JACC: BASIC TO TRANSLATIONAL SCIENCE
VOL. 1, NO. 5, 2016
ISSN 2452-302X
http://dx.doi.org/10.1016/j.jacbts.2016.05.008

STATE-OF-THE-ART REVIEW

21st Century Cardio-Oncology

Identifying Cardiac Safety Signals in the Era of Personalized Medicine

Calvin Chen Sheng, MD,[a,b,c] Laleh Amiri-Kordestani, MD,[d] Todd Palmby, PhD,[d] Thomas Force, MD,[a,b,c] Charles C. Hong, MD, PhD,[a,e,f] Joseph C. Wu, MD, PhD,[g,h] Kevin Croce, MD, PhD,[i] Geoffrey Kim, MD,[d] Javid Moslehi, MD[a,b,c]

SUMMARY

Cardiotoxicity is a well-established complication of oncology therapies. Cardiomyopathy resulting from anthracyclines is a classic example. In the past decade, an explosion of novel cancer therapies, often targeted and more specific than conventional therapies, has revolutionized oncology therapy and dramatically changed cancer prognosis. However, some of these therapies have introduced an assortment of cardiovascular (CV) complications. At times, these devastating outcomes have only become apparent after drug approval and have limited the use of potent therapies. There is a growing need for better testing platforms, both for CV toxicity screening and for elucidating mechanisms of cardiotoxicities of approved cancer therapies. This review discusses the utility of available nonclinical models (in vitro, in vivo, and in silico) and highlights recent advancements in modalities like human stem cell-derived cardiomyocytes for developing more comprehensive cardiotoxicity testing and new means of cardioprotection with targeted anticancer therapies. (J Am Coll Cardiol Basic Trans Science 2016;1:386–98) © 2016 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In the last decade, there has been a paradigm shift in cancer treatment from the use of nonselective cytotoxic agents toward targeted therapies aimed at cellular pathways that have been hijacked by the cancer (1). Indeed, in 2015, oncology was a natural choice as the initial focus of the U.S. government Precision Medicine Initiative, a $215 million investment for individualized approach to patient care (2). Conventional cancer therapies like radiation can lead to cardiovascular (CV) toxicities due to direct, nonselective myocardial injury (3). Paradoxically, several of the novel targeted oncology therapies are associated with a wide spectrum of CV complications in humans, which were unanticipated based on nonclinical (also known as "preclinical") safety studies (4,5). Such discrepancies highlight the

From the [a]Cardiovascular Division, Vanderbilt University School of Medicine, Nashville, Tennessee; [b]Cardio-Oncology Program, Vanderbilt University School of Medicine, Nashville, Tennessee; [c]Vanderbilt-Ingram Cancer Center, Nashville, Tennessee; [d]Center for Drug Evaluation and Research, U.S. Food and Drug Administration, White Oak, Maryland; [e]Research Medicine, Veterans Affairs Tennessee Valley Healthcare System, Nashville, Tennessee; [f]Accelerating Drug Repurposing Incubator, Vanderbilt Institute for Clinical and Translational Research, Nashville, Tennessee; [g]Cardiovascular Division, Department of Medicine, Stanford University School of Medicine, Stanford, California; [h]Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, California; and the [i]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. The views expressed in this article do not necessarily represent an official position of U.S. Food and Drug Administration. Dr. Wu has received funding from Sanofi; and sits on the scientific advisory board of Stem Cell Theranostics. Dr. Force has consulted for Ariad and Bristol-Myers Squibb. Dr. Moslehi has consulted for Novartis, Pfizer, Bristol-Myers Squibb, Takeda, Ariad, Acceleron, Vertex, Incyte, Rgenix, and Verastem. Dr. Croce has received funding from Ariad; and has consulted for Ariad, Bristol-Myers Squibb, The Medicines Company, Abbott Vascular, and St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 30, 2016; revised manuscript received May 21, 2016, accepted May 23, 2016.

limitations of current nonclinical strategies in predicting cardiotoxicities.

