

PROTEOMIC PROFILING IN BLOOD IDENTIFIES NOVEL PRETREATMENT AND MECHANISTIC MARKERS RELATED TO INFLAMMATORY ADVERSE EVENTS IN RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA AFTER AXICABTAGENE CILOLEUCEL

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Background Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 CAR T-cell therapy approved for patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) and follicular lymphoma. In the ZUMA-1 pivotal study, Grade ≥ 3 cytokine release syndrome (CRS) and neurological events (NE) were observed in 13% and 28% of patients, with median time to onset of any grade at 2 and 5 days, respectively.¹ Using conventional low-throughput platforms (eg, multiplex ELISA), pretreatment markers, including serum levels of LDH, IL-6, and IL-15, demonstrated a positive association with Grade ≥ 3 CRS and/or NE.² We sought to explore biological mechanisms and novel markers underlying the development of early-onset (within 5 days post-CAR T-cell infusion) Grade ≥ 3 CRS and NE using high-throughput Olink[®] proteomic profiling.

Methods Serum samples collected prior to conditioning chemotherapy (baseline) and immediately prior to CAR T-cell therapy (Day 0) for 142 patients with R/R LBCL treated in ZUMA-1 Phase 2 Cohorts 1, 2, and 4 were analyzed by Olink[®] panels comprising 1,458 markers. Association between marker expression and early Grade ≥ 3 toxicity was evaluated using Wilcoxon test and logistic regression. Weighted gene coexpression network analysis (WGCNA)³ was performed to identify highly coexpressed protein clusters, which were used for gene ontology (GO) analysis for biological interpretation. Machine learning methods were used to select features and build classifiers.

Results Twenty-four patients (17%) experienced Grade ≥ 3 CRS and/or NE within 5 days post-CAR T-cell infusion. Univariate and WGCNA analyses demonstrated that clusters of pretreatment markers were associated with these toxicities; these clusters correlated positively with poor prognosis factors (eg, International Prognostic Index and baseline tumor burden). GO analysis applied to these clusters showed enrichment of proteins involved in metabolic processes and leukocyte activation. Machine learning demonstrated excellent performance (mean AUC > 0.80 in both training and testing runs) of groups of Olink[®] markers in classifying patients with early high-grade toxicity. Further, we observed that IL-1/IL-6 pathway markers (eg, IL-1A and OSMR) were useful in identifying Grade ≥ 3 CRS, while inflammatory endothelial markers (eg, ACE2, CEACAM1, ICAM2, and ADAM15) could classify patients with both Grade ≥ 3 CRS and NE upon axi-cel treatment.

Conclusions Our proteomic analysis supports the relevance of previously described markers. In addition, we have identified potential markers that are mechanistically involved in the development of high-grade toxicity. Safety of CAR T-cell therapy may be improved by optimization of product or conditioning regimen to reduce adverse event-dependent proinflammatory activities while maintaining efficacy.

KS and GT contributed equally.

REFERENCES

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Ethics Approval The study was approved by the institutional review board at each study site and was conducted in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonization. All the patients provided written informed consent.

<http://dx.doi.org/10.1136/jitc-2022-SITC2022.0687>