Future CARDIOLOGY

OPINION
Special Focus Issue: Cardio-oncology

Improving prediction of cardiovascular complications of cancer therapy: what does the future hold?

"...growing research efforts, particularly in the areas of mechanisms of cardiotoxicity, individual susceptibility and early markers of injury, give us an insight of what may be coming to the clinical arena."

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"Prediction is very difficult, especially if it's about the future."
– Niels Bohr

In the era of improved cancer outcomes, increased therapeutic options, and growing population of cancer survivors, the acute and long-term adverse effects of cancer therapies are becoming increasingly relevant. Improved tools for cardiovascular (CV) risk prediction may allow physicians to better tailor cancer therapy, identify patients who would benefit from close CV monitoring and consider CV protective approaches prior, during and after cancer treatment.

Ongoing major advances in oncology therapeutics, with vast repertoire of new molecules targeting key tumor pathways, have brought unprecedented opportunities to combat cancer and occasionally manifested unexpected CV side effects pointing to important, unexplored interactions between new therapeutics and CV homeostasis. Probably most widely known example is the one of trastuzumab, HER2-targeted monoclonal antibody used in the treatment of HER2-positive breast cancer, that can cause left ventricular (LV) dysfunction and heart failure in susceptible individuals [1,2]. Major strides have been made to limit CV toxicity of trastuzumab and related new HER2-targeted agents, pertuzumab and ado-trastuzumab emtansine, including mandatory assessment of cardiac function prior and during treatment with HER2-targeted agents, and holding or stopping therapy in patients with abnormal LV systolic function [3–5].

These clinical practice recommendations evolved from clinical trial experiences and represent an important step forward in recognizing and limiting cardiotoxicity or HER2-targeted therapies, nevertheless a number of questions continue to challenge daily clinical practice. They include the concerns that stopping and holding HER2-therapy in patients whose cardiac function is only mildly reduced may compromise their cancer outcomes (to improve what may be a low cardiac risk). On the other side of the coin are the patients with normal cardiac function at baseline who continue to experience cardiotoxicity and

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sometimes symptomatic heart failure, pointing to the limitations of the use of LV ejection fraction as a single determinant of CV risk related to HER2-targeted therapy. This example illustrates critical deficiencies in our ability to accurately predict risk of cardiotoxicity and identify susceptible individuals prior to treatment: an advancement in this field would provide us with an opportunity to personalize therapy and improve patients' experience and outcomes.

What is the future of the prediction of CV risk associated with cancer therapies?

There is no single answer to this complex question but growing research efforts, particularly in the areas of mechanisms of cardiotoxicity, individual susceptibility and early markers of injury, give us an insight of what may be coming to the clinical arena. Highlighted are several areas that herald the path of improved CV risk prediction.

"While we still may be quite far away from having a single, 'precision' biomarker, strong collaboration between cardiology and oncology in discovering and validating links between cancer therapeutics and cardiovascular system offers an unprecedented potential to bring us closer to molecular prediction of cardiotoxicity."

CV risk prediction based on the mechanisms of CV toxicity (related to conventional & novel cancer therapeutics)

Although anthracyclines have been widely used as part of oncology regimens since the 1960s limited information is available regarding individual susceptibility to cardiotoxicity related to this group of drugs. Early investigations recognized their cumulative cardiac effects leading to limited anthracycline doses in many oncology regimens [6]. In addition, cardiac function screening became a standard prior to the initiation of anthracycline-based treatments, but beyond these recommendations clinical practice tools for CV risk stratification/optimization remain extremely limited [7]. Novel research implicating the role of topoisomerase Top2-beta in the pathogenesis of doxorubicin-induced cardiotoxicity [8] provides an important insight that may lead to the development of novel strategies to detect individual susceptibility or early disease onset. For example, preliminary studies demonstrated correlation of elevated Top2-beta levels in the peripheral blood and anthracycline-induced cardiotoxicity, thus suggesting that Top2-beta may represent a biomarker of cardiotoxicity risk [9].

The explosion of novel targeted cancer therapeutics, increasingly utilized in treatment of different cancers, alone or in combination with conventional therapies, has also been associated with increased recognition of their CV effects. In addition to LV dysfunction seen in the example of trastuzumab and HER2 targeted therapies, a number of VEGF-pathway inhibitors have been associated with hypertension and, in some instances, cardiomyopathy and heart failure [10]. Clinical observations of CV toxicity related to targeted cancer therapeutics have provided surprising insights about the links between cancer and the CV system, thus forming the foundation for the growing research into the molecular mechanisms underlying cancer biology and CV homeostasis. Some of the successes of these efforts include deepened understanding of the role of HER2 receptor and its agonist, neuregulin, in heart failure [11–13], as well as the mechanistic insights into hypertension and cardiomyopathy related to VEGF signaling pathway inhibitors where the roles hypoxia-inducible factor and myocardial vascular dysfunction have been implicated [10,14,15].

