ELSEVIER

Blood 142 (2023) 93–94

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

Multimodal Single-Cell Transcriptomic and Proteomic Correlatives of Patients Outcomes Following Anti-BCMA Cellular Therapy with Ciltacabtagene Autoleucel (Cilta-cel) in Relapsed Multiple Myeloma

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Introduction

Multimodal single cell technologies allow us to dissect the mechanisms of therapeutic resistance by integrating transcriptomics and proteomics through the combination of antibody labeling and next-generation sequencing. Using CITE-seq, mass cytometry (CyTOF) and quantitative multiplexed proteomics (Olink), we sought to understand the determinants of chimeric antigen receptor (CAR) T cell response and the overall survival of patients with relapsed or refractory multiple myeloma (RRMM) receiving ciltacabtagene autoleucel (Cilta-Cel) cellular therapy.

Methods

Twenty five patients received Cilta-Cel and had bone marrow (BM) and peripheral blood (PB) samples collected at baseline and after CAR T infusion. We isolated 262,520 BM cells and 241,657 PB cells, which were later sequenced using CITE-seq. Additionally, we submitted PB samples for CyTOF analysis and acquired 10,162,426 cells used for downstream analysis. We analyzed 92 cytokines using Olink immuno-oncology panel in PB samples. Downstream analysis was performed using the R packages Seurat, CATALYST, FlowSOM and Olink Analyze.

Results

Our cohort had a median progression-free survival (PFS) of 732 days. To focus our correlative analyses on patients experiencing early relapse, the initial cohort was divided into 2 groups: PFS <18 months (n = 10) and PFS >18 months (n = 15). CAR-T cell expansion was observed in week 2 post-infusion and continued up to week 4. The percentage of CD4 and CD8 CAR-T cells significantly increased between weeks 1-3 and weeks 4-6 weeks ($p<0.001$) and significantly decreased after week seven ($p<0.05$). We detected novel and significant differences among four cell populations associated with PFS longer than 18 months. These patients had a higher percentage of activated CD4 Central Memory (CM) and CD4 cytotoxic cells ($p<0.05$) relative to the total percentage of CAR-T cells in weeks 4-6, suggesting a key role for CD4 cells in cross priming or direct cytotoxicity in this context. In patients with a PFS longer than 18 months, the CD8 CM CART cell population had a significantly higher percentage in weeks 1-3 and 4-6 ($p<0.05$) when compared to their counterparts, suggesting that these were the cardinal effector population in these patients.

Myeloid-derived suppressor cells (MDSCs) have been shown to be a central component of the tumor microenvironment in myeloma, with subsets being capable to mount potent suppressive activity at the tumor site. In the BM CITE-seq myeloid compartment, MDSCs were significantly increased in month 1 ($p<0.05$) in patients with a shorter PFS. Our PB CyTOF data confirmed this finding as the percentage of MDSCs was significantly higher in weeks 1-3 ($p<0.05$) in the shorter PFS group when compared to their counterparts.

Using a mixed linear regression model on Olink data, we detected 26 cytokines significantly different ($p<0.05$) between the shorter and longer PFS groups. A pseudobulk analysis of the BM CITE-seq samples for differentially expressed genes encoding the 26 cytokines revealed 22 genes differentially expressed ($p<0.05$) between patients with a PFS shorter than 18 months and patients with a PFS longer than 18 months in CAR-T, T-cell, NK cell and myeloid cell populations. In the shorter PFS group, VEGFA was significantly higher in CD8 TEMRA CAR-T cells when compared to their counterparts. In the longer PFS group, we observed significantly higher levels of genes involved in T cell activation, such as CD27 and CD28, and pro-inflammatory cytokines such as TNF and IL-15 in the T cell and Myeloid cell compartments. This pattern suggests that higher production of cytotoxic and pro-inflammatory cytokines, combined with enhanced T cell activation, plays an important role in prolonging the response to CAR-T therapy.

Conclusions

Single cell immune profiling and transcriptomic sequencing identified subpopulations of CD4 and CD8 cells which in concert may influence long term CAR-T outcomes. Our findings demonstrate an early expansion of CART, with very few CART cells surviving after 3 months, suggesting that the efficacy of this therapy is related to early dynamics of these populations. We also provide additional evidence associating immunosuppressive MDSC populations in BM and PB patients with a shorter PFS. Ongoing studies will further analyze the role of the immune microenvironment and clonal T cell dynamics in relation to patient outcomes.

https://doi.org/10.1182/blood-2023-186395