Editorial

Illuminating anthracycline cardiotoxicity: the renaissance of evidence-based onco-cardiology

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Anthracyclines are potent anti-cancer agents known to cause cardiotoxicity and heart failure since the 1970s (1). For patients that have managed to survive cancer, heart failure from the chemotherapy that saved them can be a cruel and deadly irony. Despite decades of research, anthracycline cardiotoxicity remains an incompletely understood disease, with the most widely accepted concepts summarized as follows: it is dose dependent with doses less than 400-450 mg/m^2 thought to be generally safer (2); it can occur very early or very late after exposure (3); and it exemplifies Type 1 cardiotoxicity and is therefore irreversible (4). These notions, acquired over the past five and a half decades, have arisen from retrospective observational studies that have been either too small or too confounded to serve as solid evidence. In addition, many questions have remained unanswered because of the surprisingly complex nature of the disease, inconsistent definitions of cardiotoxicity, evolving technologies used to assess it, lack of large prospective studies, and an historic paucity of interaction between cardiologists and oncologists. As a result, the many published consensus and position statements from different societies are based on soft scientific evidence and thereby met with skepticism (5-7). Not surprisingly, there is great inconsistency in the care of these patients, by oncologists and cardiologists alike, and cardiotoxicity surveillance and practices vary widely among institutions.

Thanks to the efforts of Cardinale and colleagues, this state of affairs is poised to change (8). In this year's June 2 edition of *Circulation*, the authors report a 9% incidence of anthracycline cardiotoxicity over a median follow-up of 5.2 years among 2,625 patients whose left ventricular ejection fraction (LVEF) was closely monitored by echocardiography. With echocardiographic assessment of LVEF before, during, and after anthracycline therapy, cardiotoxicity (defined as a >10% decline in LVEF from baseline and a final LVEF of <50%) occurred in 98% of patients within the first year after completion of chemotherapy. Additionally, early institution of angiotensin-converting enzyme inhibitor and/or β-blocker HF treatment resulted in complete or partial recovery of LVEF in 82% of cases, and was predicted by severity of LV dysfunction and NYHA class.

The importance of this study is that it sheds light on many misconceptions related to anthracycline cardiotoxicity. It accomplishes this by (I) carefully selecting the study population and excluding patients on "cardiotoxic contaminants" such as trastuzumab; (II) compulsively monitoring for cardiotoxicity with echocardiography at short intervals; and (III) using stringent and objective criteria for cardiotoxicity. For the first time the incidence of this disease in the context of dose and time to presentation is definitively established. Similarly, Cardinale *et al.* have deconstructed the myth of "safe" anthracycline doses by showing that the mean cardiotoxic dose was 359±172 mg/m^2. Their findings mean that not only does cardiotoxicity occur well below 450 mg/m^2, but more importantly, that a large proportion occurs with doses less than 300 mg/m^2. Lastly, it proves that the vast majority of cardiotoxicity episodes (98%) occur within the

first year following the end of anthracycline therapy, at a mean time of 3.5 months.

Indeed, these findings should guide and change clinical practice. First, they establish the utility of echocardiographic surveillance by showing that almost one in ten patients treated with anthracyclines will develop cardiotoxicity. Second they provide evidence for the need for echocardiographic surveillance for the first year following completion of treatment, something not routinely done. Third, they prove that cardiac monitoring is required independent of anthracycline dose. And last, but most importantly, they provide proof that anthracycline cardiotoxicity is reversible if identified and treated early, providing evidence to support the paradigm of onco-cardiology.

In their landmark *Circulation* paper, Cardinale *et al*. illuminate many of the dogmas that have surrounded anthracycline cardiotoxicity for decades and supply the evidence to guide clinical practice and support future guidelines in onco-cardiology. We look forward to other such efforts to help transition onco-cardiology from an expert-based into an evidence-based discipline.

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Footnote

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