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POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Clinical Impact of Neoantigen Burden and HLA Loss in Aggressive B-Cell Lymphomas Treated with CD19 CAR T-Cell

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INTRODUCTION: CD19-directed chimeric antigen receptor (CAR-19) T cells have revolutionized clinical outcomes in heavily pretreated patients with aggressive B-cell lymphoma. Notably, emerging evidence suggests that the efficacy of CAR-19 therapy extends beyond direct tumor killing and includes its ability to stimulate and guide the host immune system in the fight against tumor cells. To delve deeper into this crucial aspect, our study utilized whole-genome sequencing (WGS) data to explore the impact of neoantigen burden and *HLA* loss in patients with aggressive large B-cell lymphoma (rrLBCL) who received CAR-19 therapy (WGS; Jain et al. Blood 2022).

METHODS: To characterize the importance of genomic immunogenicity in rrLBCL, we conducted a comprehensive analysis of 61 whole-genome sequencing (WGS) and 54 RNA sequencing samples from 54 rrLBCL patients who underwent CAR-19 therapy. Among these samples, 39 were collected at baseline and 15 at relapse, with samples from 7 patients obtained both before and after treatment. Our analytical workflow defined *HLA* class I mono- or biallelic loss by integrating copy number variants, structural variants, single nucleotide variants, and small insertion-deletion data with allele-specific *HLA* loss information obtained from LOHHLA software. pVACseq algorithm was used to predict the number of clonal neoantigens in each sample, along with the corresponding *HLA* allele presenting each of them.

RESULTS: *HLA* class I loss was detected in 38.9% of the patients, with no impact on progression free survival (PFS). Interestingly 7 patients had biallelic loss of *HLA-B*, and all of them experienced progression within the first year (p=0.03). To expand our analysis, we explored *B2M* an essential component of HLA class I complexes. *B2M* was lost in 33.3% of the patients without showing any association with shorter PFS. However, restricting the analysis to patients with *B2M* biallelic loss (defined as presence of deletions of both alleles, or deletion and mutation with high impact in the structure and function of the *B2M* protein) 4/4 patients progressed. Overall, all 11 patients with genomic events leading to biallelic loss of HLA class I progressed (p=0.007).

Notably, in one patient (CAR_39), biallelic inactivation of *HLA* class I was not detected at baseline but emerged with the dominant clone at disease progression. *HLA* class I biallelic loss was associated with genomic drivers previously identified in our study as significantly associated with CAR-19 failure: APOBEC (3/11) and SBS18 (oxygen radical stress; 2/11) mutational signatures, chromothripsis (4/11), *RHOA* deletions (6/11), and double minutes (4/11).

Next, we analyzed the impact of the neoantigen burden corrected for their *HLA* affinity and allelic status on the outcome of CAR-19 treatment. Patients with high number of neoantigens had shorter PFS (p=0.0095) and were enriched for genomic drivers associated with poor response after CAR-19 (e.g., APOBEC and SBS18). Interestingly, the neoantigen burden had a bimodal distribution across patients that progressed with two distinct groups: one with high neoantigen burden, biallelic loss of HLA, and high genomic complexity and the other with low genomic complexity and low neoantigen burden. Restricting the analysis to patients with retained HLA and low genomic complexity, high neoantigen burden associated with prolonged and favorable response to CAR-T therapy (p=0.04).

CONCLUSION: This study offers evidence that there is a critical relationship between CAR-19 efficacy, LBCL immunogenicity, and the endogenous immune response.

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