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Association of Thiopurine S-methyltransferase (TPMT) and cathechol O- methyl-transferase (COMT) variants with cisplatin induced ototoxicity in a UK cohort of paediatric cancer patients

Introduction: Cisplatin is a chemotherapeutic agent used to treat solid malignancies in childhood. Although highly effective, its therapeutic index is narrow and neuro- and nephrotoxic side effects occur frequently. Ototoxicity occurs typically as bilateral, irreversible, high-frequency sensorineural hearing loss in at least 50% of children. There is significant inter-individual variability in predisposition to cisplatin in-duced hearing loss and the differences in toxicity are greater than the variability in pharmacokinetics, de-spite equivalent doses. Genetic variants of several genes have been proposed to contribute to this variability, but the evidence for most of these genes remains controversial as many results could not be reliably replicated to date. The most promising candidates were *TPMT* and *COMT*(1). The aim of this study was to determine the occurrence of TPMT and COMT in a UK cohort with cisplatin induced hearing loss.

Methods: We conducted a retrospective, multicentre cohort study. Included were children ≤ 16 years who had received cisplatin after 31st December 2000 and with at least one audiogram after completion of treatment. Audiograms were graded according to Common Terminology Criteria for Adverse Events (CTCAE). SNPs for TPMT (rs12201199, rs1142345 and rs1800460) and COMT variants (rs4646316 and rs9332377) were selected and a TaqMan Gene assay was conducted according to the manufacturer's instructions. Quality control procedures were applied to the genotype data. For the initial analyses of association, an additive mode of inheritance was assumed. First, a univariate ordinal logistic regression model was fitted to each non-genetic factor and SNP in turn. Next, multivariable ordinal logistic regression models were fitted for each SNP in turn. For each SNP, two models were fitted. The first model ('baseline') included covariates to represent all non-genetic factors with $p<0.25$ univariately. Stepwise variable selection was applied to this model to remove any covariates no longer significant in the multivariable model. The second model ('genetic) was the same as the baseline model but also included a covariate to represent the SNP. The likelihood ratio test was applied to compare the two models and thus assess for statistical significance of the SNP. P-values were adjusted using Bonferroni correction for multiple testing, comparing to significance level 0.05 and adjusting for 5 tests. To reduce bias arising from ototoxicity grading, we also performed sensitivity analyses by dichotomising outcomes and using logistic regression models for analysis.

Results: 116/149 childhood cancer patients from six UK paediatric oncology centres fulfilled the inclusion and quality control criteria and were included in the analysis. 78/116 had developed hearing loss. In the multivariable analysis clinical factors associated with an increased risk of hearing loss were female gender, cranial irradiation, total dose of cisplatin and concomitant use of vincristine. None of the 5 SNPs were found to be statistically significant risk factors.

Conclusion: Our study confirmed known clinical risk factors, however the genetic association of TPMT and COMT variants described by Ross et al (1) could not be demonstrated in our cohort. These findings are consistent with those of others (2,3). It is likely that the reason for this controversy is multifactorial and likely influenced by factors such as the retrospective nature of the studies, the sample sizes and the heterogeneity of study populations with regards to diagnoses, age range, dosage, treatment schedules, hearing grading, co-administration of concurrent ototoxic agents and cranial irradiation. Further studies in a larger and carefully phenotyped cohort are required to investigate the genetic factors influencing cisplatin induced hearing loss.

(1) Ross et al. (2009). Nat Genet 41: 1345-9.
(2) Yang et al. (2013). Clin Pharmacol Ther 94: 252-9.
(3) Hagleitner et al. (2014). PLoS ONE 12.