexia or pre-cachexia reported as a diagnosis for counseling. However, four of the 21 patients (19%) met the clinical criteria for diagnosis of cachexia: *i.e.*, weight loss, low values for posterior wall thickness (PP), and interventricular septum diastolic diameter (SIV) at echocardiographic evaluation and changes in the positive and negative markers for acute phase response (C-reactive protein, albumin). One patient had significant pre-existing cardiovascular disease, whereas the others presented only recent poor blood pressure control, and not yet eligible for cardiological therapy. In these latter cases, fluoropyrimidine-based chemotherapy was adopted without any specific therapy, along with recommendation for periodic cardiological follow-up. This preliminary analysis prompted our cardio-oncology unit to plan early intervention even beyond the patients' exposure to cardiotoxic drugs, with the aim of identifying more subtle forms of cancer-induced cardiac damage, starting from pre-cachectic stages.

Our second recommendation would be that cardio-oncology teams should adhere to guidelines and the position papers from scientific cardiology societies and apply the same strategies for the prevention and diagnosis of HF also to chemo-naïve pre-cachectic cancer patients [105]. We envisage two levels of diagnostic analysis. The first should include basic or advanced monitoring of cardiac function (cardiological examination,

electrocardiogram, echocardiography) and should be carried out in all health facilities. The second should include more sophisticated tests (*i.e.*, cardiac magnetic resonance) to be performed in modern cardio-oncology units. Detailed examination of these analyses is outside the scope of this review, but some key points deserve some consideration. The tests recommended are the electrocardiogram, some blood biomarker evaluation, and echocardiography. The utility of brain natriuretic peptide (BNP) and pro-BNP as early markers of HF has largely been demonstrated [106, 107]. Other sensitive markers of cardiac damage associated with myofibril breakdown are troponin I and troponin T. In addition, C-reactive protein, TNF-α, IL-6, IL-1β, and the new generation marker galectin-3 [108], a member of a large family of β-galactoside-binding animal lectins expressed by inflammatory macrophages, correlate with negative prognosis in chemo-naïve cancer patients [109]. Similarly, high heart rate (> 75 bpm), a common condition in HF, is a significant negative prognostic factor and should be considered [110]. Echocardiographic parameters of ejection fraction and cardiac deformation are useful for identifying the patient's risk profile in terms of potential clinical or subclinical cardiac damage [105, 111, 112]. At present, agreement on how to discriminate patients based on left ventricular ejection fraction (LVEF) values is lacking. Values between 40 and 50% are predictive of failure with preserved function and can identify subclinical dysfunction [113, 114].

Even more information is provided by echocardiography in identifying alterations of myocardial deformation that may precede LVEF changes [112]. Using speckle tracking echocardiography (STE), early reduction in peak systolic global longitudinal strain (GLS) can be used to predict a drop in LVEF or HF. Cardiac magnetic resonance provides the greatest accuracy analysis for multiple cardiac parameters and is generally recommended whenever echocardiography is not diagnostically effective [115, 116]. Of note, data extrapolated from studies on anthracycline cardiotoxicity showed that early diagnosis followed by inclusion of cardiological treatments offers partial recovery of the ejection fraction in a significant proportion of patients [117, 118].

The only approved therapeutic strategy for reverting cancer cachexia is the use of antineoplastic drugs, which on the one side limits tumor growth, but on the other may induce severe cardiotoxicity [119]. This scenario is even more worrying in today's context where a wide spectrum of new therapies extends beyond the first lines of care. Thus, as a third recommendation, we wish to emphasize the importance of the "simultaneous care" model, including early introduction of every necessary palliative therapy in support of specifically oncological treatments. Simultaneous care models address all the acute and chronic needs of the patient, including physical symptoms such as cancer-related pain [120, 121], psychosocial and existential issues, toxicity, and comorbidities, with widely significant benefits in terms of quality of life and of overall survival rates [122, 123]. The therapy needs necessarily to be multimodal and should include suitable nutrition, physical exercise, cardiological drug assistance, and new pharmacological treatments for the prevention of cardiac atrophy [11, 124–126].

