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Session 3 – Poster presentation *S3-17*

THE PHARMACOGENOMICS OF VINCRISTINE-INDUCED PERIPHERAL NEUROPATHY IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS IN SERBIA

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Vincristine (VCR) is one of the key drugs in current treatment protocols for pediatric acute lymphoblastic leukemia (ALL). By destabilization of microtubules, VCR arrests cells in metaphase, inducing apoptosis of malignant cells. VCR also causes axonal degradation and impairment of axonal transport, which leads to vincristine-induced peripheral neuropathy (VIPN). The aim of this study was to determine if the selected genetic variants are associated with the development of VIPN in ALL children treated with VCR in Serbia. This study also aimed to discover candidate pharmacogenomic markers of VIPN in Serbian population. PCR and sequencing-based methodology was used to detect variants in following genes: CYP3A5 (rs776746), CEP72 (rs924607), ACTG1 (rs1135989), MIR3117 (rs12402181) and MIR4481 (rs7896283). Statistical analyses were performed for investigation of their association with VIPN in 56 pediatric ALL patients. Population VCR pharmacogenomics analysis of 17 pharmacogenes from in-house next-generation sequencing data was also done. Data on allele frequency distribution for European population were extracted from public databases. During the treatment, 17.86% of patients developed VIPN. Association analyses have shown that none of the investigated genetic variants contributed to the occurrence of VIPN in our study group. Population pharmacogenomics study didn't reveal valid candidate pharmacovariants for the occurrence of VIPN. Our results suggested that pre-emptive pharmacogenetic testing for VCR is not applicable. More comprehensive approaches are needed to identify panel of genes that could explain the VIPN development after VCR administration in ALL patients. Utilizing better designed GWAS studies and more robust artificial intelligence-based tools would provide a panel of pharmacogenes for pre-emptive tests of VIPN to individualize therapy for ALL in children.

Keywords: vincristine, vincristine-induced peripheral neuropathy, pediatric acute lymphoblastic leukemia, pharmacogenetics, CYP3A5, CEP72, ACTG1, MIR3117, MIR4481

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