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EDITORIAL COMMENT

Proarrhythmia and Oncotherapy

So Much To Be Done!*

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Proarrhythmia has been recognized as a potential side effect of antiarrhythmia drugs since the clinical application of quinidine for the treatment of arrhythmias (1). Attention to the proarrhythmia effects of nonantiarrhythmia drugs is attributable to a seminal observation by the late Lou Cantilena and his colleagues, who described torsades de pointes (TdP) arrhythmia in patients, mostly young female patients taking terfenadine (the first nonsedating antihistamine, marketed as Seldane [Marion Merrell Dow, Kansas City, Missouri]) together with erythromycin, and published case reports in 1990 (2). For 2 decades, the focus of many drug safety experts was on the identification and prevention of drug-induced TdP, a potentially life-threatening form of ventricular tachycardia, culminating in the publication of an internationally ratified regulatory document that guides the premarket assessment of drugs for the risk of TdP arrhythmia (3). Nearly every drug with significant bioavailability undergoes rigorous preclinical evaluation for the risk of TdP as an off-target effect. However, it was recognized that certain classes of drugs, such as oncotherapeutics, may not be able to follow this path because the protocols required testing in healthy individuals (4). With or without thorough pre-market testing, information on the risk of TdP is adjudicated by experts and is readily available to clinicians and the public on a website or free mobile app (5).

The system dedicated to the identification of signals for proarrhythmia is now challenged by the large number of oncotherapeutics in development, as well as by the potential for combinations of therapy in a wide variety of patient types and disease states. In addition, the internationally harmonized system of assessment for proarrhythmia focuses only on ventricular arrhythmias and not on atrial arrhythmias, conduction system disturbances, or drug-device interactions, all of which have the potential to harm patients. New approaches are needed.

In this issue of *JACC: CardioOncology*, Ye et al. (6) report on a comprehensive evaluation of publicly available data on adverse drug reactions and specifically on the risk of cardiac rhythm disturbances in patients treated with protein kinase inhibitors. More than 3 million case reports involving 32 protein kinase inhibitors were evaluated. More than 23,000 cases of atrial fibrillation and more than 66,000 cases of cardiac arrhythmia were evaluated from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS). Statistical analyses identified heightened risk for atrial fibrillation associated with exposure to ibrutinib, ponatinib, ribociclib, trametinib, osimertinib, and idelalisib. In addition, there was a signal for ventricular proarrhythmia with nilotinib and bradyarrhythmia with alectinib and crizotinib.

This study is an important read for clinicians in cardio-oncology, and it carries a similar message to the paper that Lou Cantilena published so many years ago on the risks of terfenadine. Off-target cardiac effects of noncardiac drugs are common and clinically important. Although left ventricular systolic dysfunction has been a focus, arrhythmias are also becoming an increasingly recognized complication of oncotherapy. Clinicians may not be familiar with FAERS; they should realize that this system is only a part of the post-market surveillance system worldwide, and it requires voluntary reporting by clinicians

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via MedWatch form 3500. Many clinicians are unfamiliar with adverse event reporting, and most of my colleagues have never filed a form 3500, even if they dealt with an adverse drug effect in their practice. What is in FAERS may well be the tip of an iceberg, because active surveillance for TdP in Germany revealed a nearly 10-fold increase in case detection when compared to passive, voluntary reporting of proarrhythmias (7). We not only need to be active contributors to the existing safety databases, we should be advocating for better safety assessment both pre- and post-market.

What should the cardio-oncology clinical community do in the face of a dizzying number of therapies being developed worldwide in thousands of clinical trials and potentially affecting millions of patients? A first step is to recognize that they cannot do this alone. TdP risk was addressed by a collaboration between global regulators, academics, and industry under the umbrella of the Cardiac Safety Research Consortium (8), an organization that has already hosted discussions related to safety in oncology drug development. A second step is to encourage the reporting of unexpected adverse events to the U.S. Food and drug Administration in the United States (9) or to local regulatory agencies in other parts of the world. Passive surveillance with greater participation is better than passive surveillance with limited participation. Third, and the greatest challenge, is to organize the data on safety in a way that is real time, robust, and freely available for analysis. FAERS is updated only on a quarterly basis, so it is not hard to imagine a signal of concern going undetected while numerous patients are placed at risk during the interval between updates. Our electronic records systems need to be harnessed for this purpose, and almost certainly, artificial intelligence can contribute to reducing the huge data burden post-market surveillance entails.

There is also enormous scientific opportunity, as Ye et al. (6) point out. Dissecting the biology of proarrhythmia associated with the inhibition of protein kinases will undoubtedly have beneficial effects for our understanding of the risk for cardiac arrhythmias and potentially their treatment. This is not the first call for using observations made in cardio-oncology to drive cardiovascular drug discovery. Bellinger et al. (10) pointed out the opportunities inherent in these observations but also the challenges of replicating the phenotypes in vitro and in vivo, as well as the need to dissect the on-target and off-target effects of the therapies.

I had the opportunity to meet Lou Cantilena and hear of his passion for drug safety. Ironically, Lou died in a plane crash in my state of Indiana several years ago. I wish we had been able to write this editorial together, because he would have added eloquence and experience to the message. Keen observation is important, but those keen observations must lead to actionable knowledge, and that knowledge to better systems of care. The very nature of the specialty of cardio-oncology requires a constant balance of risk and benefit. Utilizing our existing safety reporting systems is a great start, but we should all be looking for ways to expand our knowledge and improve our methods.

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