Contents

1

Cardio-oncology: How a new discipline arrived

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INTRODUCTION

Mortality rates due to cancer have decreased over the last 30 years owing to improvements in early detection strategies, improved surgical approaches, and advances in cancer treatments (1–3). By 2026, it is expected there will be over 20 million cancer survivors in the USA alone (1). Cancer survivors are at risk, not only of cancer recurrence, but of the long-term consequences of their treatment, including cardiotoxicity. Cardiovascular disease is now the second leading cause of morbidity and mortality in cancer survivors (2). Conventional chemotherapy and targeted therapies are associated with cardiac damage, including left ventricular (LV) dysfunction and heart failure, treatment-induced hypertension, thromboembolic events, coronary vasospasm, and arrhythmias. Early and late effects of radiation therapy can lead to coronary artery disease, pericardial disease, valvular heart disease, and arrhythmias. Cardio-oncology has emerged as an essential discipline in medicine, in response to the combined decision-making necessary to optimize the care of cancer patients receiving cardiotoxic cancer therapy. This chapter will focus on the history of cardio-oncology, the present landscape, and briefly discuss future challenges and directions.

(ACE inhibitors), as well as the cardiotoxicity potential and the cumulative doses of proposed treatment regimens are considered in any risk assessment (43). While there are no universally accepted recommendations as to the minimum baseline investigations required, it is preferable that patients, particularly those predicted to be at high risk, have a chest x-ray, 12-lead electrocardiogram (ECG), biomarkers such as troponin levels and/or brain natriuretic peptide (BNP), and echocardiography with strain imaging, depending on risk of cardiotoxicity (39). This comprehensive assessment serves as an important baseline for monitoring cancer therapy-related cardiac complications and may identify high-risk patients who require cardiac optimization therapies prior to commencing cancer treatment (22).

A cardio-oncology clinic also facilitates effective strategies for monitoring of cardiac complications during and after cancer treatments. A proposed protocol for monitoring of cardiotoxicity related to cancer therapies was first developed in the 1970s and 1980s, and was primarily based on a decline in left ventricular ejection fraction (LVEF) observed in patients receiving anthracycline-based therapy (44). Current guidelines emphasize the importance of a careful history and physical examination, and in some instances recommend routine surveillance imaging (e.g., trastuzumab), preferably with a transthoracic echocardiography in high-risk patients, even in absence of symptoms (45). These recommendations are based on low to intermediate quality of evidence, and do not specify the frequency and type of surveillance strategies required during and after treatment with cardiotoxic chemotherapy. The frequency of screening for cardiac complications is therefore at the discretion of the treating oncologist. Similarly, the treating oncologist and cardiologist must decide on whether or not a patient who exhibits evidence of cardiac dysfunction continues cancer treatments, as there are no recommendations offered in current guidelines (45). In the absence of evidence-based guideline recommendations, collaboration between cardiologists and oncologist in a cardio-oncology clinic facilitates early detection of cancer treatment related cardiotoxicity, and allows for the completion of life-preserving cancer treatments while optimizing CV functioning and improving survival and quality of life. Guideline recommendations for screening and monitoring of cardiotoxicity before, during, and after cancer therapies are discussed further in Chapter 6.

A cardio-oncology clinic can take many forms; it can either occupy a physical space within a cardiology practice with open communication between cardiologists and oncologists, or vice versa. Alternatively, cardiologists and oncologists can be staffed simultaneously in the same space (46). Irrespective of the model chosen, there are advantages and disadvantages to each; centers should consider logistical requirements to determine the style of clinic most easily facilitated by the local institutional needs. Ultimately, the success of a cardio-oncology clinic rests on the ability of the clinical and support staff to coordinate clinical activities, advocate for and educate patients, enhance clinical flow, and ensure timely scheduling. The

hospital and greater community have a role in promoting the success and encouraging further development and growth of the program. It is recommended that cardio-oncology clinics establish a database for future research purposes and facilitate opportunities for ongoing professional education of all staff (46).

Cardio-oncology programs

Cardio-oncology programs are usually found in tertiary and quaternary hospitals where both comprehensive cancer centers and heart failure programs coexist. Cardio-oncology programs should provide the infrastructure necessary for timely provision of clinical care for cancer patients, including early identification of risk factors for cardiotoxicity, and early detection and treatment of cardiac dysfunction during and after cancer treatment.

Once established, cardio-oncology programs should improve the CV outcomes of patients with cancers, although there are little published data on outcome measures. At MD Anderson Cancer Center, one of the first comprehensive cancer centers to establish a dedicated cardio-oncology program, the program grew from four general cardiologists into a comprehensive cardio-oncology center, consisting of interventional cardiologists, electrophysiologists, and an advanced heart failure programs (31). The number of new consults and inpatient follow-up visits grew by 48% and 95%, respectively, while the program also witnessed a significant growth in cardiac imaging as well as increasing number of cardiac catheterization and electrophysiology procedures (31). Other success stories have been reported by many large centers, including the Memorial Sloan Kettering Cancer Center, Vanderbilt-Ingram Cancer Center, University of Pennsylvania Abramson Cancer Center, Dana-Farber Cancer Institute, and the Mayo Clinic (31,39).

A dedicated cardio-oncology program should provide education in cardio-oncology for healthcare providers, patients, and their families. Institutions should support continuing medical education events via lectures, web-based tools, and printed material. Current best practices in cardio-oncology are heavily based on expert opinion and low to moderate quality evidence. Research should be an integral component of any cardio-oncology program to generate the knowledge needed to provide high quality evidence-based care.

