Cardiac Dysfunction Due to Cancer Therapy
Finding New Directions

Sergey Ryzhov, Sanjeev Francis, Douglas B. Sawyer

Cardiac toxicity of cancer therapies remains an important clinical problem, despite decades of investigation. The prevention, surveillance, and treatment of cardiac toxicity are areas of active research, stimulated by recent attention from the National Institutes of Health. This has brought new energy and novel methods to the table. For patients facing treatment of cancer, no one size fits all, and several teams of investigators have tried to identify genetic variables or biomarkers that might predict the risk for cardiac injury by anthracyclines and allow for a more personalized approach that allows for a cancer patient to receive the maximal benefit of these powerful chemotherapies at minimal risk. These studies have identified many molecular pathways that may be important determinants of cardiotoxicity and have led to recent proposals for use of genetic testing in this setting.1

As with any biomarker study, it will be critical that these findings are validated in a larger cohort. Using a specific IgE cut-off resulted in a sensitivity and specificity of 69% and 68%, whereas an IgE/IgG1 cut-off showed modest improvement to 75% and 74%, respectively. Although promising, it is not clear that this would perform well as a useful screening biomarker in clinical practice. Future research will clarify whether IgE levels add value to previously described risk prediction models incorporating troponin, myocardial strain imaging on echocardiography, and clinical risk factors.4,6

The proposed mechanisms of anthracycline and trastuzumab cardiotoxicity are distinct though clearly additive. Given the patient population studied, it is difficult to know whether IgE levels are implicated in the cardiotoxic effect of one or both chemotherapies. Future studies may provide clarity in this regard. It is important to note and perhaps somewhat disappointing that the authors did not find any diagnostic biomarkers that tracked with the development of cardiac dysfunction in this high-throughput proteomic screen.

Despite these limitations, the finding of an inverse relationship between circulating IgE and the cardiotoxicity of cancer therapy represents a novel finding that prompts a careful re-evaluation of our knowledge of the role of humoral immunity in heart disease. IgE, made in plasma cells, regulates immune system function through actions on Fc receptors for IgE (FcεRI) receptors expressed in several cells involved in regulating immune responses. This study suggests that one or more of these may be important in the cardiac response to injury.

The interaction of IgE with high-affinity Fc receptor I for IgE (FcεRI), expressed on mast cells, results in release of cytokines and growth factors (eg, interleukin-8 [IL-8] and tumor necrosis factor alpha [TNFα]) and biogenic amines (eg, histamine).7 Many of these factors may be involved in the regulation of numerous, sometimes opposite processes in normal and injured myocardium. Although IL-8 released from IgE-stimulated mast cells5 may contribute to inflammation through promotion of neutrophil infiltration,9 IL-8 directly increases survival of endothelial cells and promotes angiogenesis.10 The IgE-sensitized mast cells produce TNFα, which has been shown to activate matrix metalloproteinases and contribute to cardiac remodeling11 and cardiomyocyte apoptosis.12 However, TNFα also has been shown to mediate a cytoprotective response to LPS-induced cardiomyocyte injury through induction of autophagy.13 Moreover, the tissue level of TNFα is a crucial determinant of positive versus negative TNFα-induced signaling in cardiomyocytes.14

Histamine has been implicated in the pathogenesis of chronic heart failure, and histamine receptors antagonists might improve cardiac function.15-17 There is some evidence, however, that higher levels of serum IgE are associated with improved prognosis in patients after myocardial infarction, which has been attributed to increased histamine release from mast cells.18,19 In this context, it is interesting that histamine deficiency in histidine-decarboxylase knockout mice has increased cardiac injury after myocardial infarction.20

Monocytes express both high- and low-affinity IgE receptors. IgE-induced cross-linking of FcεRI on monocytes results...
inhibition of phagocytosis, the first step in antigen presentation in association with major histocompatibility complex class I or class II molecules to stimulate antigen-specific T cells. Anthracycline-induced death of cardiac cells, followed by release of antigen from necrotic cells, and differentiation of monocytes into antigen-presenting cells may promote induction of T cell-mediated cytotoxicity. In this context, the prevention of myeloid antigen-presenting cell activation may represent one of the potential positive effects of high level of IgE.

Direct modulation of immune system function is an exciting and relatively new direction in cancer therapy, with the rapid development of immunomodulatory agents (eg, PD-L1 [programmed death-ligand 1] inhibitors and CTLA-4 [cytotoxic T-lymphocyte-associated protein 4] inhibitors) that are now being used in melanoma, nonsmall cell lung cancer, and renal cancer, to name a few. Cardiotoxicity because of myocarditis seems to be a rare complication of this class of treatments. As such, the role of the immune system in cancer and cardiotoxicity is drawing greater interest.

There will come a day when a cancer patient can be successfully treated without threat to their heart. Continued attention to this problem, and support for innovative investigation such as that by Beer et al, will help bring us closer to that destination. The cardio-oncology community has some new directions to pursue—let’s get going!

Disclosures
None.

References

Key Words: Editorials ● anthracyclines ● attention ● cardiotoxicity ● genetic testing ● immune system
Cardiac Dysfunction Due to Cancer Therapy: Finding New Directions
Sergey Ryzhov, Sanjeev Francis and Douglas B. Sawyer

Circ Res. 2016;119:1055-1056
doi: 10.1161/CIRCRESAHA.116.309902
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/119/10/1055

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/