Anthracycline Cardiotoxicity: A New Paradigm for an Old Classic

Running title: Groarke et al.; A new paradigm for anthracycline cardiotoxicity

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Anthracyclines are potent anti-neoplastic agents with proven efficacy in the treatment of many pediatric and adult hematologic and solid organ cancers. Dose-dependent anthracycline induced cardiomyopathy is the most notorious and well-studied chemotherapy-induced cardiovascular toxicity that was first described in 1971 in 67 patients treated with adriamycin for a variety of tumors. The clinical significance of anthracycline cardiotoxicity is growing with increasing cancer survivorship and increasing use of anthracyclines in cohorts predisposed to adverse cardiac effects such as the elderly, those with cardiovascular comorbidities, and those receiving additional chemotherapies and/or thoracic irradiation. However, our current knowledge of anthracycline cardiotoxicity derives mainly from retrospective analyses of cancer patients with symptomatic heart failure during or after chemotherapy. This had led to wide variations in the estimated incidence and prognosis of anthracycline cardiotoxicity and has contributed to the lack of accepted guidelines for the surveillance and management of this potentially important complication of cancer therapy. For these reasons, the prospective study by Cardinale et al. in this issue of Circulation evaluating the incidence of cardiotoxicity, its timing of occurrence, and its clinical response to medical therapy in a large population of anthracycline-treated adults is an important step towards resolving these uncertainties.

Cardinale et al.² describe a 9% incidence of cardiotoxicity among 2,625 anthracycline-treated patients who underwent periodic, scheduled surveillance of left ventricular (LV) function, before, during and after chemotherapy, over a median follow-up of 5.2 years. In this cohort, cardiotoxicity, defined as a > 10% decline in LV ejection fraction (LVEF) from baseline and less than 50%, occurred almost exclusively (98% of cases) within the first year after completing anthracycline treatment. Late reductions in LVEF were observed in only 5 (2%) patients, occurring > 5.5 years after chemotherapy. Full or partial recovery of LVEF was observed in 82%
of cases after prompt initiation of enalapril, either alone or in conjunction with a beta-blocker, with severity of post-chemotherapy LV dysfunction and NYHA functional class being the best predictors of recovery. The study findings suggest that anthracycline cardiotoxicity represents a continuum that begins with subclinical myocardial cell injury, followed by an early asymptomatic decline in LVEF that can progress to symptomatic HF, if left untreated (Figure 1). The few cases that presented late occurred in patients with confounding risks for the development of cardiomyopathy, raising questions about the involvement of anthracyclines or suggesting a “double-hit” phenomenon in patients with myocardium made vulnerable by prior anthracycline treatment. These findings challenge the existing dogma that anthracycline cardiotoxicity represents irreversible myocardial injury that can present as either acute, early onset chronic progressive, or late onset chronic progressive cardiotoxicity.³ ⁴ The prospective and non-selective, symptom-independent approach to LVEF surveillance in the current study would suggest that “late-onset” anthracycline cardiotoxicity likely reflects the timing of detection, rather than the timing of occurrence of cardiotoxicity. These findings have significant implications for the surveillance and management of anthracycline cardiotoxicity.

Although the need for cardiac monitoring of asymptomatic anthracycline-treated adult patients is generally acknowledged, existing guidelines offer no clear consensus regarding the timing or duration of such surveillance.³ ⁵ One proposed schedule includes measurement of LVEF at 6 months following treatment, annually for 2 to 3 years thereafter, and then at 3- to 5-year intervals for life, with more frequent monitoring in high risk patients.³ Cost implications of periodic lifetime screening following anthracycline exposure are unknown, but daunting when one considers the growing population at risk. Indeed, rationing of similar lifelong surveillance schedules employed in childhood cancer survivors exposed to anthracyclines has been suggested
in an effort to improve the efficacy and cost-efficiency of screening. Cardinale and colleagues now present evidence to suggest that in adults with cancer, cardiotoxicity occurs almost exclusively within the first year after completing anthracycline treatment. Focusing cardiac screening to this “high-risk” period could significantly improve cost effectiveness, as well as physician and patient acceptance and adherence.

