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POSTER ABSTRACTS

905.OUTCOMES RESEARCH-LYMPHOID MALIGNANCIES

Germline Determinants of Toxicity and Efficacy in Patients with Large B-Cell Lymphoma Treated with Anti-CD19 Autologous CAR T-Cell Therapy

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Background. Increasing data have demonstrated that acquired genetic aberrations, including *TP53* mutations in the tumor cells and clonal hematopoiesis, can impact the efficacy and/or toxicity of anti-CD19 autologous CAR T-cell therapy (CART) in patients with large B-cell lymphoma (LBCL). Recent data have suggested that germline genetic aberrations, including polymorphisms in *CD19*, *ABCB1*, *MISP* and *CPVL* (Strati P et al, Leukemia 2022) and deleterious germline variants in *STXBP2*, can also affect outcomes in these patients. However, a comprehensive analysis of germline determinants of response and toxicity after CART in this patient population has not yet been described.

Methods. Genome-wide genotyping using the Illumina Genome Screening Array (GSAv2.0) was performed in 170 patients with relapsed or refractory LBCL treated with standard of care axicabtagene ciloleucel in third line and beyond. Response was assessed according to 2014 Lugano criteria. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to ASTCT criteria, and cytopenia according to CTCAE v5. Polygenic risk score (PRS) instruments for blood cell traits and inflammatory markers were obtained from the PGS Catalog and analyzed using PRSice. Risk of poor response and toxicity was estimated using logistic regression models with standardized PRS scores as a continuous variable adjusting for age at diagnosis, gender, and bridging therapy (yes/no). Exploratory genome-wide association study (GWAS) analyses were also performed.

Results. The median age was 58 years, 116 (68%) were male, and 91 (54%) received bridging therapy. Interestingly, increasing PRS for baseline IL-6 levels was associated with decreased risk of CRS grade (G) 2-4 (β: -0.15, 95% CI: -0.30 to -0.013, p=0.030) and ICANS G3-4 (β: -0.21, 95% CI: -0.37 to -0.066, p=0.005). Similarly, increased genetically-predicted monocyte levels decreased risk of ICANS G3-4 (β: -0.16, 95% CI: -0.31 to -0.018, p=0.027). Baseline genetically-predicted monocyte levels were also associated with increased probability of a CR at D90 (β: 0.19, 95% CI: 0.041 to 0.34, p=0.011). For prolonged cytopenia (defined as G3-4 cytopenia ongoing at day 30), risk was increased with increasing PRS for reticulocyte levels (β: 0.29, 95% CI: 0.10 to 0.48, p=0.002). No genome-wide significant ($p<5x10^{-8}$) variants were identified in the exploratory GWAS analyses, however, several loci at $p=10^{-5}$ were located within/near potential biologically-relevant candidate genes. This included an association with prolonged cytopenia for rs111940551 located upstream of *IKZF1*, a regulator of lymphocyte differentiation, and serving as a putative expression quantitative trait loci (eQTL) for this gene. An intragenic variant identified for ICANS G3-4 (rs1149927) was in high linkage disequilibrium (D'=0.97) with a variant previously shown to be associated with brain morphology.

Conclusion. PRS representing baseline levels of several key blood cell traits, particularly monocytes, and inflammatory markers may impact toxicities and efficacy of CART in patients with LBCL. The intriguing finding of an inverse association for IL-6 with both high-grade CRS and ICANS was unexpected and needs further investigation. Larger studies are warranted to confirm these observations and better understand how relevant germline genetic determinants may influence efficacy and toxicity after CART therapy. Elucidating such determinants may help in improving patient selection and in developing strategies to enhance the therapeutic index of CART.

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