Conventional therapies for cardiac muscle wasting

Nutritional therapy, aimed to overcome the anabolic resistance in advanced cancer patients, is the cornerstone of multimodal intervention, although robust scientific evidence of a causative beneficial effect is lacking [126]. Despite the general perception of cachexia as a condition that cannot be reversed by nutrition, current evidence points towards some benefits of nutritional therapy when introduced before the refractory phase [127]. Larger controlled clinical studies are however urgently needed to clarify the therapeutic potential of early intervention in the form of personalized dietary intake. Complementary therapeutic approaches, based on administration of appetite stimulants, such as megestrol acetate, have been also tested in cancer patients. Megestrol acetate, which has been successfully used in experimental cancer to reduce muscle atrophy [92], improves appetite and body weight but at the price of significant side effects, including severe thromboembolic events [128].

Physical exercise plays a leading role in multimodal treatment of cancer cachexia. A large number of experimental and clinical studies have demonstrated that, in addition to improving quality of life and reducing fatigue, physical exercise counteracts skeletal muscle wasting. Physical exercise improves insulin sensitivity, stimulates protein and organelle turnover, and modulates muscle metabolism, with substantial differences according to the type of exercise (endurance *vs* resistance), as reviewed by Stene et al. [129]. Physical exercise is therefore likely to also be beneficial for cardiac atrophy, but this specifically remains to be investigated [130].

In the treatment of cancer patients with potential or suspected HF, specific cardiological therapies should be adopted. Acute or chronic HF is substantially due to the activation of adrenergic and renin-angiotensin-aldosterone systems, whose tight control improves cardiac function (*i.e.*, ventricular ejection fraction) and reduces cardiac and skeletal muscle loss and remodeling. The efficacy of ACE inhibitors and angiotensin receptor 1 inhibitors is manifold [105, 131]. Angiotensin II reduces protein synthesis and muscle regeneration, increases oxidative stress, and decreases appetite through the activation of hypothalamic mediators. Recent controlled clinical trials conducted in patients with diverse advanced cancer diseases have demonstrated the potential efficacy of imidapril in preventing weight reduction [132]. Furthermore, a controlled clinical study with espindolol, a new beta-blocker, reported significant reversal of weight loss, improvement of fat free mass, and maintenance of fat mass [133]. These encouraging results will require further confirmation from additional randomized clinical trials.

The role of sympathetic antagonism on cachexia is also suggested in the prospective "Copernicus" controlled clinical

trial, which demonstrated that carvedilol attenuates, and partially reverts, cachexia in patients with severe chronic HF [134]. Among the new specific cardiological therapies for the prevention and treatment of HF, sacubitril/valsartan is noteworthy. This new drug, which acts as a neprilysin inhibitor and an angiotensin receptor blocker [135], inhibits profibrotic processes (valsartan) and stimulates antifibrotic mechanisms (sacubitril), being potentially effective in the treatment of HF with preserved ejection fraction (HFpEF), a frequent clinical condition in cancer patients. Figure 4 proposes a decisional algorithm that unifies current guidelines for cardiotoxicity prevention and proper monitoring of neoplastic cachexia in the clinical setting.

Innovative therapies for cardiac muscle wasting Preventing and counteracting cardiac muscle wasting in cancer patients with new therapies is a big challenge. Despite promising preclinical studies, none of the new molecular targets suitable for clinical application has approved therapies. It is noteworthy that the clinical studies conducted so far have considered a list of primary direct (body weight, lean body mass, fatigue, anorexia) or indirect (level of expression of circulating markers) clinical end-points of cancer cachexia that have not included cardiac muscle wasting. A note of caution is therefore due for the applying of the results of these studies to the heart.

Given that inflammation is the major driver of cancer cachexia, targeting this mechanism has attracted great attention. Many monoclonal antibodies targeting pro-inflammatory molecular pathways are underway in phase I–III clinical trials (Fig. 3). Significant results have been achieved in a phase I dose escalation and expansion clinical trial with MABp1, a monoclonal antibody against IL-1α. In this study, an increase in lean body mass and a reduction in IL-6 serum level, in addition to good safety, were reported [136]. This favorable clinical profile was confirmed in a 2:1 MABp1-placebo phase III trial in advanced colorectal cancer patients [137]. Despite an improved quality of life, none of these studies showed any increase in overall survival.

