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Genetic determinants of Anthracycline cardiotoxicity – ready for the clinic?

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We read with great interest the thorough and informative review by Aminkeng et al.[1] addressing the possibility that genetic screening may reduce the rate of anthracycline-induced cardiotoxicity (ACT). Predictors of anthracycline toxicity including genetic predisposing single nucleotide polymorphisms (SNPs) and biomarkers are lacking in the clinical setting. Therefore, the identification of reliable genetic predictors of ACT, as described by Aminkeng and colleagues, would be broadly welcomed as the beginning of personalised, genomic based management of long-term cardiotoxicity. However, we contend that more evidence supporting the utility of these markers for patient stratification is required before clinical guidelines can be issued.

Aminkeng and colleagues described a number of genetic variants and recommended genomic testing for RARG rs2229774 (S427L), SLC28A3 rs7853758 (L461L) and UGT1A6 rs17863783 (V209V) be performed for paediatric childhood cancer patients receiving doxorubicin or daunorubicin. Importantly, the evidence to support this was defined as "*moderate evidence reflecting a reduced confidence in scientific evidence and expert opinion"*. Moreover, these three genetic variants have only an association or correlation with the incidence of ACT within a particular patient cohort, and there is no functional validation of causation.

The genetic variants of SLC28A3 rs7853758 and UGT1A6 rs17863783 in particular require further validation since both do not alter protein-coding for these genes and UGT1A6 rs17863783 is intronic in some alternate transcripts. There are other potential explanations for an apparent contribution to anthracycline cardiotoxicity including altered RNA splicing, or the SNP being representative of a haplotype that includes variants that do alter protein function[2,3]. Neither SLC28A3 or UGT1A6 variants create splice acceptor or donor sites and so do not result in alternate transcripts. Furthermore, we note that neither SLC28A3 nor UGT1A6 are expressed in the heart, which suggests their contribution to cardiotoxicity is not related to direct effects in cardiac tissue. Without complete functional studies the downstream effects of SLC28A3 and UGT1A6 sSNPs and their clinical impact remains speculative.

Care must be taken when determining the clinical significance and utility of these genetic variants. The mechanisms of anthracycline pharmacodynamics and metabolism are complex. We are concerned about clinical recommendations arising from these studies including the suggestions for long-term follow up for high, moderate and low risk patients. More particularly, there is the potential for alteration of dosage scheduling based on insufficient genetic evidence. This could result in potentially under-dosing in patients with these alleles.

Thus, whilst we strongly support the identification of genetic predictors of anthracycline toxicity, without sufficient validation of the functional effects of these variants, it is premature to suggest patient care, particularly late effect screening and upfront changes in therapy, be considered. With the ever-reducing cost of large-scale genetic analysis and the increasing scientific collaboration between the world's leading research hubs, it is highly feasible that cohorts of sufficient size and cardiac phenotyping can be assembled to establish unequivocal evidence of genetic predictors of anthracycline toxicity. Furthermore, an international prospective trial that evaluates the relevance of the described SNPs (or others that are identified) and provides a standardized framework for detailed variant classification[4] is needed to guide clinical practice. From such international collaborations and clinical trials can flow robust data to support changes in the use of anthracyclines based on genotyping. It is important to recall that whilst anthracyclines can cause this concerning toxicity long-term, they are also one of the most efficacious therapies available to clinicians across multiple tumours within the paediatric population. Recommendations to reduce exposure should be based on the strongest possible evidence, lest this comes at the cost of increased incidence of treatment failure.

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Genes
RARG
SLC28A3

Table 1. List of genes with entries in the Guide to Pharmacology.
This Table of Links list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan et al., 2016), and are permanently archived in The Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c,d,e]Alexander et al., 2015a,b,c,d,e).