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S141 ELICITING ANTI-TUMOR T CELL ACTIVITY IN CHRONIC LYMPHOCYTIC LEUKEMIA WITH BISPECIFIC ANTIBODY-BASED COMBINATION THERAPY

Topic: 05. Chronic lymphocytic leukemia and related disorders - Biology & Translational Research

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Background: Identifying effective combination immunotherapy could offer hope to chronic lymphocytic leukemia (CLL) patients who relapse on previous lines of therapy. Although prior studies have described an exhausted and pro-tumor T cell state, there may be potential to stimulate anti-CLL cytolytic T cell activity with novel therapy.

Aims:

Investigate the ability of the CD20-targeted T-cell-engaging bispecific antibody glofitamab (CD20-TCB) to overcome T cell exhaustion and tumor microenvironment (TME)-mediated immunosuppression in CLL.

Methods:

We pre-clinically investigate CD20-TCB efficacy in CLL utilizing immune and TME model assays that include in vitro functional T cell assays, patient-derived xenografts and lymph node organotypic models.

Results:

Our previous studies of the CLL lymph node (LN) TMEs suggested that low numbers of infiltrated CD8⁺ T cells likely contribute to the generation of a “cold” TME that could represent a barrier to effective therapy. Here, we show that CD20-TCB treatment induced the activation, proliferation and migration of previously exhausted patient CD4⁺ and CD8⁺T cells and triggered the release of immunostimulatory cytokines related to immune cell recruitment and cytotoxic function. Additionally, we detected enhanced cytolytic (perforin⁺) immune synapse activity in CD20-TCB-treated cultures which correlated with high levels of T cell-mediated CLL cell death. Importantly, bispecific antibody treatment also induced high levels of anti-CLL T cell activity in both ibrutinib responding and refractory patient samples.

Given the emerging evidence that endothelial cells (ECs) that reside within the TME can possess immunomodulatory activity, we next evaluated CD20-TCB-mediated T cell responses in the presence of this stromal cell compartment. We established triple culture assays that allowed patient T and CLL cells to be cultured with CLL-activated ECs (CLL-ECs). These assays revealed that TCB-activated T cells in the presence of CLL-ECs showed a reduced ability to kill target CLL cells compared to healthy ECs. Flow cytometric and multicolor confocal microscopy analysis revealed that CLL-ECs *in vitro* and *in situ* expressed increased levels of ICAM-1 and PD-1 ligands that we demonstrated contribute to T cell suppression. In order to overcome this TME-mediated inhibition and enhance anti-CLL CD20-TCB activity, we next investigated combination immunotherapy. Combination of CD20-TCB with a CD19-4-1BBL fusion protein (tumor-targeted co-stimulatory drug) resulted in enhanced CLL cell killing in both T:CLL and triple T:CLL-EC culture assays.

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Patient-derived xenograft models further confirmed the ability of bispecific antibody combination therapy to induce higher levels of anti-CLL T cell activity compared to monotherapy. Additionally, the pairing of CD20-TCB with CD19-4-1BBL promoted the proliferation and activation of patient T cells within splenic TMEs. Finally, we established 3D organotypic cultures of excess diagnostic LN biopsies that preserve the intact TME cellular composition and spatial organization. LNs of treatment naïve, as well as ibrutinib and venetoclax relapsed CLL patient samples, were treated *ex vivo* with CD20-TCB combination for subsequent 3D image analysis. Importantly, combination immunotherapy triggered improved anti-tumor T cell killing function and promoted an inflammatory cytokine-rich “hot” TME.

Summary/Conclusion: Collectively, this preclinical study supports the concept of triggering cytolytic T cell activity in CLL with bispecific antibody combination immunotherapy that could help overcome T cell exhaustion and the immunosuppressive TME.

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