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Research paper

Cardiovascular toxicities of chemotherapies: challenging the paradigm for left ventricular ejection fraction monitoring during and after treatment

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The traditional use of cardiac imaging in oncology has been to assure drug safety. This is best illustrated by the example of anthracyclines, which were introduced into clinical oncology practice in the 1960s. The association between the cumulative anthracycline dose and cardiac dysfunction was described in the coming decades [1,2], leading to dose reductions and investigations of preventive strategies. Radionuclide angiocardiography was the first cardiac imaging modality used for clinical cardiac function assessment prior to anthracycline treatment in the 1970s and 1980s. In a retrospective analysis of 282 high-risk patients treated with doxorubicin over a period of 7 years, the presence of normal cardiac function, identified by radionuclide angiocardiography, prior to and during treatment, was associated with lower incidence of clinical heart failure [3]. Based on these results, this study also proposed a monitoring schema LVEF cut-offs for anthracycline initiation, holding, and discontinuation [3]. These recommendations remain reflected in regulatory recommendations by the United States Food and Drug Administration (FDA) for the doxorubicin label (https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/050467s070lbl.pdf) and in clinical practice where majority of patients receiving anthracyclines undergo baseline cardiac imaging [4].

In the early 2000s, cardiac function assessment was incorporated into oncology clinical trials investigating the use of trastuzumab, a monoclonal antibody targeting human epidermal growth factor receptor 2 (HER2) receptor, in the treatment of HER2-positive breast cancer [5]. The rationale for this approach was the unexpected finding of significant increase in symptomatic heart failure risk in a pivotal clinical trial in patients with metastatic HER2-positive breast cancer randomized to trastuzumab with chemotherapy vs. chemotherapy alone [6]. Subsequent clinical trials of trastuzumab in adjuvant setting introduced changes in administration (sequential dosing of anthracyclines and trastuzumab) and LVEF assessment prior to and during treatment, together with holding and early discontinuation parameters [7]. This led to much-improved safety of trastuzumab with reported symptomatic heart failure incidence of less than 2% in adjuvant trastuzumab trials and no evidence of long-term adverse cardiac events [8]. At the same time, trastuzumab and other, later developed, HER2-targeted monoclonal therapies have revolutionized the treatment of HER2-positive breast cancer with improved survival in both early breast cancer and metastatic setting [9].

The use of LVEF assessment with trastuzumab treatment has successfully improved cardiac safety, however, it has also brought new challenges into the spotlight. Most importantly, the risk of treatment interruption due to LVEF decline has raised concerns about adverse oncology outcomes [10] in addition to the patient- and health care system burden of repeated LVEF monitoring (12). On the positive side, improved understanding of trastuzumab-cardiomyopathy has led to investigations on the use of anti-HER2 therapies in patients with cardiac dysfunction, thus creating a safe environment for completion of HER2 targeted therapy without compromising cardiac outcomes [11]. There have been major advances in understanding the imaging predictors of cardiotoxicity, such as global longitudinal strain (15). Together, these studies are moving the imaging paradigm from “cardiac monitoring for all” towards improved understanding and managing the cardiac risk in patients treated with HER2 targeted therapies [12].

In contrast to trastuzumab, the vast majority of patients receiving other targeted cancer therapeutics do not undergo routine cardiac assessment prior to treatment initiation [13]. A challenge of this scenario with “cardiac imaging after the clinical event” is to discern the