Where are we now?

EDUCATION AND RESEARCH

Cardio-oncology, as a subspecialty, is undeniably growing at a rapid pace and is now recognized by major cardiology and oncology societies. The past few decades have seen an exponential increase in new publications in the field of cardio-oncology, the emergence of a *Cardio-Oncology Journal*, and the creation of an international-based data registry (47). The birth and growth of the International Cardio-Oncology

Society (ICOS) has facilitated significant collaboration among international experts and led to improved educational opportunities, including a rapidly growing number of international conferences specific to the field of cardio-oncology (47,48).

As a developing specialty, cardio-oncology provides clinicians and researchers with a multitude of opportunities in education and research. Basic scientific research on the mechanisms of cardiotoxicity associated with evolving novel cancer therapies, as well as investigation into less cardiotoxic and yet effective cancer treatments, remain areas of greatest need. There is also an urgent need to clarify the methods of detection and monitoring for cardiac dysfunction (47). The role of novel noninvasive cardiac imaging modalities, as well as the use of serum cardiac biomarkers in the early detection of cardiotoxicity in cancer patients, are areas for future research (35).

To optimize the clinical outcomes of patients undergoing treatment with cardiotoxic cancer therapies, a specialist's knowledge and understanding of the challenges in both cardiology and oncology are necessary. While conferences, monthly webinars, and web-based lecture series exist to serve the educational needs of those interested in cardio-oncology, there are only a few centers that offer recognized fellowship programs. Current training programs also suffer from a lack of standardized training requirements (49). In a recent consensus statement of ICOS and the Canadian Cardiac Oncology Network, the need for focused and structured educational fellowship programs was emphasized in order to improve the increasingly complex needs of cancer patients (47). More educational opportunities and formal fellowship programs are therefore required. Over the next few decades, we will likely witness a growing number of dedicated fellowship programs across the world, offering clinical and research opportunities in both cardiology and oncology. Now is an opportune time for trainees interested in cardio-oncology to immerse themselves in this exciting and growing field.

CARDIO-ONCOLOGY SOCIETIES AND GUIDELINES

Several clinical practice guidelines in cardio-oncology offer recommendations on the identification, risk stratification, monitoring, and management of cardiac dysfunction related to cancer treatments. These guidelines are produced by national and international oncology and major CV societies, including the European Society of Cardiology (ESC) (43), the Canadian Cardiovascular Society (50), the American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) (51), the European Society for Medical Oncology (ESMO) (6), and the American Society of Clinical Oncology (ASCO) (45). Over the last decade, the American College of Cardiology has also shown a growing interest in the field of cardio-oncology, leading to the recent creation of a Cardio-Oncology Council (31,47).

Furthermore, a growing number of cardio-oncology societies are being developed

across the world, including the British Cardio-Oncology Society (http://bc-os.org), the Canadian Cardiac Oncology Network (http://cardiaconcology.ca), and the ICOS (www.ic-os.org). These societies aim to promote education and research, develop best clinical practice guidelines, and promote a better understanding of the effects of cancer treatments on CV health. Collaborations are rapidly developing between local, national, and international communities with the sole goal of improving the care and clinical outcomes of patients with cancer.

As cardio-oncology is still a developing specialty, many aspects of clinical practice remain to be clarified. Current guideline recommendations are based on of low to intermediate quality evidence, and many clinicians are left without guidance on the management of patients with high CV burden undergoing cancer therapies. Evidence is lacking on the optimal surveillance strategies during and following treatment with cardiotoxic cancer therapies. The role of biomarkers in monitoring and early detection of cardiotoxicity remains to be clarified due to conflicting results in the literature.

Furthermore, although many large centers are rapidly developing comprehensive cardio-oncology programs and clinics, there are still many challenging obstacles to overcome. Strong data demonstrating the effectiveness of cardio-oncology programs are still lacking; program pioneers may have trouble acquiring institutional support (52). It is expected that the rapid growth of this novel specialty, as well as the growing national and international collaborations, will help close these knowledge gaps in the next few years. Existing cardio-oncology programs will be expected to grow, while new societies will develop in countries such as Australia, where such societies have not yet formed. Stronger evidence-based clinical recommendations, informed by large international multicenter clinical trials, will continue to be developed, and will be expected to improve clinical practice in cardio-oncology.

OUTLINE OF BOOK CHAPTERS

The aim of this book is to provide healthcare professionals with a practical guide outlining the application of our current knowledge in cardio-oncology. Changes in cancer treatments and associated CV toxicity, as well as strategies for minimizing this risk, are reviewed. Primary and secondary preventative strategies are discussed in the context of evidence-based medical practice. Cardiac imaging modalities for assessment of cardiotoxicity and the role of serum biomarkers are explored. The long-term CV consequences of cancer therapy are discussed in chapters on adult and childhood cancer survivorship. Physicians will gain a better understanding of risk assessment, an overview of the current guidelines, treatment, prevention and detection strategies, and management in the context of survivorship.

A practical approach to setting up a cardio-oncology clinic as well as easy-to-implement guidelines are provided for readers. Nursing roles in cardio-oncology,

including a practical approach to assessment, monitoring, and treating cancer therapy-related cardiac complications are discussed. Clinical factors are brought together in a presentation of case studies to emphasize key learning points. In the final chapters, the current state in cardio-oncology training, clinical care, education, and future research are presented.

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