Here, we discuss new insights on CV safety in the development of novel targeted anticancer drugs. Successful and efficient drug development is predicated on establishing nonclinical models that can be high-throughput, cost-effective, and comparable to human physiology for the purposes of clinical efficacy and safety. In addition, these models must help in understanding mechanisms of CV toxicities and strategies for CV toxicity protection. We explore drug-induced cardiotoxicity testing strategies and review the existing nonclinical models (in vitro, in vivo, and in silico), which focus on identifying CV complications with high mortality risk such as sudden cardiac death secondary to arrhythmia and heart failure (**Figure 1**). In particular, we highlight recent advances in human pluripotent stem cell-derived cardiomyocytes (PSC-CMs) as a revolutionary in vitro model that can improve cardiotoxicity assessment via personalized medicine and discuss the merits of in vivo and in silico models. Combining data from these respective methods will ensure a better translation to improving patient safety. Last, we conclude with a discussion of the clinical implications of monitoring and reducing CV toxicities gleaned from nonclinical studies.

THE EMERGENCE OF CARDIO-ONCOLOGY

Over the past several decades, improved understanding of the cellular and molecular biology underlying various types of cancer has led to rapid advancements in drug discovery and treatment efficacy. From 1991 to 2012, the overall cancer death rate declined by 23% (6). In the United States alone, there were 14.5 million cancer survivors in 2014, with a projected 19 million survivors by 2024 (7). Cardio-oncology (CV and cardiometabolic care of cancer patients), also called oncocardiology, has emerged as a new medical discipline for several reasons. First, cancer survivors are at risk of CV disease because CV disease is prevalent in the general population. Second, both conventional and novel cancer therapies are associated with CV and metabolic toxicities (**Table 1**). These adverse sequelae include acute and chronic CV toxicities and include a variety of complications such as cardiomyopathy, coronary and peripheral vascular disease, conduction abnormalities, thrombosis, hypertension, and metabolic disorders (4,8). However, because novel cancer drugs can revolutionize treatment and prolong life, cardiotoxicity risk must be carefully weighed against the overall benefit of cancer treatment.

Within the same class of "targeted" therapies, the CV toxicity can be complex. This is illustrated in the case of small molecular inhibitors targeting tyrosine kinase pathways (so-called TKIs or tyrosine kinase inhibitors), used for the treatment of chronic myeloid leukemia (CML). Imatinib, a first-in-class TKI targeting the ABL1 kinase, which is aberrantly activated in CML, revolutionized treatment by roughly doubling the 5-year survival rates of newly diagnosed CML to 89% (9). Subsequently, second- (nilotinib, dasatinib, and bosutinib) and third- (ponatinib) generation TKIs were developed for CML treatment. Initially, these TKIs were developed to overcome imatinib resistance, but given their greater potency against ABL1 kinase, they were positioned for front-line therapy in CML. However, while imatinib carries minimal CV risk, dasatinib is associated with pulmonary hypertension, and nilotinib is associated with hyperglycemia and vascular events (5). Ponatinib held great promise as an ideal TKI for CML treatment given its potent activity in all patients, including those who had developed resistance to other TKIs. Indeed, in late 2012, ponatinib achieved approval through the U.S. Food and Drug Administration (FDA) Accelerated Approval pathway. However, in the fall of 2013, in a subsequent phase 2 study, at a median follow-up of 28 months, 19% of patients had serious vascular events, including cardiovascular (10%), cerebrovascular (7%), and peripheral vascular (7%) events, leading to transient suspension of ponatinib marketing in the United States (10). Nevertheless, given ponatinib's efficacy in TKI-resistant patients (and specifically, for one "gatekeeper" mutation, BCR-ABL1^{T315I}), the sale of ponatinib resumed, although under narrower indications, with a boxed warning regarding adverse vascular events.

The experience with TKIs in CML generates several important issues that apply to all new cancer therapies. A TKI with a novel mechanism that demonstrates unprecedented activity in disease areas of highly unmet need has a benefit-to-risk acceptability profile that is different from the second-generation drug in that same class. As other drugs with similar mechanisms are developed for the same cancer type, it is expected that there will be an improvement in the safety profile. To achieve this goal, a more robust CV monitoring plan needs to be implemented during the nonclinical and early clinical trials of newer compounds of the same class (**Table 2**). Finally, understanding the mechanisms of CV toxicities that do

ABBREVIATIONS AND ACRONYMS

CML = chronic myeloid leukemia

CRISPR = clustered regularly interspaced short palindromic repeats

CTCAE = Common Terminology Criteria for Adverse Events

CV = cardiovascular

FDA = Food and Drug Administration

hERG = human ether-à-go-go-related gene

NRVM = neonatal rat ventricular myocytes

PSC-CM = pluripotent stem cell-derived cardiomyocyte

TKI = tyrosine kinase inhibitor