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POSTER ABSTRACTS

641.CHRONIC LYMPHOCYTIC LEUKEMIA: BASIC AND TRANSLATIONAL

Enhancing CAR-T Therapy in CLL By Modulating the Immunosuppressive Tumor Microenvironment: A Novel Approach with Significant Therapeutic Potential

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BACKGROUND Adoptive cell therapies have revolutionized the treatment paradigm for B-cell neoplasms, including acute lymphoblastic leukemia and non-Hodgkin lymphomas. However, in chronic lymphocytic leukemia (CLL), lower response rates are observed for anti-CD19 chimeric antigen receptor T cell (CAR-T) therapies. This therapeutic failure is mainly attributed to the profound T-cell exhaustion seen in CLL and the highly suppressive tumor microenvironment (TME). Here, we present a novel approach to improve CAR-T therapy by targeting the alarmin S100-A9. This protein plays a pivotal role in the TME of solid tumors and other hematologic malignancies by promoting the accumulation of myeloid-derived suppressor cells (MDSCs). We recently demonstrated that S100-A9 contributes to activating inflammatory pathways in B-CLL cells. We hypothesize that S100-A9 inhibitors could indirectly potentiate T cell fitness by decreasing chronic inflammation and modulating the CLL TME, ultimately leading to lower T cell exhaustion and suppression.

METHODS Flow cytometry assessed S100-A9 expression in B-CLL cells in the peripheral blood (PB) and bone marrow (BM) of 20 CLL patients. Nurse-like cells (NLCs) were obtained using PBMCs from individuals with CLL. MDSCs were differentiated from the BM of Eμ-TCL1 mice and treated in vitro with an S100-A9 inhibitor. To evaluate the *in vivo* immunomodulatory effect of targeting S100-A9, C57BL/6 were injected with splenocytes from Eμ-TCL1 mice and treated with the oral S100-A9 inhibitor, tasquinimod (TasQ). T cells were isolated from the spleen of TasQ-treated and control mice, activated with CD28/CD3 beads, transduced with the CAR construct, and then injected into Eμ-TCL1 mice with established disease. All immunophenotyping analyses were performed using a BD FACSymphony cytometer.

RESULTS Significantly higher S100-A9 expression was found in B-CLL cells from the patient's BM compared with PB. Additionally, NLCs and myeloid and T cell co-stimulatory signals enhanced S100-A9 expression in leukemic lymphocytes. S100-A9 was expressed in neoplastic B-CLL cells and in MDSCs from CLL patients. Similar to previously shown in multiple myeloma and several solid tumors, in vitro treatment with the S100-A9 inhibitor, TasQ decreases PD-L1 and Arginase 1 expression in MDSCs derived from the BM of CLL-bearing mice. To evaluate the in vivo effect of TasQ, adoptive transfer Eμ-TCL1 mice were treated with this oral inhibitor or vehicle for four weeks. TasQ-treated mice showed more prolonged survival, less accumulation of MDSCs, and fewer patrolling monocytes in the spleen. Additionally, T cells were skewed toward a predominant naive and central memory phenotype in the TasQ group. Given the immunomodulatory benefits of S100-A9 inhibitors, we evaluated whether T-cells from TasQ-treated mice can be an excellent source to build more efficacious CAR-T cells. Notably, CAR-T cells manufactured from TasQ-treated T cells expanded faster in vitro and maintained their central memory phenotype after one week of expansion. Likewise, TasQ-treated CAR-T cells lasted longer in the PB of adoptive transfer Eμ-TCL1 mice. They could control CLL progression more effectively than CART manufacture from vehicle-treated mice.

CONCLUSION Our study demonstrates that targeting S100-A9 decreases the suppressive TME in CLL. This finding makes S100-A9 inhibitors promising candidates for bridge therapy to improve T-cell fitness and enhance the effectiveness of CAR-T therapy.

Disclosures No relevant conflicts of interest to declare.

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