Cardiac Biomarkers and Early Detection of Cardiotoxicity

Daniel Lenihan, MD[1], Benjamin D. Humphreys, MD[2]

[1] Division of Cardiovascular Medicine, Vanderbilt University, Nashville, Tennessee, United States

[2] Washington University School of Medicine, St. Louis, Missouri, United States

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An outstanding opening lecture by Thomas Wang, MD, Chief of the Division of Cardiovascular Medicine at Vanderbilt University Medical Center, outlined the field of biomarkers in cardio-oncology. Dr Wang has a long history of clinical investigation into the utility and prognosis of novel biomarkers in cardiovascular disease and his perspective on the role of biomarkers in cardio-oncology was invaluable and served to set the goals very high for the development of clinical knowledge in this area. He identified that the epidemiology of cardiac disease in cancer patients is compelling and the numbers of cancer survivors is ever increasing. He further recognized that the gaps between clinical care, clinical research and education are substantial and need to be narrowed. There is an opportunity for precision medicine, utilizing genetic determinants to correctly guide treatment, that is ever present in cardio-oncology. Furthermore, he outlined that there are unanswered questions that truly require innovative clinical/translational research to improve that care of patients with cancer.

Dr Wang provided an overview of where cardiovascular prevention utilizing biomarkers plays a crucial role in cardio-oncology [1]. Furthermore, several unique metabolites may aid in assessing the prognostic utility of a combination of markers, especially those markers of cardiac stress [2]. Taken together, the promise of biomarkers in the discipline of cardio-oncology is bright but a lot of challenging clinical research is needed to carefully answer the important outstanding questions.

Benjamin D. Humphreys MD
Division of Nephrology
Washington University School of Medicine
660 S. Euclid Ave., CB 8126
St Louis, MO 63110
e-mail: humphreysbd@wustl.edu

Correspondence:
Daniel J. Lenihan, MD
Division of Cardiovascular Medicine
Vanderbilt Heart and Vascular Institute
1215 21st Ave South, Suite 5209, Nashville, TN 37232.
e-mail: daniel.lenihan@vanderbilt.edu

Dr Wang was followed by Daniela Cardinale, MD, PhD who is a worldwide leader in the cardiac biomarker investigation in cardio-oncology patient. She is the Director of the CardiOncologyUnit at the European Institute of Oncology in Milan, Italy. She presented:

The practical use of cardiac biomarkers to optimally treat cardiac issues in cancer patients

Dr Cardinale presented elegant data about the utility of high sensitivity troponin I in a variety of cardio-oncology patient populations to identify those at high risk for the development of cardiac dysfunction [3]. Furthermore, she reported cardiac outcomes in a large group of patients that had been followed for many years at her institution and the importance of the appropriate treatment of heart failure with cardioprotective medications [4]. She presented several specific case studies that illustrated how the measurement of cardiac biomarkers can be integrated into assessments of left ventricular ejection fraction (LVEF) to form a comprehensive approach to ensuring cardiac safety while patients undergo potentially cardiotoxic therapy. Additionally, Dr Cardinale recently published an extensive and authoritative review of this field [5].

The final lecture in this session was an excellent and thorough review by Dr Ron Witteles who presented:

Can we use cardiac biomarkers to assist in cardiac management with newer targeted based treatment?

Dr Witteles, who is the program director for the internal medicine residency at Stanford University in Stanford, CA, examined the utility of troponin and NT-proBNP to help guide therapy in patients being actively treated with chemotherapy for cancer. He provided an authoritative and careful examination of previously published data regarding those biomarkers assessed during various treatment protocol utilizing anthracyclines, HER2 directed therapy, and anti-vascular endothelial growth factor based chemotherapy. He discussed the limitations of the techniques and the details of study protocols. He fashioned this presentation into a manuscript that has recently been published [6].

The next excellent presentation was from Dr Benjamin Humphreys who is the chief of nephrology at the Washington University School of Medicine in St Louis, Missouri.

Can Novel Biomarkers be Used to Assess Tumor Responsiveness and Risk of Cardiotoxicity?

Current targeted therapies are designed to specifically inhibit a select signaling pathway that drives cancer growth. These drugs are so specific and potent, however, that they also inhibit the same pathway that may be active in healthy organs, leading to toxicity. Three examples of these mechanism-dependent toxicities include anti-angiogenic therapy induced hypertension and proteinuria, and anti-fibroblast growth factor receptor induced hyperphosphatemia. The first two toxicities are consequence of inhibition of vascular endothelial growth factor (VEGF) signaling. In the case of hypertension, VEGF inhibition with drugs such as bevacizumab or sunitinib causes inhibition of VEGF-dependent vasodilation as well as capillary rarefaction. Both of these effects increase afterload and raise blood pressure.

VEGF inhibition in the kidney may lead to proteinuria by acting at the glomerulus, the site of filtration. Healthy podocytes maintain the glomerular filtration barrier, preventing protein from leaking into the nephron. Podocytes express high levels of VEGF during homeostasis, and secreted VEGF acts on glomerular endothelial cells to keep the filtration barrier intact. Disruption of this paracrine signaling pathway leads to barrier dysfunction and proteinuria [7, 8]. Finally, the FGFR pathway in kidney regulates phosphate balance by modulating the degree to which filtered phosphate is reabsorbed in the tubule. FGFR inhibitors cause dose-dependent hyperphosphatemia as a consequence. In preclinical studies, high doses of these drugs caused metastatic calcification in myocardium – lending concern that this may be a new toxicity seen in humans treated with this class of therapy as it moves into the clinic.

Paradoxically, patients that do not develop mechanism-dependent toxicities on targeted therapies may be underdosed [9]. For example, a growing body of evidence suggests that patients developing hypertension while on anti-angiogenic therapies may have superior anti-tumor responses compared to patients that do not develop hypertension [10]. Similar evidence is emerging for patients that develop proteinuria on this class of therapy [11]. Thus the mechanism-dependent toxicities of targeted therapies may serve as pharmacodynamics efficacy biomarkers. Going forward, balancing dosing to achieve maximal anticancer benefit while minimizing mechanism-dependent toxicities represents an important clinical challenge.

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