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Editorial

Chemotherapy, cardiovascular disease and precision medicine: Toward truly individualized treatment for precision cardio-oncology?

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The purpose of medical art is health, the goal is to get it.
[Aelius Galenus]

According to the World Health Organization cardiovascular disease and cancer are the leading causes of death worldwide [1,2]. Because of the increasing number of cancer survivors, chemotherapy-induced cardiomyopathy is however becoming an important issue. Indeed, the prevalence of end-stage heart failure (HF) induced by chemotherapeutic agents has increased to 3%, and cardiovascular disease (CVD) is the leading cause of long-term morbidity and mortality among cancer survivors. In light of this, the discipline of cardio-oncology is growing rapidly paralleled by the growing number of cancer survivors and expanding awareness that cardiovascular (CV) toxicity is one of the most important complications of cancer therapy. Recognized CV adverse effects of cancer chemotherapies are various and include chemotherapy related cardiac dysfunction (CRCD), hypertension, adverse vascular effects, cerebrovascular disease, coronary artery disease, thromboembolism, diastolic dysfunction, and arrhythmias. Most importantly, chemotherapy may lead to acute, subacute or late cardiotoxicity. The most common subacute cardiac adverse effects are pericarditis and myocarditis, while the adverse effects of chronic cardiotoxicity are typically dilated cardiomyopathy, left ventricular (LV) systolic dysfunction and congestive HF [1] (Fig. 1). Anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin and mitoxantrone), are cardiotoxic type I drugs commonly used in the treatment of solid tumors (i.e., breast cancer, osteosarcoma, etc.) and hematologic malignancies (Hodgkin/non-Hodgkin lymphoma, acute lymphoblastic leukemia, etc.), which can cause significant LV disease (LVD). Anthracycline-related LVD has been considered to be dose-dependent, cumulative, and progressive, manifesting as decreased LV ejection fraction (LVEF) and, ultimately, symptomatic HF in up to 5% of patients [2]. Instead, the cardiotoxic type II drug trastuzumab has effects that are unrelated to the cumulative dose and whose side effects seem to be often reversible after treatment discontinuation. The molecular mechanisms of cardiotoxicity are still not completely understood, but it seems that the foundation of cardiac injury is mitochondrial damage. This can arise from an increased production of reactive oxygen species [3], alterations in cardiac energy metabolism, ultrastructural changes of cardiomyocytes, suppression of myofilament protein synthesis and topoisomerase II beta-mediated DNA damage. Nevertheless chemotherapy represents a mainstay in the management of cancer because of its ascertained capability to improve outcomes in many conditions. Despite several studies, both basic and clinical, on the mechanisms and features of chemotherapeutics cardiotoxicity, uncertainty remains regarding the incidence of this adverse event and its possible clinical predictors. Cumulative dose, administration scheme, and concomitant radiotherapy have been associated in several studies with the development of cardiotoxicity. An integrated approach combining biomarkers as well as imaging data may prove useful at predicting chemiotherapy-related CV toxicity. Potential markers of cardiotoxicity have been investigated in small studies. These include markers of endothelial dysfunction, markers of myocardial ischemia, as well as markers of oxidative stress and inflammation [4–6]. However, the exact timing of biomarkers measurement, the variability in techniques to detect these markers and the small sample sizes of the pertinent studies make these methods very variable to predict the cardiotoxicity of chemotherapy. Recently, genetics is playing an important role in predicting the cardiotoxic effect of chemotherapy.

The article by *Lee* et al. published in this issue of the *International Journal of Cardiology* extends our knowledge providing important insights concerning non-anthracycline cardiotoxicity [7]. This meta-analysis examined 35 studies taking into account a total of 219 single-nucleotide polymorphisms (SNPs) in 80 genes, 11 antineoplastic agents from five drug classes such as tyrosine kinase inhibitor, monoclonal antibody, antimetabolite, alkylating agent and immunomodulatory agent and 5 types of CV toxicities such as decreased left ventricular ejection fraction (DLVEF), hypertension, arrhythmia, venous thromboembolism (VTE) and cardiovascular disease (CVD). The authors indicate that 34% of SNPs in 40 genes are significantly associated with risk of particular antineoplastic related CV toxicities. Among these findings, the polymorphisms rs1136201 and rs1058808 of HER2 are potential predictors for

