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The changing perspective of cardiology in cancer care

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> "…advances in cancer therapeutics have resulted in an ever-expanding cohort of long-term cancer survivors, who more frequently experience the long-term cardiovascular complications of cancer therapy."

During recent years, the role of the cardiologist in the care of cancer patients has evolved significantly. First, the outlook for many malignancies has improved to the point that cardiovascular diseases, such as coronary artery disease and hypertension, sometimes take precedence over cancer. In any case, conditions such as coronary artery disease and hypertension frequently coexist in cancer patients. However, more importantly, advances in cancer therapeutics have resulted in an ever-expanding cohort of long-term cancer survivors who more frequently experience the long-term cardiovascular complications of cancer therapy. This is most vividly illustrated in the case of Hodgkin's lymphoma. Advances in cancer therapeutics have improved clinical outcomes to such an extent that cardiac disease, rather than recurrent primary malignancy, is currently the most common cause of nonmalignant death in survivors of Hodgkin's lymphoma [1,2].

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Second, with contemporary cancer chemotherapy, cardiotoxicity and other cardiovascular complications have become more frequent and clinically concerning. Cardiovascular complications may arise from cytotoxic agents (e.g., anthracyclines), monocloncal antibodies (e.g, trastuzumab), receptor tyrosine kinase inhibitors and antiangiogenic agents. The cardiotoxicity associated with anthracyclines has been well characterized, which is related to the cumulative dose and method of administration. Pathologically, cardiotoxicity is associated with vacuolization and loss of contractile elements, and is mostly irreversible. However, cardiotoxicity associated with newer targeted agents such as trastuzumab, a monoclonal antibody that targets the extracellular domain of EGF receptor 2 (HER2/neu), is fundamentally different. Although it is usually reversible, patients are usually required to receive trastuzumab for prolonged periods of time, sometimes combined with a cytotoxic agent, resulting in a greater incidence of cardiotoxicity. The advent and dissemination in clinical practice of multiple antiangiogenic agents such as bevacizumab, sunitinib, sorafenib and pazopanib has been associated with the emergence of a distinct profile of cardiovascular complications, such as hypertension, myocardial ischemia and thromboembolic disease. These cardiovascular adverse events have different pathophysiologic underpinings from atherosclerotic disease. While the ischemia of atherosclerotic disease is associated with vascular obstruction, the ischemia of antiangiogenic therapies is associated with vasoconstriction and

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microvascular rarefaction. Moreover, vascular-disrupting agents, that is, agents that target the endothelial cells and pericytes of the already established tumor vasculature, are advancing in clinical development. By virtue of their antiangiogenic nature, certain cardiovascular adverse events associated with their use are to be expected.

Given the cardiovascular toxicity of contemporary chemotherapy, the concept of pre-emptively treating anticipated cardiovascular adverse events, especially in high-risk individuals, is receiving wider acceptance. In selecting the optimal treatment in cancer patients, cardiologists usually extrapolate from existing guidelines and rely on established and extensively investigated medications. However, they may not realize that many of these widely prescribed cardiovascular medications, such as cardiac glycosides, statins, β-blockers and ACE inhibitors, have attracted the interest of many researchers in cancer medicine for their anti-tumor effects. In clinical practice, such an effect may not be easily discerned as it may be masked by the concurrent cardiovascular morbidity or the overriding malignancy. However, despite this clinical reality, there is enough evidence at the preclinical level, as well as at the clinical level for medications such as digoxin and statins, to suggest that the benefits of commonly used cardiovascular medications in cancer patients extend beyond a reduction of cardiovascular morbidity and mortality.

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Cardiac glycosides have a long history in cancer therapeutics. Early observations in breast cancer were consistent with more benign histologic characteristics and lower proliferative capacity in tumors from women on digitalis compared with women not on cardiac glycosides [3]. Women on cardiac glycosides had also lower recurrence rates, and in a 20-year follow-up study their death rate from breast cancer was significantly lower compared with their counterparts [4]. Multiple mechanisms have been identified that may account for the anti-tumor effect of cardiac glycosides, which mainly promote apoptosis in cancer cells as well as target other tumor-related processes.

