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Pharmacogenomic Screening for Anthracycline-Induced Cardiotoxicity in Childhood Cancer

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LETTER TO THE EDITOR

Pharmacogenomic screening for
anthracycline-induced cardiotoxicity in
childhood cancer

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We read with interest the comments from Craig *et al.* [1] regarding our recently published clinical practice guidelines for pharmacogenomic testing in anthracycline-based cancer treatment [2]. Craig *et al.* [1] specifically posit that a functional and mechanistic understanding of pharmacogenomic associations is required prior to the issuance of clinical practice guidelines.

RARG rs2229774 (S427 L), *SLC28A3* rs7853758 (L461 L) and *UGT1A6* rs17863783 (V209 V) have been shown to be significantly and strongly associated with anthracycline-induced cardiotoxicity in three independent well-characterized paediatric patient populations [3–5]. The overall strength of the pharmacogenomic associations (*P*-values and odds ratios [OR: effect sizes] with 95% confidence intervals [CIs]) were as follows: *RARG* rs2229774 – *P* = 5.9×10^{-8} , OR (95%CI) = 4.7 (2.7–8.3); *SLC28A3* rs7853758 – *P* = 1.6×10^{-5} , OR (95%CI) = 0.36 (0.22–0.60); and *UGT1A6* rs17863783 – *P* = 2.4×10^{-4} , OR (95%CI) = 4.30 (1.97–9.36) [3–5].

Functional studies of *RARG* rs2229774 have tied this variant to dysregulation of topoisomerase IIb, in line with the role of TOP2B in anthracycline-induced cardiotoxicity [3, 6, 7]. As pointed out by Craig *et al.* [1], *UGT1A6* and *SLC28A3* may not be expressed in the heart. However, the robustness of these associations suggests that they exert at least indirect effects on cardiac tissue, possibly through anthracycline biotransformation in other tissues. Notably, *UGT1A6* rs17863783 (V209 V) is a variant in the *UGT1A6**4 haplotype that has been shown to have reduced (30–100%) glucuronidation activity *in vitro* [8–10], linking this variant to impaired drug metabolism. Anthracycline metabolites undergo glucuronidation and a reduction in this metabolic step may lead to accumulation of reactive oxygen species and toxic alcohol metabolites [11, 12]. The *SLC28A3* rs7853758 variant is suggested to be a *cis*-expression quantitative trait locus for this drug transporter, which is broadly selective for anticancer drugs and contributes to the influx of anthracyclines in cancer cell lines [13]. The L461L minor allele has been

associated with reduced *SLC28A3* expression in multiple cell lines [14, 15], which may therefore reduce cardiac cell exposure to anthracyclines and hence exert its protective effect.

Despite the robust pharmacogenomic associations that have been demonstrated as well as replicated, we agree that studies in additional cohorts, including patients of different ancestries, would be helpful in developing a more fulsome understanding of all the genomic predictors of anthracycline-induced cardiotoxicity and protection against this serious adverse drug reaction. As Craig *et al.* [1] point out, anthracycline treatment remains one of the most important therapeutic options for a variety of paediatric cancers. We recognize, that for clinicians, the primary focus is the efficacy and cure rates in cancer patients. However, a significant proportion of patients are affected by this devastating and life-threatening adverse effect and, as such, it is imperative to balance the benefits of treatment against the risks of toxicity. It is important to note that our current recommendations do not specify dose reductions (until such time as trials are done to compare both toxicity and drug effectiveness at varying doses) and the recommendations explicitly advocate for adherence to the current standards of care [2]. We recommend low-risk therapeutic options that include increased screening frequency for cardiotoxicity and monitoring for cardiovascular diseases such as portal vein thrombosis, hypertension, diabetes, hypercholesterolaemia, dyslipidaemia, atrial fibrillation, myocardial infarction and hypolipidaemia. As studies are conducted to determine how best to ensure anthracycline effectiveness while minimizing harm, these clinical practice guidelines, like all guidelines, should be revised as new evidence mounts. The challenge with the treatment of any population of patients with severe disease is to ensure that human variability in response (both harm and effectiveness) is studied more robustly to better understand what is best for each patient and not assume that all patients should be treated in the same way. This is not in contrast to current population-based treatment approaches as both such trials and precision medicine trials can and should co-exist. It is not just new drug discovery that has resulted in substantive gains in cancer survivorship, but also improved use of existing agents. With the discovery of robust pharmacogenomic associations for treatment-related adverse effects, however, there is also an ethical quandary of when to act. Specifically, there is a reasonable ethical concern that not acting on robust results such as these is not in keeping with the best interests of the patients where the severity of the adverse drug reaction can be fatal.

