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Review Article

Cardio-oncology: Concepts and practice

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ABSTRACT

Substantial progress in cancer therapy increasingly allows higher cure rates, and even advanced disease can be stabilized, allowing improved survival with quality of life for months to years, meaning comorbid diseases are a growing determinant of outcome. Cardiovascular events substantially contribute to long-term morbidity and mortality in people living with or surviving cancer. In recognition of this, the subspecialty of cardio-oncology has emerged, and aims to promote cardiovascular heath, whilst facilitating the most effective cancer therapy. This review describes the concept of cardio-oncology, and illustrates the role played by a specialist team in improving outcomes, using heart failure secondary to breast cancer treatment as an example. We aim to highlight pivotal original research and comprehensive summaries of the most relevant topics, providing an overview for cardiologists and oncologists about this increasingly important medical problem.

In recent decades, remarkable progress in the detection and management of many common cancers has translated to substantial improvements in disease-free and overall survival.[1,2] Even in patients with noncurable cancer, contemporary therapies can often achieve medium-term and sometimes long-term disease control, requiring management strategies more akin to many other chronic diseases. Similarly, impressive reductions in cardiovascular mortality during this period mean that an increasing proportion of the population live with chronic cardiovascular diseases.[3] Unsurprisingly, these secular trends have also resulted in a growing population of people with coexisting cancer and cardiovascular disease, leading to challenging management decisions that cross the boundaries of traditional medical specialties. In particular, some recently introduced cancer therapies achieve improved cancer outcomes, but with greater cardiovascular toxicity, and so require careful case-by-case consideration. In response to these concerns, the subspecialty of cardio-oncology has developed. This review not only describes the role of the cardio-oncologist, using the prevention and management of heart failure in the setting of breast cancer as a paradigm, but also discusses the background and breadth of this evolving discipline.

1. Cardiovascular risk in people with cancer

When managing cardiovascular disease in people with cancer, it is important to consider the shared origins and potential interactions of these diseases. Major cardiovascular risk

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factors, such as increasing age, cigarette smoking, and obesity, are also unequivocally associated with the development of many common cancers.[4] Therefore, by the time cancer is detected, many patients already have established or subclinical cardiovascular disease, and conversely, increasing cardiovascular disease survivorship means more people survive to develop cancer. For example, it has been shown that prior to the onset of cancer treatment, patients with colorectal cancer have reduced peak oxygen uptake during exercise, reduced heart rate variability, and reduced left ventricular ejection fraction, versus matched controls.[5] It is also conceivable that cancer per se exacerbates cardiovascular disease, perhaps by creating a systemic proinflammatory state. Supporting this assertion, recently published data from a heterogeneous treatment naïve cancer cohort show that the concentrations of many established cardiovascular and inflammatory biomarkers rise with advancing cancer stage.[6] It is therefore unsurprising that if a period of cancer therapy successfully achieves disease remission, future cardiovascular events may represent a substantial risk to ongoing survival and quality of life. For example, cardiovascular mortality is reported to become the principal cause of death 10 years after the diagnosis of breast cancer.[7] Importantly, in many countries, more than 75% of women survive 10 years after a diagnosis of breast cancer, emphasizing the importance of cardiovascular disease prevention in improving their overall survival.

2. The concept of cardio-oncology

The discovery and application of anthracycline chemotherapy in the 1970s was perhaps the first event to foster partnership between oncologists and cardiologists, after it was recognized that these agents were associated with the development of heart failure.[8] Since then, a number of other factors, including improving cancer survival and the cardiovascular toxicity of radiotherapy and molecular targeted therapies (e.g. Trastuzumab, Bevacizumab, and tyrosine kinase inhibitors), have prompted the need for increasingly formal cardiology–oncology collaborations. The concept of cardio-oncology as a subspecialty in its own rite has been embraced more rapidly in some healthcare systems than others, but remains a nascent discipline in the context of clinical cardiology or oncology.[9] The overarching aims of the cardio-oncologist are to facilitate effective cancer therapy, whilst minimizing cardiovascular sequelae, and this requires careful consideration of the risks and benefits of the treatment strategies being considered. Most often, continuing optimal cancer therapy is appropriate, whilst minimizing, and ideally preventing, interruption of cancer therapy unless it is likely that continuing will result in a net adverse outcome. Even in these circumstances, it is often possible to rapidly optimize a patient's cardiovascular status, such that cancer therapy can safely recommence with appropriate monitoring.

These potentially life-changing decisions require clear communication between a large multidisciplinary team including cardiologists, oncologists, the patient, and their family, and often require periodic reconsideration during a course of therapy. The additional complexities of considering optimal cancer care can make decision-making challenging, emphasizing the importance of understanding the mechanisms of toxicity, and benefits of cancer therapy, which requires clear communication with the oncology team. Furthermore, many decisions must be based on limited evidence, and in the context of rapidly evolving cancer therapeutics, so experience and expert opinion become increasingly important. These challenges make cardio-oncology an exciting and dynamic field, with major opportunities to improve clinical outcomes, both through organized systems of current clinical care and research programs. In spite of the complexity of individual patient circumstances, the majority of referrals to a cardio-oncology service conform a relatively small number of broad themes (Fig. 1). It is beyond the scope of this review to discuss each comprehensively, so we use the examples of heart failure prevention and management in the setting of breast cancer for the purposes of illustration. Importantly, the general principles we discuss are transferable to many other scenarios encountered by cardio-oncology teams.

3. Mechanisms of cardiac toxicity

Breast cancer is often managed with an array of highly effective, yet potentially cardiotoxic therapies. Our understanding of the mechanisms underlying this toxicity remains incomplete, although emerging studies have provided potentially important insights. Anthracycline toxicity has for many years been attributed to the myocardial oxidative stress, and recent work from Ichikawa et al. suggests this may be secondary to mitochondrial iron overload.[10] Furthermore, they showed that Dexrazoxane, which may mitigate anthracycline cardiotoxicity in humans, is able to reduce the accumulation of iron within mitochondria. Zhang et al. have proposed anthracycline-mediated inhibition of myocardial Topoisomerase-2β as the causal mechanism, leading them to hypothesize that Topoisomerase-2α specific agents may target cancer with less cardiac toxicity.[11] It is also possible that Dexrazoxane reduces anthracycline toxicity by interfering with their binding to Topoisomerases.[12] It is likely that toxicity is multifactorial, with both of these mechanisms and others potentially playing a role. These studies provide hope for a mechanistic basis for strategies to reduce the cardiovascular effects of these crucial chemotherapeutic agents.

Trastuzumab (or Herceptin) is another important therapeutic agent in patients with HER2 (human epidermal growth factor receptor-2, or ErbB2) overexpressing breast cancer. This monoclonal antibody binds to ErbB2, interfering with its growth and survival promoting effects in tumor cells, although when clinical trials showed an increased risk of heart failure, it became apparent that ErbB2 was also important in the myocardium. Indeed, we now recognize that cardiac epidermal growth factor receptor signaling plays an important role in the survival response to pathological stressors,[13] although this insight has not yet resulted in the development of cancer therapies with less cardiac toxicity. It is also important to remember that the heart and wider vasculature are sensitive to the DNA-damaging effects of radiotherapy used in many breast cancer treatment regimens[14]; nontumor tissue dose reductions represent the best means of mitigating this toxicity.