Statins, on the other hand, have attracted significant attention in cancer medicine owing to their pleiotropic properties. Conceptually, cancer and atherosclerotic disease share similar molecular underpinnings such as aberrant inflammation and metabolism, processes that are effectively targeted by statins. The molecular underpinnings of statins' anti-tumor effects are multiple. By blocking the generation of prenyl units, statins impair prenylation, an important post-translational modification of multiple proteins whose function depends on membrane anchoring. Many of these prenylated proteins, such as the Ras family of small GTPases, are key signaling molecules along aberrantly activated pathways that promote growth, angiogenesis and metastasis. Statins may also adversely affect the folding and *N*-glycosylation of surface proteins [5], such as mutated or amplified receptors that transmit aberrant signals of growth and proliferation to the nucleus. Statins have also been shown to inhibit histone deacetylation [6] and the upregulation of cholesterol synthesis associated with chemotherapy resistance [7]. Besides acting on tumor cells, statins may affect the tumor microenvironment, which often facilitates processes such as tumor growth, angiogenesis and metastasis.

The clear role of β-blockers in mitigating the cardiovascular toxicity associated with cancer chemotherapy has been shown in prospective clinical trials [8,9]. Sympathetic nervous system stimulation and catecholamine release represent one of the principal signaling pathways underlying the link between stress, and cancer onset and progression. Notably, adrenergic receptors have been identified on multiple cancer cells, and β_2-adrenergic stimulation has been associated with accelerated tumor growth and an aggressive phenotype [10]. β-blockers have been shown to inhibit tumor growth and metastasis in cell lines and mouse models by blocking β_2-adrenergic stimulation on tumor cells and cells of the tumor microenvironment [10–12].

The vasoconstrictive effects of angiotensin II and the benefits of abrogating angiotensin II receptor signaling in hypertension, heart failure and diabetic nephropathy are well known. A possible cancer-preventive effect associated with the use of ACE inhibitors has been implied in a large retrospective study [13]. Although this effect has not been confirmed in a subsequent study [14], angiotensin II has been shown to have mitogenic [15] and angiogenic effects [16] on cancer cells and their microenvironment. Angiotensin II receptor signaling has also been suggested to play a role in cancer development and progression [17], or transformation into an invasive phenotype [18]. Despite these observations, in a recent meta-analysis angiotensin II type 1 receptor blockers have been associated with a modest increase in cancer incidence [19]. The reasons for this observation are unclear, but unopposed angiotensin II type 2 receptor stimulation may be a logical hypothesis [19]. By acting upstream in the renin–angiotensin–aldosterone system, ACE inhibitors block the cleavage of angiotensin I to angiotensin II, thereby inhibiting angiotensin signaling altogether, as well as inhibiting the generation of downstream cleavage products of angiotensin II, which also possess potent angiogenic properties [20].

"A possible cancer-preventive effect associated with the use of angiotensin-converting enzyme inhibitors has been implied in a large retrospective study."

In conclusion, the involvement of the cardiologist in the care of cancer patients is increasing. While contemporary cancer chemotherapy is more tolerable and effective than ever, its cardiovascular toxicities cannot be overlooked. Common cardiovascular medications can mitigate or treat the cardiovascular adverse events associated with contemporary cancer chemotherapy, thereby potentiating its effect by preventing dose reductions or treatment

discontinuations. Conceptually, similar to the advances made in the prevention and management of chemotherapy-induced nausea and vomiting, common cardiovascular medications can make chemotherapy more tolerable from the cardiovascular perspective. Moreover, medications such as cardiac glycosides, statins, β-blockers and ACE inhibitors have, at least in preclinical studies, an obvious anti-tumor effect. This anti-tumor effect in cancer patients represents an additional benefit 'superimposed' on their well-known benefit of reducing cardiovascular morbidity and mortality. The prospect of enhancing the efficacy of cancer chemotherapy while mitigating its cardiovascular toxicity offers an additional reason for early involvement of the cardiologist in the care of the cancer patient, and for a tighter interdisciplinary collaboration.

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