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EDITORIAL

Advanced cancer as a heart failure like syndrome due to cardiac wasting cardiomyopathy: facts and numbers

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Abstract

Cancer remains a leading cause of global morbidity and mortality, with nearly 20 million new cases and 9.7 million deaths reported in 2022. Cardiovascular disease is one of the most common causes of death in cancer patients, accounting for up to 40% of fatalities. While the field of cardio-oncology has greatly focused on mitigating cardiotoxicity from cancer therapies, mounting evidence suggests that cancer itself induces significant cardiovascular dysfunction. Treatment-naïve cancer patients often have impaired left ventricular ejection fraction, reduced exercise capacity, lean mass loss, and altered heart rate variability. Patients with advanced cancer, who often face symptoms resembling heart failure, including dyspnea, exercise intolerance, and muscle wasting, also exhibit structural and functional cardiac alterations. Cachexia, prevalent in up to 50–80% of advanced cancer cases, contributes to cardiac wasting. Studies reveal significant reductions in left ventricular mass and myocardial wall thickness in cancer patients, with these structural abnormalities linked to declines in physical performance and quality of life. Echocardiographic analysis revealed a significant reduction in left ventricular (LV) mass of up to 25% in cancer patients with and without cachexia, compared to healthy controls with similar age and sex. During on average 4 months of follow-up, 90 patients with cancer lost on average 9.3% of LV mass, and 44% of these patients lost >10% of LV mass. Loss of LV mass >10% may be a new way to define presence of cardiac wasting cardiomyopathy. Wasting of the heart was independently associated with poor prognosis, but only when raw data or adjustments for height were used, but not when body surface area adjustment was applied. Body surface area contains body weight and is hence not useful in a setting of whole body cachexia. Proposed mechanisms for cardiac wasting in cancer include cancer-induced pro-thrombotic states, oxidative stress, local hypoxia, disordered neovascularization, and direct myocardial injury from oncometabolites. Preclinical studies highlight the potential of heart failure therapies, such as beta-blockers (e.g., bisoprolol) and mineralocorticoid receptor antagonists (e.g., spironolactone), in mitigating cardiac wasting and improving survival in cancer. In preclinical studies these drugs reduce ventricular mass loss, attenuate cardiac dysfunction, and enhance survival outcomes. Given the strong parallels between advanced cancer and heart failure syndromes, clinical trials are urgently needed to explore the benefits of heart failure therapies in cancer patients. Such interventions may offer both clinically meaningful symptomatic relief and quality of life benefits, reshaping the approach to cardio-oncology care.

Key words: cancer; heart failure; cachexia.

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Cancer and cardiovascular disease

Cancer is responsible for a large percentage of global morbidity and mortality with nearly 20 million new cancer cases and 9.7 million deaths in 2022.[1] Recent data suggest cardiovascular disease is one of the most common causes of death in cancer.[2] It is estimated that up to 40% of deaths in patients with cancer occur due to cardio-vascular disease.[3] The recently established field of cardio-oncology has primarily focused on mitigating cardiotoxicity due to anti-cancer therapeutic strategies such

as anthracycline-induced chemotoxicity and radiotherapy-induced cardiac damage.[4] However, many cardiovascular parameters can be potentially impaired in treatment-naïve cancer patients such as left ventricular ejection fraction (LVEF), exercise capacity, lean mass, and heart rate variability (HRV).[5] This suggests that cancer itself may lead to pathological changes in the cardiac tissue.[6]

Advanced cancer, different from terminal cancer with a life expectancy of <6 months, has a longer course, with a life expectancy of up to 1-5 years.[7] Although death may be an inevitable outcome, symptom burden and quality of life, along with longevity, is a high priority in these patients. Patients with advanced cancer frequently exhibit symptoms and signs mimicking heart failure, such as dyspnea, impaired physical activity and exercise tolerance, congestion, and a higher risk of sudden death.[8] Muscle wasting and, particularly cachexia, is prevalent in both heart failure (5% to 15%) and cancer (up to 50% to 80%) patients in advanced stages.[9-11] The muscle hypothesis explaining the pathophysiology of skeletal myopathy and inflammation leading to increased metabo-ergoreflex and shortness of breath has been described previously.[12] There is a significant predominance of dyspnea in both cancer (~50%) and heart failure (up to 100%) of patients.[13] Such symptoms of breathlessness and fatigue result in impaired quality of life and are independent predictors of poor prognosis.[14] Thus, we hypothesize that guideline-recommended therapies that have proven to improve outcomes in heart failure may provide significant benefits in patients with advanced cancer, independent of chemotherapy-induced cardiotoxicity.

