Aim: Neurotoxicity is known of both platinum and taxane agents. Factors associated with increased risk of peripheral neuropathy (PN) include cumulative dose and comorbidity. Individual genetic susceptibility may play a role. Applying GWAS methods to patients of ICON7 (NCT00483782), a phase 3 ovarian cancer trial of adding bevacizumab to carboplatin and paclitaxel, we evaluated the association of heritable genetic markers with PN.

Methods: Germline DNA from 437 patients were genotyped using an Illumina Omni Platform. In a cumulative-dose/m²-to-toxicity analysis, Cox proportional hazard models generated hazard ratios (HR) and 95% confidence intervals for the development of Grade 2 or higher PN. Baseline clinical multivariate models of toxicity, stratified by treatment arm, were compared with and without inclusion of individual genetic markers through likelihood ratio tests (LRT), assuming an additive genetic inheritance model.

Results: After quality control steps, 396 predominantly genetic European patient samples and 727,683 markers were evaluable. 28% of patients developed Grade 2+ PN. Study country but not pre-existing diabetes was significantly associated with PN in clinical multivariate models; the bevacizumab arm was associated with a trend for increased PN (adjusted HR, aHR, 1.32 (1.0–1.7; P = 0.054). Although no single marker reached genome-wide significance level after adjustment for clinical factors, top identified multiple markers associated with PN were in the pyrin (PYR; P = 9.9x10^{-7}) and RNA editing pathways (REP; P = 1.3x10^{-6} by LRT). In both, the presence of each additional at-risk allele was associated with a doubled odds of developing Grade 2+ PN: for PYR, the top variant had an aHR of 1.92 (95%CI: 1.5-2.5), while for REP, the top variant had an aHR of 2.12 (95%CI: 1.5-2.9). PYR pathway is associated with a caspase-activating platform, the inflammasone, and Schwann cell damage. The REP affects neuronal structure and physiology in several animal model systems.

Conclusions: PYR and REP polymorphisms were the top markers associated with PN in carboplatin-paclitaxel treated ovarian cancer patients. Validation in other trials is warranted.

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