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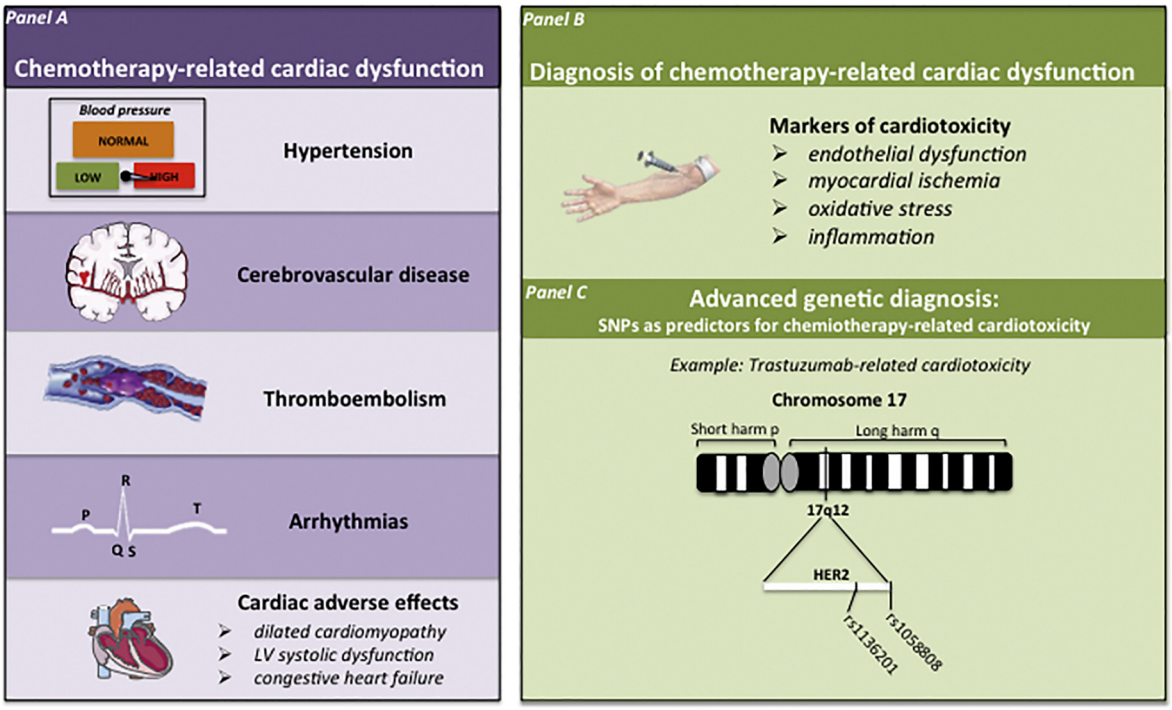

Fig. 1. Transition toward precision cardio-oncology entails recognition of the main features of chemotherapy-related cardiac dysfunction (panel A), their accurate detection (panel B), and comprehensive shift toward molecular diagnosis for individualized risk-prediction and therapy (panel C).

trastuzumab-related cardiotoxicity (Fig. 1C). This paper is in line with the attempts to understand the genetic contribution in the setting of cardiovascular toxicity, a topic that has increasingly been explored over the past few years. This meta-analysis has several strengths. Firstly, included studies examining the role of HER2 SNPs had included a relatively large sample of participants. Secondly, all studies had used an objective outcome of LVEF and last, had a relatively homogenous definition of decreased LVEF. These findings are highly clinically relevant because they can be exploited to provide predictions, toward the development of individualized treatments for populations or patient groups and, to a more limited extent, for individual subjects, keeping in mind that precision medicine, a relatively new concept, refers to the tailoring of medical treatment to the individual characteristics of each patient. Patient-tailored therapy is indeed now possible, especially given the availability of different chemotherapy regimens, safer anthracycline analogs such as liposomal doxorubicin, and cardioprotective medications such as carvedilol, dexrazoxane, or enalapril [8,9]. Moreover, given the number of patients who receive these agents and the relative frequency of CV toxicity, it seems logical that more advanced approaches such as human genome-wide association studies or whole exome or whole genome sequencing should be undertaken with proper population stratification [10]. Some weaknesses of the paper by *Lee* et al. must however be borne in mind. First of all there was a high level of heterogeneity in the reported analyses. The authors themselves recognized that while they attempted to explore the causes of such heterogeneity for all the results, the small number of studies for each SNP, which in most cases were fewer than five studies, limited further analysis using meta-regression. As such, findings should be interpreted with caution due to the limited statistical power to detect bias.

In conclusion, a new approach based on the use of genetics together with some cardiac biomarkers could help oncologists predict cardiotoxicity due to chemotherapy. Further trials are necessary to confirm their use in clinical practice and the collaboration between oncologists and cardiologists will play an increasingly important role to improve the care of patients with cancer.

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Conflicts of interest

Prof. Biondi-Zoccai has consulted for Abbott Vascular and Bayer.

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