In summary, we have reported on existing functional and mechanistic work to understand how anthracyclines cause cardiotoxicity and the relationship to existing genomic findings. We agree wholeheartedly that additional mechanistic understanding of the identified associations will enhance the utility of the pharmacogenomics of adverse drug reactions and this is an ongoing focus of our research. Through international collaborations, we and others are studying patient-specific stem-cell derived cardiomyocytes to assess genotype–phenotype relationships related to anthracycline cardiotoxicity. The validity of these pharmacogenomic associations is strengthened by their robustness and replication to a degree that justifies inclusion in a clinical practice guideline that summarizes the evidence and highlights at the same

time the specific need for additional evidence [2]. The level of evidence ascribed to each variant in these guidelines was generated in accordance with the Grading of Recommendations Assessment, Development and Evaluation working group guidelines [16, 17]. This in turn led to therapeutic recommendations such as increased frequency of monitoring and aggressive screening and management of cardiovascular diseases as these are options where the benefits of pharmacogenomic screening clearly outweigh risks of the specific recommendations.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: F. A., C.J.D., A.P.B., M.R.H. and B.C.C. have applied for patents based upon some of the work related to the predictive markers of adverse drug reactions to anthracyclines described in this letter; S.R.R., S.H., M.J.R., S.S., D.B. and U.A. declare no conflict of interest. The funding agencies had no role in the writing of the letter.

References

- 1 Craig LA, Ekert PG, Conyers R, Elliott DA. Genetic determinants of Anthracycline cardiotoxicity – ready for the clinic? *Br J Clin Pharmacol* 2017; 83: 1141–2.
- 2 Aminkeng F, Ross CJ, Rassekh SR, Hwang S, Rieder MJ, Bhavsar AP, *et al.* Recommendations for genetic testing to reduce the incidence of anthracycline-induced cardiotoxicity. *Br J Clin Pharmacol* 2016; 82: 683–95.
- 3 Aminkeng F, Bhavsar AP, Visscher H, Rassekh SR, Li Y, Lee JW, *et al.* A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer. *Nat Genet* 2015; 47: 1079–84.
- 4 Visscher H, Ross CJ, Rassekh SR, Sandor GS, Caron HN, van Dalen EC, *et al.* Validation of variants in *SLC28A3* and *UGT1A6* as genetic markers predictive of anthracycline-induced cardiotoxicity in children. *Pediatr Blood Cancer* 2013; 60: 1375–81.
- 5 Visscher H, Ross CJ, Rassekh SR, Barhdadi A, Dube MP, Al-Saloos H, *et al.* Pharmacogenomic prediction of anthracycline-induced cardiotoxicity in children. *J Clin Oncol* 2012; 30: 1422–8.
- 6 Zhang S, Liu X, Bawa-Khalife T, Lu LS, Lyu YL, Liu LF, *et al.* Identification of the molecular basis of doxorubicin-induced cardiotoxicity. *Nat Med* 2012; 18: 1639–42.
- 7 Maillet A, Tan K, Chai X, Sadananda SN, Mehta A, Ooi J, *et al.* Modeling doxorubicin-induced cardiotoxicity in human pluripotent stem cell derived-cardiomyocytes. *Sci Rep* 2016; 6: 25333.
- 8 Nagar S, Zalatoris JJ, Blanchard RL. Human *UGT1A6* pharmacogenetics: identification of a novel SNP, characterization of allele frequencies and functional analysis of recombinant allozymes in human liver tissue and in cultured cells. *Pharmacogenetics* 2004; 14: 487–99.

- 9** Saeki M, Saito Y, Jinno H, Sai K, Kaniwa N, Ozawa S, *et al.* Genetic polymorphisms of UGT1A6 in a Japanese population. *Drug Metab Pharmacokinet* 2005; 20: 85–90.
- 10** Krishnaswamy S, Hao Q, Al-Rohaimi A, Hesse LM, von Moltke LL, Greenblatt DJ, *et al.* UDP glucuronosyltransferase (UGT) 1A6 pharmacogenetics: II. Functional impact of the three most common nonsynonymous UGT1A6 polymorphisms (S7A, T181A, and R184S). *J Pharmacol Exp Ther* 2005; 313: 1340–6.
- 11** Minotti G, Licata S, Saponiero A, Menna P, Calafiore AM, Di Giammarco G, *et al.* Anthracycline metabolism and toxicity in human myocardium: comparisons between doxorubicin, epirubicin, and a novel disaccharide analogue with a reduced level of formation and [4Fe-4S] reactivity of its secondary alcohol metabolite. *Chem Res Toxicol* 2000; 13: 1336–41.
- 12** Sacco G, Giampietro R, Salvatorelli E, Menna P, Bertani N, Graiani G, *et al.* Chronic cardiotoxicity of anticancer anthracyclines in the rat: role of secondary metabolites and reduced toxicity by a novel anthracycline with impaired metabolite formation and reactivity. *Br J Pharmacol* 2003; 139: 641–51.
- 13** Nagasawa K, Nagai K, Ohnishi N, Yokoyama T, Fujimoto S. Contribution of specific transport systems to anthracycline transport in tumor and normal cells. *Curr Drug Metab* 2001; 2: 355–66.
- 14** Dimas AS, Deutsch S, Stranger BE, Montgomery SB, Borel C, Attar-Cohen H, *et al.* Common regulatory variation impacts gene expression in a cell type-dependent manner. *Science* 2009; 325: 1246–50.
- 15** Zeller T, Wild P, Szymczak S, Rotival M, Schillert A, Castagne R, *et al.* Genetics and beyond—the transcriptome of human monocytes and disease susceptibility. *PLoS One* 2010; 5: e10693.
- 16** Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336: 924–6.
- 17** Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, *et al.* Going from evidence to recommendations. *BMJ* 2008; 336: 1049–51.