Anthraclycline cardiotoxicity is traditionally described as type 1 cardiotoxicity that features cardiomyocyte death resulting in irreversible injury. This is in contrast to type 2 cardiotoxicity, associated with trastuzumab, that is characterized by cardiomyocyte dysfunction, rather than cell death, and is therefore felt to be reversible. In the study by Cardinale et al., initiation of cardio-protective medications, promptly after the detection of cardiotoxicity was associated with recovery in 82% of patients over a mean period of 8 ± 5 months. These data challenge the concept of type 1 cardiotoxicity and indicate significant potential for reversibility with early detection and treatment, providing further support for periodic surveillance early after anthracycline therapy. It is interesting and intuitive to note that the mean LVEF prior to the initiation of heart failure treatment was significantly lower among patients without LVEF recovery. Furthermore, patients without LVEF recovery had a higher incidence of adverse cardiac events. These observations also support the concept of a spectrum of cardiotoxicity where the likelihood of reversibility reduces as LVEF worsens.

Recent studies have investigated the utility of prophylactic angiotensin converting enzyme inhibitors and/or beta-blocker use in anthracycline-treated patients. Combined prophylactic treatment with enalapril and carvedilol achieved a lower incidence of death, heart failure, or a final LVEF < 45% compared to controls (24.4% versus 6.7%, p=0.02) in a randomized, placebo-controlled trial of 90 patients embarking on predominantly anthracycline-
based chemotherapy. In earlier work by Cardinale and colleagues, troponin elevation within 72 hours of high dose chemotherapy was used to randomize 114 patients to an enalapril-treated or control cohort; the incidence of an absolute decrease in LVEF of $>10\%$ from baseline and below the lower limit of normal was significantly higher in control subjects (43\% versus 0\%, p<0.001). In patients with established LV dysfunction, time to heart failure treatment is an independent predictor of incomplete LV recovery, suggesting that delays in the initiation of cardio-protective medications should be minimized. Universal prophylaxis with cardio-protective agents, while seemingly effective, commits patients without cardiotoxicity to treatment, which is particularly undesirable in the context of frequent polypharmacy and variable blood pressures during active cancer therapy. Thus, screening and selection of patients for prompt initiation of heart failure therapy based on objective evidence of myocardial injury (e.g. troponin elevation, decrease in global longitudinal strain, or decrease in LVEF), with or without symptoms, represents a more clinically reasonable strategy. The high rate of reversible cardiotoxicity in the current study by Cardinale et al. should be validated using screening algorithms that advocate the use of biomarkers and echocardiographic parameters of early myocardial injury to guide therapy.

In tandem with the introduction and up-titration of cardioprotective agents, the clinical response to cardiotoxicity during chemotherapy often includes a reassessment of chemotherapeutic regimens, which may result in interruption, dose reduction, or substitution of cancer treatments. Cardinale and colleagues do not describe the breakdown of oncologic responses, if any, that accompanied detection of cardiotoxicity and do not explore associations with oncology end-points. These data would be particularly interesting given that 97\% of deaths (n=792) were due to tumor-related causes. A fundamental principle governing cardio-oncology
practice is that reducing the risk of cardiovascular toxicity must be balanced against maintaining the efficacy of cancer treatment. To date there are no data on the effects of prospective cardiac monitoring during anthracycline treatment on oncology outcomes. It is imperative that cardiac monitoring recommendations and downstream reactive changes in cancer treatments do not cause more harm than good.

