

UCLA

UCLA Previously Published Works

Title

Editorial commentary: Searching for the sweet spot of cardioprotection in cancer treatment related cardiotoxicity: Who will benefit?

Permalink

<https://escholarship.org/uc/item/1r3212t2>

Journal

Trends in cardiovascular medicine, 30(1)

ISSN

1873-2615

Authors

Cheng, Richard K
Yang, Eric H

Publication Date

2020-01-15

Data Availability

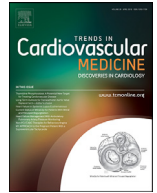
The data associated with this publication are within the manuscript.

Peer reviewed



Contents lists available at ScienceDirect

Trends in Cardiovascular Medicine

journal homepage: www.elsevier.com/locate/tcm

Editorial commentary: Searching for the sweet spot of cardioprotection in cancer treatment related cardiotoxicity: Who will benefit?

Richard K. Cheng^{a,*}, Eric H. Yang^b^a UW Cardio-Oncology Program, Division of Cardiology, Department of Medicine, University of Washington, Seattle, WA, United States^b UCLA Cardio-Oncology Program, Division of Cardiology, Department of Medicine, University of California at Los Angeles, Los Angeles, CA, United States

ARTICLE INFO

Keywords:

Cardio-oncology
Breast cancer
Cardioprotection
Cardiotoxicity

The role of cardioprotection in breast cancer

The evolution of breast cancer treatment, both with advances in detection and treatment, has led to a significant increase in survival rates. Although approximately 268,600 new cases of female breast cancer are projected to occur in 2019 with 41,760 estimated deaths [1], the overall 5-year survival rate at all stages remains high at 89.7% for all cases, and 98.7% for localized female breast cancer [2]. There were an estimated 3.56 million breast cancer survivors living in the United States as of 2016, which is projected to increase to 4.57 million in 2026 [3].

As a result, with many cases either deemed curable or controllable under maintenance therapy, the focus inevitably turns to the attention of the short- and long-term cardiovascular health of the breast cancer patient. Cardiovascular disease remains the top overall cause of death in adult females, and it is likely that this will affect many of those who survive breast cancer. In a minority of patients, cardiotoxic effects of cancer treatment will potentiate the risk for cardiac events – whether it be exposure to anthracyclines and/or anti-HER2 agents such as trastuzumab, with the possible addition of radiation therapy, whose older techniques are linked to long-term cardiac events. Despite the emergence of the multi-disciplinary field of cardio-oncology with international efforts to elucidate the mechanisms and devising strategies to prevent cardiotoxicity through randomized controlled trials, it still largely remains a mystery as to which patients are at risk for cardiotoxicity, and which patients benefit most from cardioprotective strategies.

In a systematic fashion, Padegimas and colleagues perform a state-of-the-art review [4] of cardioprotective trials with results thus far that have overall shown only limited efficacy. Most of these cardioprotection trials have borrowed treatment strategies from other subspecialties in cardiology, particularly heart failure (HF). However, the data regarding neurohormonal blockade from a cardioprotective approach is not well-established compared to the numerous studies confirming efficacy in patients with existent left ventricular dysfunction (LVD). Regardless, beta-blockers (BB) and angiotensin converting enzyme inhibitors (ACEi) have most often been tested.

These pharmacologic medications have proven their benefit in other cardiomyopathy cohorts and shown some cardioprotective role in smaller institutional studies. However, in these larger-scale trials being discussed, many of which have been conducted on a multi-institutional scale, results are at odds with earlier observational studies. For instance, Cardinale and colleagues previously demonstrated that in patients with anthracycline induced cardiomyopathy, early detection and introduction of cardioprotection can increase the likelihood of ejection fraction (EF) recovery and reduce cumulative cardiac events [5]. She followed this study with a prospective evaluation of a heterogenous cohort of patients receiving anthracyclines. Of the breast cancer patients in this group, 9.7% experienced cardiotoxicity, with 98% of cardiotoxicity occurring within the first year after treatment, with 11% achieving full and 71% showing partial recovery of EF with aggressive medical therapy [7]. In other disease states, carvedilol and enalapril reduced the incidence of LVD in a randomized cohort of patients undergoing hematopoietic stem cell transplantation [6]. These limited studies suggest that in an older patient cohort with cardiovascular disease and/or risk factors, and with higher doses of chemotherapy and radiation therapy, cardiotoxicity is more frequently seen.

