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POSTER ABSTRACTS

705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALLY AVAILABLE THERAPIES

CAR-T Phenotype and Efficacy Is Impaired By Lymphoma-Associated CD39 + T Cells

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Background: Autologous chimeric antigen receptor (CAR) T-cell therapy is standard of care for patients with relapsed or refractory Large B cell Lymphoma (R/R LBCL). Each patient's CAR T product is unique, and the patient-specific determinants of CAR T-cell quality are poorly understood. CD39 is an ectonucleosidase that participates in the conversion of ATP and ADP and is upregulated in cancer. On T-cells, CD39 is expressed on CD4+ Tregs and on exhausted CD8+ T-cells that are prone to apoptosis.
Methods: This is a retrospective single-center cohort study (N=72) of patients who received CD19 CAR T-cell therapy for LBCL (axi-cel n=52; tisa-cel n=20). Leukapheresis material was obtained from n=51 patients and flow cytometry was performed to phenotype CD4+ and CD8+ stem-central memory, memory, and effector T-cell subsets (using CCR7 and CD45RO), and for immune checkpoint expression (PD-1, LAG3, TIGIT, and CD39). 10x multiome (ATAC and RNA) single cell sequencing (scRNA-seq) was performed on n=8 leukapheresis products for deeper characterization. Serum metabolomics was performed on paired samples from n=21 patients. 10X Genomics Chromium scRNAseq was also performed on n=57 CAR T-cell infusion products, including n=36 with paired leukapheresis material previously phenotyped by flow cytometry. *In vitro* CAR T-cells were manufactured from starting patient T-cells and analyzed for CAR T-cell phenotype and function.
Results: In the leukapheresis material of patients that did not achieve long-term remission after CAR T-cell therapy, and in those with high tumor burden, we found higher numbers of CD4+CD39+ and CD8+CD39+ T-cells (**Figs. 1 and 2**). 10X multiome sequencing confirmed that CD39+ T-cells exhibit characteristics of exhaustion. Recent platinum-based chemotherapy did not affect CD39+ T-cell levels. In n=21 patients with paired serum analyzed by metabolomics, high CD8+CD39+ T-cells associated with reduced metabolites in the inosine-hypoxanthine pathway, which are downstream of the ectonucleotidase function of CD39 (inosine; P=0.006; hypoxanthine P=0.07). Increased numbers of CD39+ T-cells in the starting leukapheresis material translated into manufactured CAR T-cells having less favorable product characteristics, including higher CD39 expression and fewer memory cells in both paired patient samples and in experiments of *in vitro* CAR T-cell manufacturing.

ScRNA-seq of the infused CAR T-cell product revealed differential gene signatures, both globally and in association with response, between axi-cel and tisa-cel CAR T-cell products, highlighting the profound product-specific differences. Nonetheless, both products were adversely affected by high CD39+ T-cells in the leukapheresis material used for manufacture.
Conclusions: CD39+ T-cells, found in patients with high lymphoma tumor burden and an unfavourable immunometabolic environment, associate with poor CAR T-cell quality and adverse patient outcomes in R/R LBCL. Strategies are needed to improve patient T-cell quality prior to leukapheresis and/or improve CAR T-cell manufacturing from patients with high levels of exhausted CD39+ T-cells.
Figure 1: Progression-free survival (PFS) stratified by leukapheresis CD8+CD39+ T-cells in the leukapheresis product. Blue - below cohort median percentage of CD8+T-cells that are CD39+ (low); Red - above median percentage of CD8+T-cells that are CD39+ (high). P-value by Log-Rank test. Overall survival (not shown) P-value 0.01.
Figure 2: Proportion of CD8+CD39+ T-cells found in patients with low or high baseline metabolic tumor volume (MTV) based on a previously established cutoff (Dean et al. Blood Adv. 2020). MTV was measured on the pre-CAR T-cell PET/CT. P-value by T-test.
MDJ, XY, and RMA are co-first authors with equal contribution.

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Figure 1

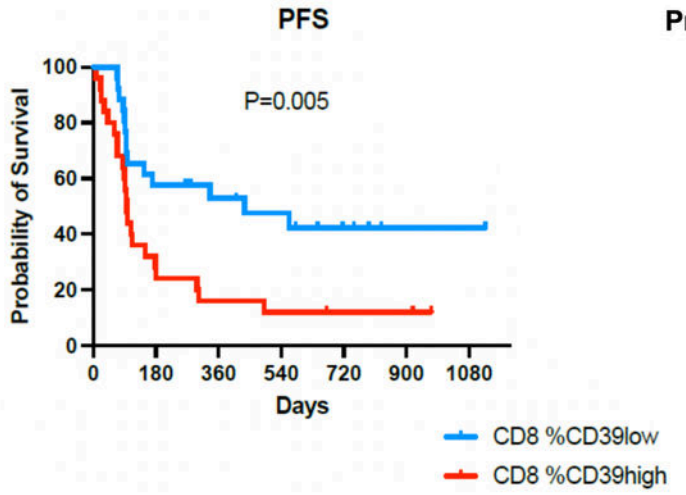

Figure 2

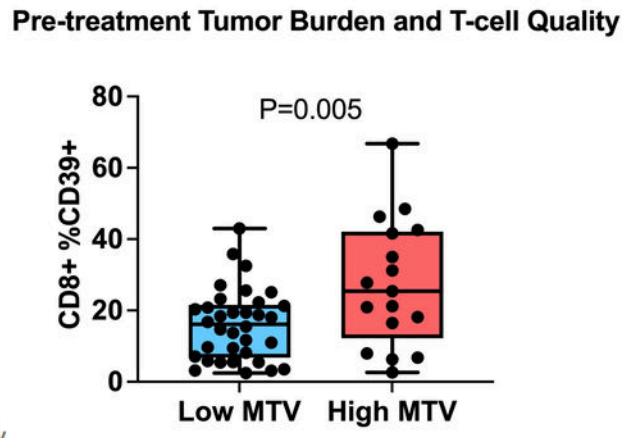

Figure 1

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