Despite the incremental contribution of the study by Cardinale et al., there are several unresolved questions surrounding anthracycline cardiotoxicity. In this study, all patients who manifested sufficient LV dysfunction were promptly treated with heart failure medications, irrespective of symptoms. However, the natural history of anthracycline induced LV dysfunction in terms of spontaneous recovery and cardiovascular outcomes remains uncertain. Similarly, the clinical relevance of troponin elevations or reductions in global longitudinal strain that can precede overt deteriorations in LVEF, and the optimal management of these abnormalities require further investigation. Not all subclinical cardiotoxicity progresses to overt LV dysfunction or warrants intervention and the challenge lies in distinguishing irrelevant cardiac effects from prognostically meaningful anthracycline toxicity. In the current study, 82% of patients treated for cardiotoxicity demonstrated some recovery, with LVEF returning to baseline values in 11%.

Cardiac medications were continued throughout the duration of this study, but the appropriate duration of treatment remains uncertain. Whether cardio-protective agents can be safely weaned or discontinued in patients who achieve full recovery is unclear. Younger and asymptomatic patients may be particularly reluctant to commit to long-term cardio-protective medications in the absence of supportive data. Lastly, it is uncertain whether the findings of this study are applicable to childhood cancer survivors of anthracycline therapy. A prior randomized trial of enalapril in 135 pediatric survivors with evidence of asymptomatic and symptomatic
anthracycline cardiotoxicity, treated at least 2 years after completion of cancer therapy, failed to show a benefit in cardiac function.\textsuperscript{17} This may suggest divergent pathophysiologys in children and adults exposed to anthracyclines or may reflect a lack of efficacy due to the delayed institution of heart failure therapy.

Clinical decision-making in cardio-oncology is often limited by a dearth of long-term prospective studies and robust, evidence-based guidelines. The American Society of Clinical Oncology Cancer Survivorship Expert Panel deemed evidence identified from a systematic review of the literature insufficient to support a practice guideline to direct screening for chemotherapy- and radiation therapy-induced cardiac effects.\textsuperscript{18} This panel highlights the relative lack of prospective studies compared to cross-sectional or retrospective studies in this field. As such, existing guidelines are based on consensus rather than evidence\textsuperscript{19} and differences between guidelines have hindered effective implementation of recommendations.\textsuperscript{20} This has contributed to significant practice variation in surveillance for and management of anthracycline cardiotoxicity, as well as in other areas of cardio-oncology. This study by Cardinale and colleagues offers evidence that could inform guidelines and lead to greater standardized cardiac care of patients exposed to anthracyclines. This study will hopefully inspire others to systematically evaluate the role of periodic non-invasive testing for cardiac dysfunction and the role of treatment to prevent cardiac disease in asymptomatic cancer patients receiving other potentially cardiotoxic treatments such as tyrosine kinase inhibitors, proteasome inhibitors, and other novel agents. Cardio-oncologists have a responsibility to push forward with similar clinical research in an effort to improve the cardiovascular care of a growing population of cancer survivors predisposed to adverse cardiovascular outcomes.

\textbf{Conflict of Interest Disclosures:} None.
References:


Figure Legend:

Figure 1. Continuum of anthracycline cardiotoxicity.
RISK FACTORS FOR ANTHRACYCLINE CARDIOTOXICITY
Cumulative anthracycline dose
- Extremes of age
- Female gender
- Cardiovascular comorbidities
- Adjuvant chemotherapies
- Adjuvant thoracic RT

ANTHRACYLINE CARDIOTOXICITY
- No cardiotoxicity
- Subclinical myocardial injury
- Asymptomatic LV dysfunction
- Symptomatic HF
- Refractory HF/Cardiogenic shock
- Death

DIAGNOSIS
- Cardiac biomarker abnormalities
- Myocardial strain imaging
- LVEF assessment
- Symptoms & signs

MANAGEMENT STRATEGIES
- ACE-I ± β blocker
- ± Change in cancer treatment
- ? Statin
- ? Dexrazoxane

TIME FROM ANTHRACYLINE THERAPY
- REVERSIBLE
- PROGNOSIS
- IRREVERSIBLE
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