Advanced cancer is a heart failure syndrome: pathophysiology

Cancer patients often present with a clinical syndrome of HF. A possible underlying pathophysiology is cardiac wasting-associated cardiomyopathy due to the underlying sarcopenia and cachexia seen in these patients.[15] Cancer results in significant inflammation, oxidative damage and neurohormonal dysregulation due to altered homeostasis.[16] The ventricular thinning due to cardiac muscle wasting and fibrosis can impair electrical pathways and predispose the patients to arrhythmias. Left ventricular dysfunction and cardiac remodeling may lead to loss of heart weight.[17]

Among these, a cancer-induced pro-thrombotic state can increase the risk of clot formation, while local tissue hypoxia—resulting from inadequate oxygen supply—can lead to cellular stress and damage. Additionally, oxidative stress caused by an imbalance between free radicals and antioxidants may further harm cardiovascular tissues. Disordered neo-vascularization, or abnormal formation of new blood vessels, may also disrupt normal tissue perfusion and repair mechanisms.[15] Oncometabolites have been shown to directly damage cardiac tissue in animal models.[18] Pathways described which may contribute to damage include nuclear factor κ B (NFκB), myostatin and its receptor via activation of the catabolic ubiquitin-proteasome system and autophagy all contribute to damage at a cellular level.[19,20] Together, these processes highlight the complex interplay between cancer and cardiovascular health. The pathophysiology and clinical syndrome are summarized in Figure 1**.**

Clinical implications

Patients with cancer are predisposed to life-threatening arrhythmias, including premature ventricular contractions and ventricular tachycardias.[21,22] A study of 177 cancer patient autopsy reports showed that the average heart weight was 19% lower (84 g) in patients with cachexia than in those without cachexia.[3] Heart failure drugs such as beta-blockers like bisoprolol and mineralocorticoid receptor antagonists like spironolactone have shown to improve mortality and are recommended in heart failure patients with reduced ejection fraction.[23]

Studies have shown benefits of these drugs also in cancer. In a very early animal study on cancer cachexia in rat models, administering bisoprolol or spironolactone helped prevent global body weight loss and cardiac wasting, while also enhancing survival outcomes.[24] This was again found in another animal study with hepatoma cancer cachexia rat models which showed bisoprolol and spironolactone significantly reduced left ventricular mass atrophy, attenuated cardiac dysfunction, and improved survival.[25] The same study found that in human patients with cancer cachexia aldosterone and brain natriuretic peptide (BNP) levels were significantly elevated and there was widespread cardiac fibrosis.[25]

Recent clinical studies provide extensive evidence of cardiac wasting in cancer patients. A study of 300 patients with advanced cancer and no significant pre-existing cardiovascular disease (i.e. LVEF ≥50%) demonstrated cardiac wasting across various cancer types, regardless of anticancer therapy status, including patients receiving no therapy, non-cardiotoxic treatments, or cardiotoxic treatments.[26] Cachexia was also associated with structural cardiac changes, such as decreased left ventricle size and thinner myocardial walls. These structural abnormalities were correlated with declines in functional performance measures, including reduced six-minute walking distance, stair-climbing power, and maximum handgrip strength.[26] Echocardiographic analysis revealed a significant reduction in left ventricular (LV) mass of up to 25% in cancer patients with and without cachexia, compared to healthy controls with similar age and sex.[5,26] During on average 4 months of follow-up, 90 patients with cancer lost on average 9.3% of LV mass, and 44% of these patients lost >10% of LV mass.[26] Loss of LV mass >10% may be a new way to define presence of cardiac wasting cardiomyopathy.[6] Wasting of the heart was independently associated with poor prognosis, but only when raw data or adjustments for height were used, but not when body surface area adjustment was applied. Body surface area contains body weight and is hence not useful in a setting of whole body cachexia.[26]

Apart from beta-blockers and mineralocorticoid receptor antagonists, angiotensin-converting enzyme inhibitors (ACEi)

