DSEN Abstract

Identification of Pharmacogenomic Markers of Anthracycline-Induced Cardiotoxicity in Children

Summary

Anthracycline-induced cardiotoxicity (ACT) is a serious adverse drug reaction limiting anthracycline use and causing substantial morbidity and mortality. Our aim was to identify genetic variants associated with ACT in patients treated for childhood cancer. This study identified a major genetic cause of anthracycline-induced cardiotoxicity in children.

Key messages

Patients who are at a high risk of anthracycline-induced cardiotoxicity can be identified before treatment begins.

Predictive testing will enable clinicians, patients, and their families to better evaluate the risks of anthracycline treatment and incorporate preemptive protective measures to minimize harm.

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What is the issue?

- Anthracyclines are chemotherapeutic agents that are widely used to treat over 70% of childhood and adult cancer and have helped to significantly improve cancer survival rates.
- However, up to 16% of anthracycline-treated patients develop cardiomyopathy and heart failure.
- This heart failure is often resistant to therapy and has a near 80% mortality rate if severe.
- The pathophysiology of anthracycline cardiotoxicity is not yet fully understood, and there was no prior means to predict in whom the toxicity will occur.

Objective

- To identify genetic variants that are highly associated with anthracycline-induced cardiotoxicity in children by enrollment of those affected and matched control patients (those who got the same drugs but without toxicity), followed by in depth clinical characterization of their cardiotoxicity and genomic analyses.

How was the study conducted?

- Pediatric patients who have received anthracycline-chemotherapy were enrolled in the study from adverse drug reaction surveillance sites in pediatric oncology treatment centres across Canada in collaboration with Canadian Pharmacogenomics Network for Drug Safety (CPNDS) surveillance network, and a replication cohort of patients was recruited in the Netherlands.
- Patient biological samples and clinical data collected and analysed and patient DNA samples tested for nearly 1 million genetic variants throughout the genome.
- Statistical genetic analyses were conducted with the clinical and genetic data to identify factors that predispose patients to developing anthracycline cardiotoxicity.

What did the study find?

- The study identified a variant in the RARG gene that is highly associated with anthracycline-induced cardiotoxicity. This variant disrupts the normal activity of the gene, and is critical for heart regeneration and regulation of a key drug target of anthracyclines.
- Patients who carry this variant are SIX TIMES more likely to develop anthracycline-induced cardiotoxicity.
- These findings were subsequently replicated in two additional independent cohorts of patients, including patients of worldwide ancestries and Canadian First Nations patients.

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