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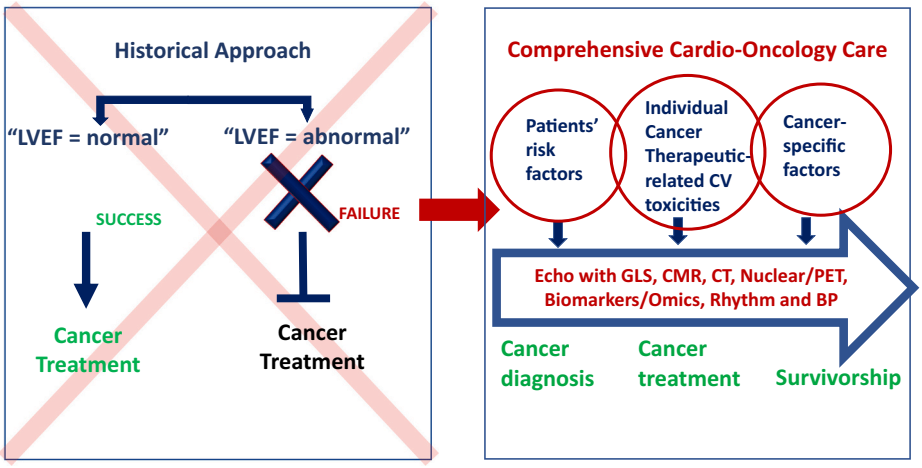

Fig. 1. Proposal for cardiac imaging as part of comprehensive cardio-oncology care. Historically, the use of cardiac imaging has been largely limited to LVEF monitoring, the results of which have been used as a gatekeeping tool for the initiation and/or continuation of cancer therapy. The figure illustrates a call for contemporary cardio-oncology practice with individualized cardiac imaging. The type/modality and frequency of imaging is informed by the patients' risk factors, cancer-specific factors, and cardiovascular effects related to cancer therapeutic(s) being used during cancer treatment continuum. Importantly, comprehensive cardiovascular assessment needs to incorporate advances in multimodality cardiac imaging techniques, biomarkers and precision medicine tools. LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; CMR: cardiac magnetic resonance; BP: blood pressure.

effects of cancer treatment from pre-existing cardiac conditions on the development of the event, such as heart failure. This is particularly relevant to agents associated with cardiotoxicity, such as VEGFi's or proteasome inhibitors, where lack of understanding of baseline cardiac function parameters may lead to erroneous attribution of cardiotoxicity and treatment discontinuation. In addition, the exponential growth of targeted oncology therapies and improved survival in many malignancies has resulted in their increasing use in older patients with significant cardiovascular burden. Inclusion of baseline cardiovascular assessment in these patients would offer an opportunity for optimal risk factor treatment, more accurate diagnosis in patients with symptoms, and consideration of prevention strategies.

Another class of anticancer biologics with relevant cardiovascular toxicities are immune checkpoint inhibitors (ICIs) which have revolutionized the treatment of many malignancies and are among the fastest growing oncology therapies [14]. These agents activate the T-cells and the immune system, thus in turn, potentially leading to immune-related adverse events (IRAEs), affecting different organs. While ICI-related myocarditis is a rare event, with incidence of less than 1% of patients, early diagnosis and treatment initiation with steroids are critical to prevent fatal outcomes [15]. Cardiac imaging, in particular cardiac magnetic resonance (CMR), plays an important role (alongside biomarkers) in the diagnosis of ICI-related myocarditis and may confirm the diagnosis without the need for endomyocardial biopsy [16]. The key CMR diagnostic criteria include presence of edema (e.g., prolonged myocardial T2 relaxation time or increased signal intensity in T2-weighted images) and evidence of abnormal late gadolinium enhancement or increased myocardial T1 time. Importantly, LVEF may be normal in up to 50% of patients [15], and is not part of the diagnostic criteria, while global longitudinal strain measured by echocardiography was prognostic of major cardiovascular outcomes [16,17].

These findings are even more relevant for oncology literature where normal LVEF has long been considered "a marker of cardiac health" being the primary endpoint of oncology drug cardiac surveillance. New cancer treatments, such as ICIs, pose the risk for new, diverse cardiovascular adverse events, and point to the need for pathophysiology-driven cardiac imaging.

Together, the time is prime for changing the cardio-oncology monitoring from its focus on assuring safety (by stopping treatment) to better understanding and managing cardiac risk (Fig. 1). Critical partnership will be needed in basic and clinical science to advance the use of cardiac imaging parameters in risk stratification and management guidance during cancer treatment continuum. Inclusion of cardiac imaging, as well as biomarkers, into oncology clinical trials and registries, has the potential to inform clinical care and ultimately improve oncology and cardiology outcomes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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