Recombinant IL-1β receptor antagonist (anakinra) and inhibitor of IL-1β (canakinumab) were also tested in cancer patients. A prospective study on a large number of vasculopathic patients showed that canakinumab reduces the incidence of pulmonary neoplasms [138]. This intriguing result opened new clinical studies, many of which are currently underway (CANOPY-1-NCT03631199, CANOPY-2-NCT03626545). Anakinra has been tested in patients with smoldering multiple myeloma, having progression-free survival as its primary endpoint. A significant decrease in circulating acute phase markers, such as CRP, was detected [139]. Further studies are required to conclusively affirm that targeting IL-1β pathway is beneficial in neoplastic cachexia.

TNF-α antagonists infliximab and etanercept failed to provide any significant improvement in cachectic patients and had strong adverse effects, resulting in increased fatigue, inferior global quality of life [140], and HF [141]. However, recent findings showed that TNF-α produces both detrimental and cardioprotective effects on the heart depending on the binding to TNFR1 and TNFR2 receptors [142, 143]. This phenomenon prompts to reconsider more appropriate adjustment of conventional anti-TNF-α therapies in the prevention of cardiac cachexia.

Anti-IL-6 antibody clazakinumab has been tested in clinical phases I and II trials in patients affected by non-small cell lung cancer. The treatments ameliorated fatigue and reduced cancer-related cachexia [144]. Given that acute exposure to IL-6 is cardioprotective, but chronic exposure appears to be detrimental [51, 52], more studies are required to establish the specific effects of anti-IL-6 treatment on cardiac muscle wasting.

Potentially new therapeutic avenues may derive from the use of drugs with multiple molecular targets and combined treatments. Administration of the antineoplastic selumetinib, an allosteric inhibitor of MEK1- and MEK2-dependent phosphorylation of ERK1/2, has also been seen to be anti-cachectic. In a phase II clinical study, patients with cholangiocarcinoma treated with selumetinib had significant skeletal muscle anabolic response [145], possibly because ERK inhibition activates FoxOs [146, 147].

Similarly, the use of thalidomide to reduce the inflammatory response in cancer patients is worthy of mention. Thalidomide mediates suppressive effect on different cytokines, including TNF-α and IL-6 [148], and is therefore successfully used to treat some autoimmune and oncological diseases. Thalidomide has additional effects, like inhibition of the TGF-α pathway and block of cereblon, the substrate receptor of E3 ligase Cullin-ring ligase-4 (CRL4) [149]. Whether these mechanisms are active in skeletal and cardiac muscle remain to be investigated. In the context of anti-cachectic effects, thalidomide has been tested in placebo-controlled phase II trials in different advanced malignancies [148, 150, 151]. Given high drop-out rates and low compliance, only one study in patients with advanced pancreatic cancer demonstrated significant increased body weight [148]. Encouraging results were however recorded when thalidomide was used in association with other molecules (megestrol acetate and medroxyprogesterone acetate) or with specific nutrients in the same clinical settings [152, 153]. Based on these inconclusive results, the use of thalidomide is not currently recommended as a treatment for cancer-related cachexia and deserves to be further explored [154].

Signaling pathways to counteract protein breakdown in cardiomyocytes have also been considered as a possible therapeutic target. To date, no therapy specifically blocking myofibril protein degradation has been validated and translated to clinical practice. Experimental results targeting TGF family members, and promising results in the treatment of sarcopenia

