Reviews

This Introduction is the first article in a new thematic series on Cardiovascular Toxicities/Effects of Anticancer Therapeutics, which includes the following articles:

### Introduction to Cardiotoxicity Review Series

Molecular Mechanisms of Cardiovascular Toxicity of Targeted Cancer Therapeutics
The Vulnerability of the Heart as a Pluricellular System: Lessons From Unexpected Triggers of Heart Failure in Targeted Cancer Therapy
Cardiovascular Disease: Hidden Killer in Adult Survivors of Childhood Cancer
Emerging Anticancer Strategies: Is There Cause for Concern? Yes!

Thomas Force, Guest Editor

### Introduction to Cardiotoxicity Review Series

Thomas Force

Nowhere have greater strides been made in the treatment of lethal diseases than in oncology. Part of this stems from the fact that in the majority of cancers, tissue is available to clinicians and researchers. This has allowed the identification of specific mutations and/or gene amplifications that drive cell transformation and cancer progression. Not surprisingly, these proteins have become central targets for anticancer drug therapy.

Many of these mutations or amplifications are in tyrosine kinases or, to a lesser extent, serine-threonine kinases, and identification of these has created an explosion in the development of “targeted therapeutics,” drugs aimed specifically at the causal or contributory molecule(s) driving the cancer. Targeted therapeutics directed at specific kinases are either small molecule inhibitors or monoclonal antibodies. This field has had some notable clinical successes, including the monoclonal antibody trastuzumab (Herceptin) that targets the human epidermal growth factor receptor 2 (H-receptor, known as ErbB2 in the mouse), which is overexpressed in many breast cancers. Similarly imatinib (Gleevec) is a small molecule inhibitor of the Bcr-Abl fusion protein that is created by the balanced translocation that produces the Philadelphia chromosome. Bcr-Abl is causal in >90% of cases of chronic myeloid leukemia, and imatinib has revolutionized treatment of this disease.

Targeted therapeutics not only promised the possibility of better efficacy but also less toxicity. This is because specific factors driving cancer progression are targeted, whereas traditional chemotherapeutics typically target processes important in many types of normal cells (eg, modulators of the cell cycle, thus affecting many types of proliferating cells). However, although many targeted agents are very well tolerated, some have shown significant cardiotoxicity. We believe it is critical to understand both why these agents can be so effective in cancer treatment and how they induce cardiotoxicity, especially because development of therapeutics targeting kinases has become a major focus of drug development in the pharmaceutical industry, second only to drugs targeting G protein-coupled receptors. Indeed, there are more than 1000 kinase inhibitors presently in development and tens of thousands of patients, including children, are receiving these agents as part of clinical trials.

The first part of this series will examine the molecular mechanisms that drive cardiotoxicity of targeted therapeutics, focusing on the small molecule, ATP-competitive inhibitors (by far the largest class), and will discuss what can be done at the molecular level to predict and potentially prevent the toxicity. In addition, we will try to give the reader a sense of the potential power of these agents as research tools to identify novel functions of kinases in the heart (ie, a chemical biology approach) because these agents are potent inhibitors of normal, as well as mutated, kinases.

In the second part of the series, Gilles de Keulenaer will take a closer look at the cardiotoxicity of trastuzumab.
We hope the series, which will be highly translational in nature, will give the reader a thorough understanding of how these agents work at the molecular level, why they can induce cardiac and vascular toxicity, what might be done to prevent and/or treat it, how one can predict potentially problematic new agents, and how the agents can be used by basic researchers to identify heretofore unknown functions of signaling pathways and cardiotoxicity.

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**References**


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