* Corresponding author at: University of Washington Medical Center, Box 356422, Seattle, WA 98195, United States.

E-mail address: rkcheng@uw.edu (R.K. Cheng).

<https://doi.org/10.1016/j.tcm.2019.02.003>

1050-1738/© 2019 Elsevier Inc. All rights reserved.

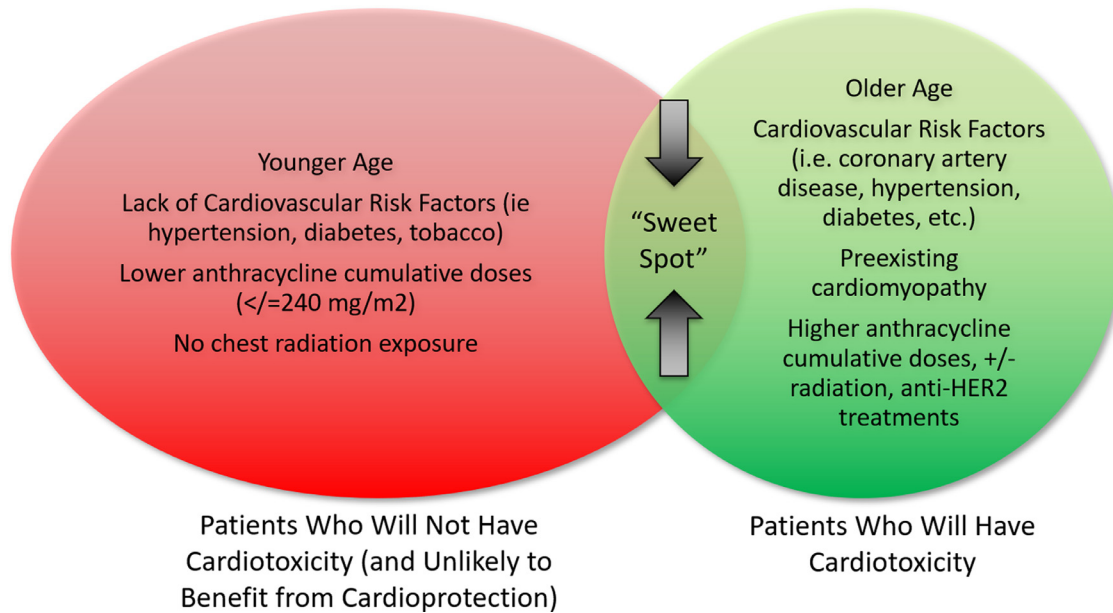


Fig. 1. Finding the “sweet spot” (middle ground) of patients who will benefit from cardioprotective strategies for cancer treatment.

Thus, along the entire spectrum of breast cancer patients, there remains a challenging-to-identify subcohort of patients who can potentially benefit from cardioprotective therapy, with most patients on one end of the spectrum who experience no significant consequences from cancer treatments (Fig. 1). On the other end, there is a minority of patients who experience cardiotoxicity, which have variable response to treatment, of which many do not completely recover and with unclear long term cardiovascular prognostic implications. Our knowledge remains nascent compared to the wealth of data that has arisen from vast, large-scale trials performed in other cardiovascular diseases.

What the trials have taught us so far

To address the discordance in results, it is imperative to consider several fundamental features of cardioprotection studies. One crucial element is the baseline risk for developing cardiovascular events. Taking a young, low risk cohort would yield very different results than an older, higher risk cohort due to drastically diverging event-rates and residual cardiac reserve for additional exposure. Higher risk patients are not only more likely to develop cardiac events from initial exposure, but also more likely to suffer events with additive, incremental insults. In large cardioprotection trials to date, cohorts have been predominantly low-to-intermediate risk, excluding most high-risk patients.

