A new role for genetics in cancer therapy-induced cardiomyopathy

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Recent advances in the development of cancer therapies have increased long-term survival and prognosis. However, the increased burden and prevalence of harmful side effects, including cardiomyopathy, have emerged alongside those therapeutic benefits. In particular, there have been increases in cancer therapy-induced cardiomyopathy (CCM)—a heart condition which may compromise a patient's quality of life and long-term prognosis after the cancer has been treated. And while certain clinical risk factors for CCM are known, the factors that contribute to an individual's susceptibility remain a mystery. A team of investigators from Brigham and Women's Hospital and Harvard Medical School finds that genetics may be at play and elucidates rare genetic variants which may influence risk for developing CCM. Results are published in *Circulation*.

"With improved long-term survival of cancer patients and advancement in cancer therapies, we have been seeing more patients with cardiotoxicity from cancer therapy," said Yuri Kim, MD, Ph.D., lead author and cardiology fellow at HMS. "Our study is the first to consider the association between rare genetic variants in a large set of cardiomyopathy genes and the occurrence of CCM."

To investigate the role of genetics in CCM, Kim and colleagues recruited 213 adult and child patients with CCM from three academic centers in Philadelphia, Madrid and London. These patients had diverse background malignancies, including breast cancer and leukemia. A majority of patients (90 percent) received anthracyclines—a cancer drug

known to cause cardiotoxicity in up to 10 percent of patients. Next generation sequencing was conducted in all patients to identify rare pathogenic variants in CCM susceptibility genes. The team then compared results with reference populations.

Interestingly, investigators discovered that truncating variants in the gene TTN (TTNtv), which encodes the protein titin, were significantly increased in CCM patients compared to control cohorts. Clinical outcomes were also significantly impacted in patients with TTNtv.

"Adverse outcomes from cardiomyopathy, including heart failure, atrial fibrillation and impaired myocardial recovery were more prevalent in adult CCM patients with TTNtv than those without," noted Kim.

One notable highlight in this study was the researchers' ability to reproduce and validate their clinical findings in animal models. Mice with the TTNtv variant were also found to have increased susceptibility to the cardiotoxic effects of anthracyclines, displaying significantly decreased levels of left ventricular function compared to control.

While the authors are optimistic about their findings, they acknowledge certain limitations to their study, including the use of data from participants in the Cancer Genome Atlas, some of whom may have also developed CCM, as a control group. Inclusion of CCM patients in the control group would lower, not inflated statistical significance, and thus the reported findings represent a conservative association between genotype and CCM. In addition, they note that while the patient cohorts consisted of individuals of various ethnic backgrounds, Caucasian participants comprised nearly 80 percent of the group.

These caveats aside, the authors are excited about the potential clinical implications of their work. In light of the limited strategies that currently exist for diagnosing CCM in cancer patients, they hope that the

identification of genetic risk factors may open up a new path to identify and better manage cancer patients at high risk for CCM.

"We believe that identification of cancer patients with high CCM risk based on genetic testing will enable health care providers to tailor their cardiovascular and oncological monitoring and treatment regimen, which will ultimately improve patients' cardiovascular and oncological prognosis," said Kim.

"Our next steps are to find ways to directly mitigate the adverse effects of TTNtv on cardiac biology, which would benefit not only CCM patients, but many cardiomyopathies that are caused by these prevalent and damaging human mutations," said co-corresponding author Christine E. Seidman, MD, the director of the Cardiovascular Genetics Program and a cardiovascular medicine specialist at the Brigham, as well as the Thomas W. Smith Professor of Medicine at HMS.

More information: Garcia-Pavia, P. et al. "Genetic Variants Associated with Cancer Therapy-Induced Cardiomyopathy" *Circulation*, 2019.

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