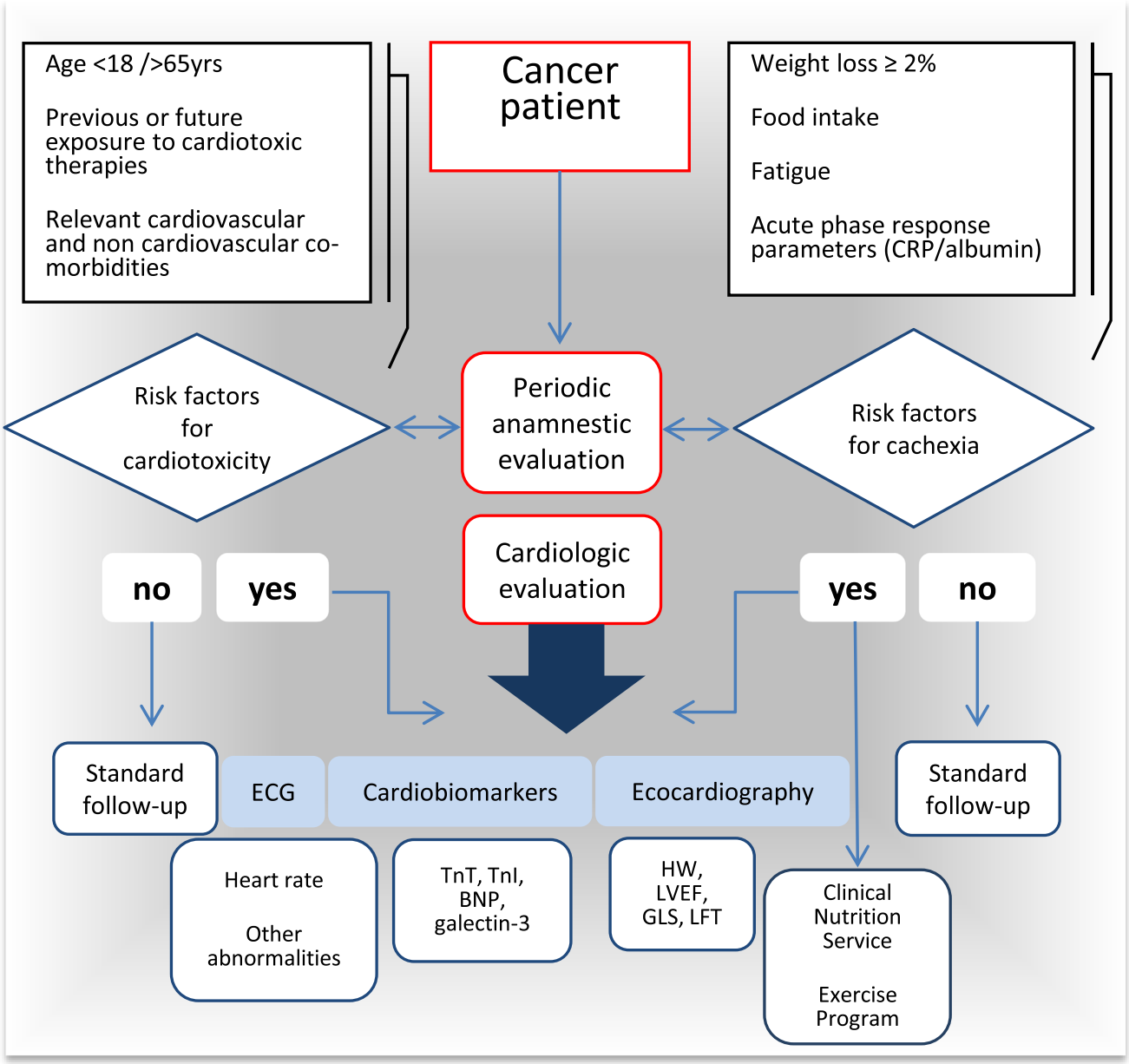

Fig. 4 Diagnostic flow chart for risk of iatrogenic cardiotoxicity and cancer-derived cardiac cachexia. Decision-making algorithm highlighting the need to integrate the guidelines for risk parameters for cardiotoxicity and cachexia in periodic evaluation of cancer patient. Primary goals are early diagnosis of cardiac damage and dysfunction and implementation of supportive care. Abbreviations: CRP, C-reactive protein; ECG, electrocardiogram; TnT, Troponin T; TnI, Troponin I; BNP, brain natriuretic peptide; HW, heart weight; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain

