How to Develop a Cardio-Oncology Clinic

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KEYWORDS

• Cardio-oncology clinics • Cardio-oncology programs • Cardiotoxicity • Multidisciplinary practice

KEY POINTS

- Cardio-oncology is an evolving field and so is its clinical practice service line.
- Three milestones, each with 3 steps, are proposed as a road map to the successful implementation of a cardio-oncology clinic.
- Variant practice models and settings dictate the individual cardio-oncology clinic model.

EVOLUTION OF CARDIO-ONCOLOGY

Cancer and heart disease are the 2 leading causes of death and have been for some time in Western societies but continue to be viewed as 2 separate entities without much interaction. Interestingly, even though the prognosis of some cardiovascular diseases is worse than that of some cancers, the perception has usually been the opposite. Cancer has been perceived as universally fatal, and for this reason, historically, there has been a high acceptance rate of complications and comorbidities.[1–12] On this background, unwanted cardiovascular side effects of cancer therapies were relatively unrecognized until they were noted to be associated with dosing thresholds in patients receiving anthracycline therapy.[13] It was further recognized that an antecedent decline in left ventricular ejection fraction often heralded the clinical presentation of anthracycline-induced heart failure and that recognizing this trend and suspending therapy could potentially avert further asymptomatic or symptomatic loss of cardiac function.[14] Although a comfort level was reached for the management of the cardiotoxicity risk with anthracyclines during the active treatment period, it became apparent that there also was a late presentation of anthracycline cardiotoxicity. An exponential dose-effect relationship was identified and thereby created an opportunity for a cutoff selection of acceptable risk and benefit. This initially was thought to be accomplished at a cumulative dose of 550 mg/m^2 based on therapeutic efficacy and a predicted risk of clinical heart failure of 5% at this level. More than 2 decades later, however, it was recognized that anthracyclines were more cardiotoxic than initially appreciated, and cumulative doses of 450 mg/m^2 already yielded a 5% clinical heart failure risk.[15–17] Furthermore, significant interindividual differences were noted, and recent studies confirm that some patients have significant cardiotoxicity at doses well less than the deflection point of 300 mg/m^2 currently used, for instance, in the US Food and Drug Administration approval label for the cardioprotective agent dexrazoxane.[18]

Although the described evolution of anthracycline cardiotoxicity in itself is compelling, the completely unexpected occurrence of heart failure events in the pivotal trastuzumab metastatic

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breast cancer trial of 2001 generated the final momentum for greater attention to the cardiovascular care of cancer patients.[19] Development of symptomatic (New York Heart Association class III or IV) heart failure was the most important adverse event and occurred in 27% of patients with combined anthracycline, cyclophosphamide, and trastuzumab therapy (vs 8% in the group with anthracycline and cyclophosphamide). The impact of these findings was tremendous not only for the development of any future trials with HER-2 inhibitors but also for clinical practice leading to the implementation of every-3-month cardiac surveillance protocols for patients on trastuzumab therapy. Moreover, studies evaluating the mechanisms underlying this clinical observation led to completely new discoveries on the significance of HER-2 signaling for the heart.

A second group of targeted therapies, collectively called *tyrosine kinase inhibitors* emerged in the 1990s, similarly with the occurrence of unanticipated cardiovascular side effects that have continued to intrigue ever since. A recent prominent example is ponatinib, a BCR-Abl tyrosine kinase inhibitor used in patients with chronic myeloid leukemia, which has been found to cause adverse vascular events.[20] With anticancer therapeutics being the leading class in drug development and more than 1500 anticancer compounds in clinical trials currently,[21] one may postulate that (unexpected) cardiovascular side effects will continue to emerge. Furthermore, as preclinical screening is not as rigorous as it could be, newer anticancer therapies are poised to continue to create challenges in cardiovascular clinical practice for years to come.[22]

These developments have generated a level of complexity that is unprecedented, requiring familiarity with both the beneficial and the unwanted cardiovascular side effects of an ever-increasing number of chemotherapeutic agents. This fact is compounded by the increasing number of cardiovascular comorbidities or risk factors in the oncologic population presenting for cancer treatments. Such patients have a reduced cardiovascular reserve and require thorough pretreatment assessment, on-treatment management, and posttreatment care that is truly comprehensive and longitudinal.

Based on this escalating level of complexity in the care for cancer patients, a multidisciplinary approach has been enthusiastically embraced in recent years. This team-based approach is very much at odds with the classical 1-provider practice model of the universal physician who manages everything.[23] As a consequence, a multidisciplinary effort is sometimes viewed as fragmentation, not complementation. However, the goal of the cardio-oncology clinics should be to achieve complementation. Although it may be perceived as trivial, the mindset is key to how much any subspecialty is welcomed into the care of cancer patients in any given clinical practice. For the cardiovascular aspects, the integration of specialist care has become known as *cardio-oncology* or *onco-cardiology*. This care model has evolved and has been developed with examples on both sides of the provider equation. There has been a tremendous growth in the presence of cardio-oncology clinics in the United States over the last 5 years (**Fig. 1**).

In 2014, the American College of Cardiology Early Section on Cardio-Oncology conducted a nationwide online survey of more than 400 adult and pediatric cardiology division chiefs and fellowship program training directors with a response rate of 24%.[24] Of those who responded, and likely skewed to a group more familiar with the topic, the key responses were as follows. Most felt that this service line was important and would improve the care of patients but was largely not well developed. A significant number of participants did not feel confident in providing cardiovascular care to cancer patients and gave mostly an average rating to the understanding of the mutual impact of care on the individual disciplines. At the time of the survey, cardio-oncology activities fell within preoperative consultation services managed by general cardiology in one-third of the centers. Only one-quarter of centers had an established, specialized cardio-oncology service with multiple clinicians, 16% of respondents relied on a single cardiologist with expertise in this area, and 12% had plans to add a cardio-oncology service. Importantly, the following barriers to a cardio-oncology service line were mentioned: lack of national guidelines (44%), lack of funding (44%), limited interest/perceived value (38%), limited infrastructure (36%), and limited educational opportunities (29%). More than 40% of the programs had no formal training in cardio-oncology, whereas an equal number seemed to provide at least an exposure during regular clinical rotations. Only 11% offered lectures in cardio-oncology as part of a core curriculum. Most participants, however, stated that they would likely use educational material for their fellows and staff if those were available.[24] This article aims to address these needs, focusing on the cardio-oncology clinic.