Despite these and other major advances in our understanding of molecular pathways shared by the cancer and CV system, no single molecule or pathway has yet entered into clinical arena as a potential marker of CV toxicity related to targeted therapies. Current and future challenges lie in the increasing number of multitargeted inhibitors affecting different pathways potentially important for CV system, as well as the lack of effective models to study CV effects before they become clinically relevant [16]. The National Cancer Institute and National Heart Lung and Blood Institute-sponsored workshop on cancer treatment-related cardiotoxicity summarized some of the highly promising opportunities in this field including collaborative approach to development and testing of cancer therapeutics, inclusion of CV phenotypes in clinical trial design and further 'bench-to-bedside-to-bench' research [17]. While we still may be quite far away from having a single, 'precision' biomarker, strong collaboration between cardiology and oncology in discovering and validating links between cancer therapeutics and CV system offers an unprecedented potential to bring us closer to molecular prediction of cardiotoxicity.

Markers of cardiac injury: biomarkers & cardiac imaging

Different pathways may underlie cardiac effects of the individual cancer therapeutics but cancer-treatment-induced cardiac injury often shares similarities with other cardiac insults, such

as ischemia or inflammation. This rationale underpins the studies investigating the use of the known biomarkers of cardiac cell injury and death in detecting and predicting treatment-related CV toxicity. A number of reports have documented predictive value of cardiac troponins in adult and pediatric patients, mostly receiving anthracycline-based chemotherapies [18–21]. However, the use of high-sensitivity troponin to predict cardiotoxicity in the USA remains mostly in the research sphere. Further investigations into assay platforms and reproducibility, definition of range values associated with specific oncology regimens, and validation of these values against diverse clinical phenotypes, are critically needed before troponin can be established as a clinical biomarker of CV toxicity.

Following the rationale that development of cancer treatment-related cardiomyopathy likely shares common pathophysiology with cardiomyopathies related to environmental or other insults, a number of biomarkers implicated in cardiac remodeling and heart failure have been investigated in cardio-oncology. Some of the prominent examples include BNP (including N-terminal pro-BNP), GDF-15, MPO, PlGF, soluble Flt-1 and galectin-3 but their definitive role in prediction of CV toxicity remains to be determined [22,23]. At the same time, growing understanding of the mechanisms of heart failure and emerging markers of cardiac remodeling [24] continue to offer opportunities to improve our understanding of the pathogenesis of cancer treatment-cardiomyopathy and to identify novel biomarkers of risk.

Several important advances in the field of cardiac imaging have also been utilized to measure cardiac injury and predict clinical CV toxicity, often in combination with biomarkers. Global longitudinal strain by speckle tracking has shown promise in the detection of subclinical and clinical myocardial injury in cancer patients during or post chemotherapy [25,26], and a number of studies in adults with cancer have demonstrated abnormal strain with cardiotoxic cancer therapy exposure [27]. In the pediatric population, recent studies have also demonstrated abnormal strain in long-term childhood survivors [28]. Developments in other imaging techniques such as cardiac magnetic resonance also offer intriguing promise in imaging myocardial fibrosis and cell injury *in vivo* [28–32] but have yet to be validated in prospective clinical cohorts of patients with cardiotoxicity.

Exciting studies using combination of mechanistic biomarkers and imaging measures have recently showed to increase predictive accuracy of cardiotoxicity [23,29], thus opening the door to future investigations using complementary markers of CV toxicity.

Clinical risk prediction models

Epidemiologic research offers an opportunity to assess CV burden of cancer therapy in large cohorts of patients and investigate risk of CV toxicity through its associations with demographic, clinical, cancer and cancer therapy-related factors [33–35]. A recently published clinical risk score developed using the Surveillance, Epidemiology and End Results (SEER)-Medicare database identified women with breast cancer who were at increased risk for cardiomyopathy and heart failure after receiving adjuvant trastuzumab [36]. This model, developed in real-life older population, importantly complements the risk scores developed using clinical trial participants data [4]. Future steps need to include prospective validation of the existing models and development of cancer therapy-specific registries and databases with CV data elements. These efforts will result in improved understanding of the epidemiological and clinical risk profiles associated with cardiotoxicity risk. In turn, they will allow further development of clinical risk scores for patients undergoing cancer therapies, as well as prediction of CV risk in the large and growing population of cancer survivors.

Summary of future prediction

Research advances spanning basic science, translation and imaging techniques, and clinical and population trials continue to improve our knowledge about cancer treatment-related CV toxicity and have been setting a broad platform for validation of known and novel markers. Active collaborations across research and clinical disciplines will be critically needed to move these 'candidates' into 'ideal biomarkers' and advance our clinical practice [37]. A number of stakeholders are taking part and moving the field of cardio-oncology forward [17,38]. We look forward to an exciting journey toward improved prediction of CV risk associated with cancer treatment and improved CV precision treatment and prevention.

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