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Abstract LB370: Tumor-infiltrating lymphocytes-derived CD8 clonotypes infiltrate the tumor tissue and mediate tumor regression in glioblastoma FREE

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Abstract

Adoptive cell therapy using tumor-infiltrating lymphocytes (TILs) has shown remarkable efficacy in treating melanoma and other "hot" tumors characterized by high tumor mutation burden (TMB), a biomarker increasingly recognized for predicting immunotherapy success in solid tumors. However, gliomas show no clear correlation between TMB and immunotherapy efficacy due to the immunosuppressive tumor microenvironment, defective antigen presentation and the restrictive blood-brain barrier, hindering the effectiveness of immunotherapy. We report the successful treatment of a rapidly progressing high-TMB glioblastoma patient with TILs expanded using a defined cytokine cocktail comprising IL-2, IL-15, and IL-21. The therapeutic regimen included lymphodepletion with a single dose of cyclophosphamide prior to TIL intravenous infusion followed by a single dose of IL-2 post-infusion. Remarkably, complete tumor regression was achieved following two TIL infusions administered two weeks apart. Sequential cranial MRI showed complete tumor remission 22 days after the second infusion, with biopsies of the tumor showing complete necrotic tissue transformation. The TIL products were enriched for CD8 T-cells with high IFNg production and CD107a expression. They exhibited dose-dependent, specific cytolytic activity against autologous tumor cell lines but not against an autologous EBV-transformed B-cell line, the allogeneic glioblastoma cell lines U-373 and DBTRG05, or the unrelated Daudi B-cell lymphoma cell line. After TIL infusion, peripheral blood T-cells exhibited TCR downregulation, indicating activation, alongside with increased numbers of effector memory CD8 T-cells and CD4 Th1 and Th17 subtypes, while terminally differentiated CD8 T-cells decreased. A surge in serum IL-6 and sIL-2R levels was seen after each TIL infusion, confirming the strong systemic T-cell activation. Hematological analyses revealed persistent lymphopenia despite the use of reduced conditioning regimen. Surgical tumor samples collected before and after TIL infusions were analyzed by whole-exome sequencing (WES), RNA-seq and T-cell receptor (TCR) next-generation sequencing. WES revealed a high mutation burden (>10/Mb) across all samples, including mutations on EGFR, TP53 and BRCA1/2. Transcriptomic analysis of post-infusion tumor biopsies demonstrated enhanced expression of genes associated with immunological synapse formation and T-cell effector function, in line with the observed clinical response. TCR sequencing demonstrated that TIL-derived CD8 T-cells effectively infiltrated the tumor tissue and were strongly associated with tumor clearance. Hyperexpanded clonotypes within the tumor indicated robust TIL expansion in vivo, highlighting the significant contribution of TIL-derived CD8 T-cell proliferation to tumor control. CD4 T-cells, despite presenting greater TCR diversity than CD8 T-cells within the infused product, showed limited infiltration. This case highlights the potential of TILs expanded with IL-2/IL-15/IL-21 to overcome the challenges of glioblastoma's immunosuppressive microenvironment, achieving significant clinical outcomes. These findings support the exploration of optimized TIL-based therapies as a viable treatment strategy for glioblastoma and other "cold" tumors.

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