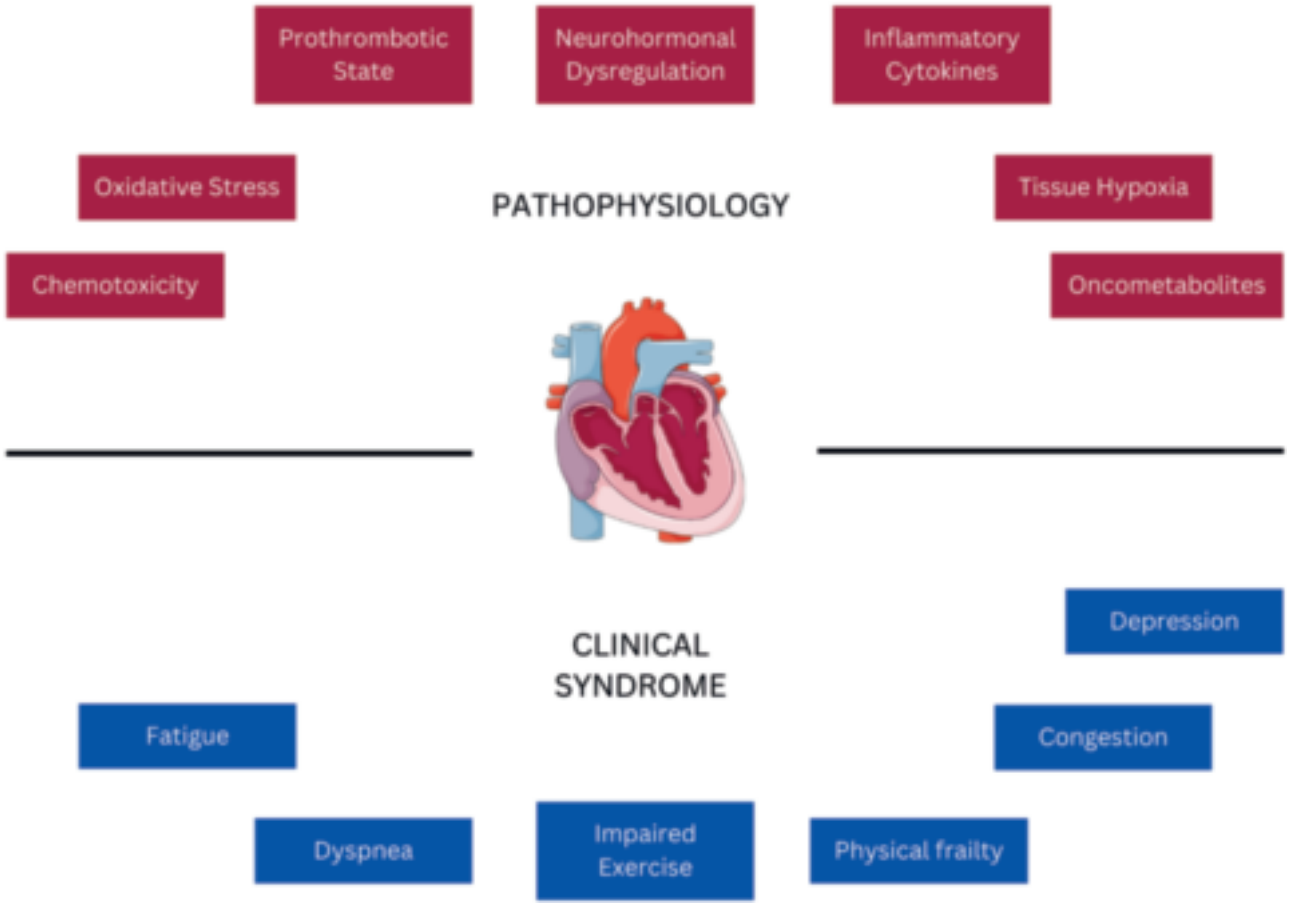

Figure 1. Advance cancer as a heart failure syndrome.

have also been studied in preclinical models. Although one preclinical study found no improvement in survival, ACEi can reduce cardiac load, cardiac dysfunction, and the progression of cardiac wasting in tumor-bearing mice.[25,27] Another intervention worth exploring is physical activity, which has been proven to improve the quality of life in patients with sarcopenia as well as heart failure, which is highly predominant in cancer patients.[28,29]

In conclusion, there is evidence that shows that cancer itself is a kind of heart failure syndrome, with cardiac wasting, remodeling, and benefits with heart failure drugs in preclinical studies. There is a need for clinical trials to explore whether heart failure drugs can provide both symptomatic and survival benefits in cancer patients.

Contributions

All authors made a substantive intellectual contribution, performed part of the experiments. All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

MSK received fees from Bayer and Novartis. J.B. has received personal fees from Abbott, American Regent, Amgen, Applied Therapeutic, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiac Dimension, Cardior, CVRx, Cytokinetics, Edwards, Element Science, Innolife, Impulse Dynamics, Imbria, Inventiva, Lexicon, Lilly, LivaNova, Janssen, Medtronics, Merck, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Roche, Sequana, SQ Innovation and Vifor. LAK and MSA report no conflict of interest.

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