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EDITORIAL COMMENT

Genetic Susceptibility for Anthracycline-Induced Cardiomyopathy

Novel Insights by Combining SNPs*

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Anthracyclines are a class of chemotherapeutic agents widely used in the treatment of various types of cancer. However, anthracycline-induced left ventricular dysfunction and heart failure, which can occur up to decades after exposure, remains a significant concern in cancer survivors.[1] Through large cohort studies over the past decades, several risk factors for anthracycline-induced cardiomyopathy have been identified, including higher cumulative anthracycline dose, concomitant treatment with chest radiotherapy, younger age at diagnosis, and the development of traditional cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia.[2] However, these risk factors fail to fully capture individual risk, as some patients develop cardiotoxicity at lower anthracyclines doses, whereas others treated with high doses do not. This discrepancy in susceptibility to the toxic effects of anthracyclines suggests that genetic variation might play a role.

Over the past years, genome-wide association studies have identified and replicated several single nucleotide polymorphisms (SNPs) implicated in DNA damage response, oxidative stress, iron metabolism, sarcomere dysfunction, mitochondrial dysfunction, and anthracycline metabolism and transport that were associated with anthracycline-induced cardiomyopathy.[3,4] The effect size of the SNPs identified thus far in anthracycline-induced cardiomyopathy are weak to moderate, which limits their clinical use in individual patients. Testing for genetic variants to inform long-term cardiomyopathy surveillance is currently not recommended by the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) because it is unclear whether the presence or absence of a genetic variant would reclassify patients to a different risk category then when defined by clinical risk factors only (ie, anthracycline dose and chest radiotherapy dose).[5] The European Society of Cardiology guideline on cardio-oncology also currently does not recommend routine genetic testing for cardiotoxicity risk stratification in adult cancer patients.[6]

In this issue of *JACC: CardioOncology*, Sharafeldin et al[7] took a clever step by combining multiple SNPs on the same gene that together may have a much larger effect on gene expression compared with individual SNPs. The investigators performed whole exome sequencing to test over 7,000 genes in the Children's Oncology Group (COG) discovery cohort and used logic regression—a type of machine learning that combines SNPs with Boolean operators (AND, OR NOT)—to identify gene-level SNP combinations that were associated with anthracycline-induced cardiomyopathy. They subsequently used ordinal logistic regression adjusted for clinical risk factors and principal components to test gene-level associations with anthracycline-induced cardiomyopathy (categorized as severe, mild, or no cardiomyopathy).

The main finding of the study was a protective gene-level association for loss of function variants in P2RX7 (Purinergic Receptor P2X7; OR: 0.10), which was successfully replicated in the CCSS (Childhood

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Cancer Survivor Study; HR: 0.65). P2RX7 encodes a purinergic receptor mainly expressed in immune cells but also in cardiac smooth muscle and cardiac endothelial cells.[8] P2RX7 is activated by extracellular ATP released from injured (myocardial) cells and, when activated, promotes inflammatory cell death and induces release of proinflammatory cytokines.[8] Interestingly, P2RX7 activation and the subsequent inflammatory response has been linked to cardiac fibrosis and cardiomyopathy in several studies in humans and animals.[8] Thus, there is biological support for the findings of the study.

However, it is important to note that the gene-level association of P2RX7 was replicated in only 1 (CCSS replication cohort) of the 3 replication cohorts with a much smaller effect size (discovery OR: 0.10, replication HR: 0.65). This could be due to a lack of power in the COG and BMTSS (Blood or Marrow Transplant Survivor Study) replication cohorts compared with the CCSS cohort. It would be valuable to test whether the P2RX7 gene-level association with anthracycline-induced cardiomyopathy can be replicated in other large cancer survivor cohorts. In addition, validation of the biological effect of P2RX7 loss-of-function variants in cancer therapy-induced cardiomyopathy in experimental studies (ie, animal studies or human induced pluripotent stem cell-derived cardiomyocytes) would further strengthen the findings.

To advance the clinical usefulness of genetic testing, future studies may focus on integrating genetic variants or polygenic scores with patient and treatment related risk factors to improve individual prediction for heart failure in cancer survivors.[9] This will be important to assess if and to what extent genetic testing helps to better risk stratify cancer patients for heart failure compared with risk prediction models based on clinical risk factors only. Eventually, such genetic risk prediction models may be used to guide preventive strategies (ie, liposomal anthracyclines, dexrazoxane, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-blockers) and to personalize long-term cardiomyopathy surveillance strategies. International collaboration will be critical to develop, externally validate, and implement these genetic risk prediction models.

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