JACC: CASE REPORTS VOL. 1, NO. 3, 2019

EDITORIAL COMMENT

Tales of the Unexpected

The Value of Case Reports in CardioOncology*

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If we do not want to be overwhelmed and struck numb by rare events as if they were unprecedented ones; fortune needs envisaging in a thoroughly comprehensive way.

—Seneca (1)

As Seneca, the Roman Stoic philosopher, recognized greater than 2,000 years ago, even rare scenarios require focus to share knowledge and develop strategies to prevent future events. Cardio-oncology is an emerging subspecialty with the principal aim of enabling patients to safely receive optimal cancer treatments while ensuring early detection and treatment of cardiovascular toxicities. The remit, however, is ever-expanding: attention was initially focused on left ventricular dysfunction related to anthracycline and HER2-targeted therapy, but toxicities are now recognized to span the full breadth of cardiovascular medicine, including vascular, cardiometabolic, and electrophysiological abnormalities (2). In contrast to conventional chemotherapies, typically directed against common cell proliferation machinery, newer anticancer drugs (also known as biologics) target specific molecules relevant for tumor growth, expansion, or regulation of the immune system. The development and use of kinase inhibitors, which affect multiple groups of kinases across different tissues, have resulted in a spectrum of on- and off-target effects on the cardiovascular system (e.g., hypertension, cardiomyopathy, pro-coagulopathy, QT-prolongation), with an impressive potential for new and different forms of toxicity (3). In this setting, cardiovascular toxicity may emerge late, remain unrecognized, and result in serious complications that require prompt and specialist management.

Drug development in oncology is rapid, with agents passing swiftly from initial Phase I and II trials, through Phase III studies and into clinical use, far more quickly than for other drug indications, including cardiovascular (4). In 2017, for example, there were >2,000 immuno-oncology agents against >200 targets (5), leading to an increase in active immunotherapy trials from 1,502 to 2,250 in just 12 months (6). The relative share of new drug approvals, which was 5 times greater for cardiovascular drugs than for oncology drugs in the 1980s, is now 2.5 times greater for oncology (3). The reasons for this finding are multifactorial, but relative investment in oncology drug development has risen exponentially.

One byproduct of this successful and productive pipeline for drug development is that recognition of cardiovascular toxicities is often delayed, frequently only late after completion of Phase III studies (7). A number of reasons may contribute to this phenomenon, including the exclusion of patients with preexisting cardiovascular disease from clinical trials, lack of baseline comprehensive cardiovascular data collection, and significant limitations of the adjudication systems (e.g., Common Terminology Criteria for Adverse Events) used for oncology trials that lack contemporary definitions of cardiovascular conditions and make communication with cardiology teams a challenge. Finally, the concomitant and/or sequential use of multiple agents with potential toxicity in "real-world" patients may result in

*Editorials published in *JACC: Case Reports* reflect the views of the authors and do not necessarily represent the views of *JACC: Case Reports* or the American College of Cardiology.

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ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2019.07.018

unexpected patterns of toxicity, resulting in risk stratification and clinical management challenges.

It is therefore essential that clinicians are able to disseminate the experiences of these rare cardiovascular events to highlight potential toxicity signals and create a scientific exchange of information related to diagnostic and treatment approaches: publication of case reports offers an ideal platform for this. An excellent example is immune checkpoint inhibitor-related myocarditis in which the first case report was published in 2016, five years after ipilimumab was first approved for use in metastatic melanoma (8). In the subsequent year, there were 77 reported cases (9), and within 24 months of the initial reported case, recommendations were published for diagnosis and management of this potentially fatal toxicity (10). Through the simultaneous launch of *JACC: Case Reports* and *JACC: CardioOncology*, we now have an outlet and bridge for both publicizing initial cardiovascular safety concerns and subsequently sharing more detailed insights from research in cardio-oncology.

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In this issue of *JACC: Case Reports,* Mandal et al. (11) describe a successful diagnosis and treatment of a cardiac lymphoma using tailored dose-attenuated chemotherapy, showing the importance both of multimodality imaging and multidisciplinary team work within cardio-oncology. Cardiac tumors represent arguably the most traditional part of cardio-oncology; however, the complexity of diagnosis and management highlights the evolution of both specialties and even more so the importance of collaboration. Publication of diagnostic and management strategies used in relatively uncommon clinical scenarios may aid future clinical decision-making as well as facilitate communication between specialists. Cardiovascular specialists may benefit from the insights presented in this case showing the value of multimodality imaging for establishing a differential diagnosis and guiding biopsy together with the critical importance of establishing the tissue diagnosis. Distinct therapeutic strategies involving different oncology specialists will be used for treatment of lymphoma versus sarcomas versus metastatic tumors, and timely referral based on the findings of cardiac imaging may prove to be critical. Cardiac tumor boards are increasingly being established in large tertiary/quaternary centers to enable shared decision-making for these complex patients, with representation from cardio-oncology, cardiac imaging, medical and radiation oncology, hematology, cardio-thoracic surgery, and histopathology as well as immunology.

The landscape of oncology is changing, and cardiologists are struggling to keep up. Publication of case reports in cardio-oncology may provide an invaluable early warning system to enable strategies to be developed to prevent and manage a tsunami of emerging cardiovascular toxicities.

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KEY WORDS cardio-oncology, case report