Another factor is the degree of treatment risk; it is known that with certain cancer treatments such as anthracyclines and radiation therapy, risk is related to increasing doses of exposure, while other therapies such as trastuzumab are not dose-dependent. Newer agents including the tyrosine kinase inhibitors and immunotherapy require additional evaluation for specific thresholds and timing of risk. We lack data on high-risk cohorts being exposed to high-risk treatment, even though these are the patients that stand to benefit most from an effectively implemented cardioprotection strategy.

Thirdly, the intensity and timing of intervention must be considered. Are patients being given monotherapy (ACEi or BB alone) or dual therapy (ACEi and BB), how aggressively are patients up-titrated on these medications, and what proportion of patients meet target dosing? Dose titration can be challenging in an otherwise healthy cohort without pre-existing hypertension and in

many cases, target doses used in HF trials will not be achieved. For most therapies, we do not know the effective dose for a cardioprotection strategy, which may not necessarily align with threshold dosing for treating HF.

Timing of intervention may also be essential, as it is unclear whether cardioprotection should be instituted prior to treatment, during treatment, or only when there is evidence of injury. The recent ICOS-one (International CardioOncology Society) trial found that a preventative treatment strategy was not more effective than one targeting patients after injury. These results suggest that use of ACEi might only be effective in those that suffer injury, rather than in a primary prevention approach [7]. This could explain why observational studies have shown benefit of neurohormonal blockade in cases of cardiotoxicity that has not been consistently reproduced in clinical trials that start therapies prior to treatment.

For any ideal clinical trial, judicious selection of the outcome measure is critical. It remains unclear whether commonly used surrogate endpoints in cardio-oncology trials including reduction in EF, reduction in strain, or elevation in biomarkers translates to hard clinical events of clinical heart failure or short/long term cardiovascular mortality. Confounding endpoints such as cancer related comorbidity and mortality can also pose unique challenges in cardio-oncology.

Also problematic is that within the confines of a specific outcome, there may be variability in the definition of cardiotoxicity. For example, LV function was measured differently in several landmark cardioprotection trials. In the PRADA (prevention of cardiac dysfunction during adjuvant breast cancer therapy) study, LV function was estimated based on cardiac MRI, with a primary outcome measure of change in LVEF from baseline of 5% as the threshold for clinical importance [8]. In MANTICORE-101 (multidisciplinary approach to novel therapies in cardio-oncology research), LV function was measured with cardiac MRI with definition for cancer-related cardiac dysfunction defined as a drop in LVEF $\geq 10\%$ to a value of $< 53\%$ [9]. More recently, the CECCY (carvedilol for prevention of chemotherapy-related cardiotoxicity) study used echocardiography with a drop in LVEF of at least 10% from baseline until the end of chemotherapy at 6 months as the endpoint [10]. Standardized image acquisition and definitions for cardiotoxicity would ensure consistency in the management of patients and permit accurate comparisons between studies. Further, consistent use of core labs

should be considered a priority in cardio-oncology trials to guarantee the reproducibility and reliability of measurements in a field closely aligned with imaging.

Projecting future directions of the field

Although the early cardioprotection trials have been truly landmark studies in an underexplored field, current trials extend this knowledge to higher risk treatment and have expanded the domain of cardioprotection beyond pharmacologic intervention to other aspects of care, including biomarker and imaging guided strategies. Although not discussed in the current review, there is mounting interest in exercise as a cardioprotective strategy during breast cancer treatment.

Moving forward, there remain many unanswered questions. We lack comprehensive studies targeting aggressive risk factor reduction to determine if it would translate into meaningful benefit during cancer treatment. There is robust literature from childhood survivors on the effectiveness of treating comorbidities that is lacking in the adult population [11]. A “one size fits all” strategy may not be the best approach for cardioprotection. In an era of personalized medicine and targeted strategies in oncology, we need to consider a similar approach in cardio-oncology, as not all patients are of equivalent risk or similar exposure.