with bimagrumab, a monoclonal antibody blocking ActIIR [71, 155], have paved the way to the carrying out of controlled clinical trials. In one study involving patients affected by lung or pancreatic cancers, no benefit was achieved in terms of survival or of weight gain [ClinicalTrials.gov identifier: NCT01433263]. Similarly, no benefit was reported with the use of anti-myostatin antibody LY2495655 in patients with advanced pancreatic adenocarcinoma [156]. Bortezomib, a 26S proteasome inhibitor, currently used for patients affected by multiple myeloma or mantle-cell lymphoma, has been proposed for the prevention of cancer cachexia. Case reports however, and subsequent larger clinical trials, have given alarming signs that treatment with bortezomib might be associated with cardiotoxicity [157, 158]. New-generation proteasome inhibitors have been developed to reduce the adverse effects of bortezomib while maintaining anti-cancer activity. Preliminary results with one of these compounds, carfilzomib, have however indicated significant cardiotoxicity, with a substantial group of patients developing symptomatic HF [159]. At

the moment, there are no sufficient guidelines for the use of these new therapeutic agents in direct clinical patient care.

Neuromediated mechanisms of neoplastic cachexia have aroused interest, although the conversion of experimental data into clinical practice is at a preliminary stage only. Macimorelin, a ghrelin agonist, is under clinical trial [160]. Anamorelin, the agonist of ghrelin segretagogue receptor, has been tested in phase-III controlled studies on patients with advanced lung cancer. In this setting, anamorelin improved physical parameters and symptoms related to neoplastic cachexia [161]. More recently, anamorelin has been also tested in 50 patients with advanced gastrointestinal cancer and concomitant severe cachexia. Treatment improved anorexia, resulting in rapid increase of body weight and good toleration over 12 weeks [162]. The beneficial effects of these new therapies on heart function await appropriate investigation, with cardiac amelioration being included in the co-primary endpoints.

7 Conclusion and perspectives

In the light of the data presented here, it is evident that cardiac muscle should be a primary object of study in cancer cachexia. Experimental models need to be implemented. Although animal models are typically and purposely designed to be monothematic, efforts to combine genetically modified backgrounds with cancer and a pro-inflammatory state would be welcome. The relative contribution of UPS, autophagy, and mitochondrial dysfunction should be clarified, in order to be able to establish what is cause and what is effect in the pathogenesis of cardiac atrophy and wasting. Even more important is the mismatch between the clinical reality and animal models: the vast majority of cancer cachexia experiments were not conducted in a metastatic context (only 15% in cachexia studies between 2007 and 2017) [20], although cachexia and metastatic disease predominantly occur together in patients. In addition, more myocardial tissue from autoptic hearts needs to be analyzed to reinforce integrative physiology studies in humans.

From a clinical perspective, translational and clinical research is urgently necessary to overcome the current lack of prevention guidelines. Greater attention to the identification of pre-cachexia and to the use of sensitive circulating and instrumental markers for early detection of cardiac disease is essential for prevention of cardiac cachexia. The ideal approach for prevention is without doubt multimodal. It requires an interplay of multiple professional competences and the provision of suitable pharmacological treatment combined with nutritional support and exercise training. We currently have at our disposal many potential new drugs to target the main pathogenetic mechanisms of cachexia, and yet the actual effectiveness of most approaches is limited by a lack of large-scale controlled clinical trials. So far, the best clinical results have been obtained with multiple molecular targets, and with combined treatments. It is therefore desirable for the new molecular therapies to be employed according to rational combination models or in association with the best available support therapies. We should be aware, moreover, that basic and translational research on cachexia is constantly advancing, and many studies are underway that could enrich the scenario presented in this review. We refer in particular to the studies of microRNAs, epigenetic factors, proteome, microbiota, and, on the clinical side, to the new nutrients and new therapeutic molecules [163]. Moving forwards, a strong cooperative interaction between cardiologists and oncologists is something that should be encouraged. The vulnerability status of cancer patients developing cardiac dysfunction requires very careful assessment and customized management.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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