426 Genetic Variations Associated with Overall and Progression-Free Survival in Multiple Myeloma Patients Treated with Thalidomide Combinations

Oral and Poster Abstracts
Oral Session: Myeloma - Biology and Pathophysiology, excluding Therapy II
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It is anticipated that inherited single nucleotide polymorphisms (SNPs) in genes involved in drug absorption, distribution, metabolism and excretion influence individual response to thalidomide therapies in Multiple Myeloma. We extracted peripheral blood DNA from 631 myeloma patients of European descent enrolled in the MRC Myeloma IX trial who had received induction thalidomide (50-200mg). We genotyped 3404 SNPs selected in 983 candidate genes that may influence myeloma disease response, toxicity, and/or survival, on a “Bank on a Cure” (BOAC) Affymetrix® true-tag array. The BOAC array is a custom genotyping chip focused on coding and predicted regulatory SNPs. Quality control (QC) measures were applied on the resulting genotype data such that individual samples failing a chip call rate (> 95%), and SNP assays with missing data (< 0.05%) or with extreme departures from Hardy-Weinberg equilibrium ($p > 10^{-5}$) were excluded from the statistical analysis. We then performed 2-way log rank tests under recessive, dominant and trend genetic models for each SNP which passed QC for both overall survival and PFS on the training and validation sets. Our training set consisted of 379 myeloma patients from the intensive pathway of the Myeloma IX trial who received CTD (cyclophosphamide, thalidomide, dexamethasone), with a validation set of 252 myeloma patients from the non-intensive pathway who received an attenuated CTD regime. Although the overall and progression-free survival is shorter for individuals in the non-intensive arm in comparison to the younger and fitter patients in the intensive arm, we expected variants influencing overall survival and PFS related to thalidomide to associate with outcome, if both pathways were analysed separately. We looked for significant associations (log-rank chi-squares > 6.5, $p > 10^{-3}$) across both the training and validation sets, and discounted associations where the number of cases in any one genotype group <10. We detected significant cross validating associations in the survival analysis with genes involved in double-strand break repair: *BLM*, *LIG1*, *MRE11A*, *SHFM1* and *RAD51L3*, and also saw associations with genes important in response to DNA damage stimulus: *CYP19A1*, *GSTA4* and *MGST1*, along with other notably associations in genes *NFKBIE*, *NFKB1* and *SELL*. We saw cross validating SNP associations in the progression-free survival analysis in genes including the cytokines: *IL10*, *IL13*, as well as *NFATC1*. In this large study we have seen results indicating that genetic variation plays a role in both overall and progression free survival following thalidomide treatment in multiple myeloma patients, and in doing so we have highlighted SNPs and pathways that may be important and informative in predictive classification of patients for overall survival and PFS following treatment with thalidomide containing regimes.

Disclosures: No relevant conflicts of interest to declare.