Improved insights into the mechanisms for cardiotoxicity may identify novel therapeutic targets. The hope is not for newer interventions to displace ones currently being tested, but to uncover ones with incremental and synergistic benefit. The National Cancer Institute (NCI) has shifted their focus from the use of biomarkers, standardizing imaging, and prevention with established cardiac medications to more mechanistic evidence-based models, risk stratification, and modifiable risk factors [12], aligning with many researchers seeking to expand cardioprotection strategies into uncharted realms.

Recent studies have highlighted the interaction of biological pathways on cancer and cardiovascular outcomes. For example, inflammation is a common mechanism for atherosclerosis and cancer risk. In the CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study), use of a human monoclonal antibody targeting interleukin 1 β conferred both cardiovascular benefit and a decrease in lung cancer incidence [13]. Whether similar pathways linking cancer and LV dysfunction requires further exploration but leads to the intriguing concept of whether underexplored pathways may play key roles in both disease states and serve as potential targets.

In summary, future studies would benefit from rigorous selection for baseline risk, preexisting cardiovascular risk factors,

treatment exposure, intensity of intervention, and endpoints. Expanding beyond our current repertoire of pharmacologic options is needed, including better understanding of how aggressively we should treat comorbidities, and discovery of new therapeutic targets in this unique population. Clearly, there are more unknowns than knowns in this field. These are exciting times in cardio-oncology as there are many ongoing and upcoming trials designed to address some of these gaps as Padegimas and colleagues highlighted, and we move toward an era of effective cardioprotection in a coordinated effort with our oncology colleagues to find the “sweet spot” of patients who will benefit.

References

- [1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019;69:7–34.
- [2] Cancer Stat Facts: Female Breast Cancer. From: <https://seer.cancer.gov/statfacts/html/breast.html>. Accessed 30 January 2019.
- [3] Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin* 2016;66:271–89.
- [4] Padegimas A, Clasen S, Ky B. Cardioprotective strategies to prevent breast cancer therapy-induced cardiotoxicity. *Trends Cardiovasc Med* 2019.
- [5] Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomo G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol* 2010;55:213–20.
- [6] Bosch X, Rovira M, Sitges M, Domenech A, Ortiz-Perez JT, de Caralt TM, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (prevention of left Ventricular dysfunction with Enalapril and carvedilol in patients submitted to intensive Chemotherapy for the treatment of Malignant hEmopathies). *J Am Coll Cardiol* 2013;61:2355–62.
- [7] Cardinale D, Ciceri F, Latini R, Franzosi MG, Sandri MT, Civelli M, et al. Anthracycline-induced cardiotoxicity: a multicenter randomised trial comparing two strategies for guiding prevention with enalapril: the International CardioOncology Society-one trial. *Eur J Cancer* 2018;94:126–37.
- [8] Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 \times 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. *Eur Heart J* 2016;37:1671–80.
- [9] Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ, et al. Multidisciplinary approach to novel therapies in cardio-oncology research (MAN-TICORE 101-breast): a randomized trial for the prevention of trastuzumab-associated cardiotoxicity. *J Clin Oncol* 2017;35:870–7.
- [10] Avila MS, Ayub-Ferreira SM, de Barros Wanderley MR Jr, das Dores Cruz F, Goncalves Brandao SM, Rigaud VOC, et al. Carvedilol for prevention of chemotherapy-related cardiotoxicity: the CECCY trial. *J Am Coll Cardiol* 2018;71:2281–90.
- [11] Armstrong GT, Oeffinger KC, Chen Y, Kawashima T, Yasui Y, Leisenring W, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. *J Clin Oncol* 2013;31:3673–80.
- [12] Shelburne N, Simonds NI, Adhikari B, Alley M, Desvigne-Nickens P, Dimond E, et al. Changing hearts and minds: improving outcomes in cancer treatment-related cardiotoxicity. *Curr Oncol Rep* 2019;21:9.
- [13] Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377:1119–31.