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B Cell Aplasia In a Patient with Relapsed B Cell Acute Lymphoblastic Leukemia Following Re-Induction and Consolidation with Autologous T Cells Genetically Targeted to the CD19 Antigen

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Abstract

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Despite high initial remission rates following induction chemotherapy, most adults with B cell acute lymphoblastic leukemia (B-ALL) ultimately relapse and the overall prognosis is poor. In light of the overall poor outcomes seen with currently available chemotherapy regimens as well as allogeneic stem cell transplantation, novel and effective treatment approaches are needed for these patients. To this end, we have developed a program utilizing a patient's own T cells genetically modified *ex vivo* to express a chimeric antigen receptor (CAR), termed 19–28z, specific to the CD19 antigen expressed on normal B cells as well as most B-ALL tumors. In preclinical studies, human T cells modified to express the 19–28z CAR effectively eradicated systemic human B-ALL NALM-6 tumors in SCID-Beige mice. Based on these findings we have recently opened a phase I clinical trial (IRB #09-114) wherein patients with relapsed B-ALL are initially treated with re-induction chemotherapy followed by consolidation with high dose cyclophosphamide (3gm/m^2) and a subsequent infusion of autologous T cells genetically modified

to express the 19–28z CAR. Herein, we report the initial findings of the first patient treated on this clinical trial. This patient, a 67-year-old male, with B-ALL (normal cytogenetics), achieved a complete remission following induction chemotherapy with mitoxantrone and high-dose cytarabine. The patient remained in remission following treatment with vincristine (consolidation B) and cyclophosphamide (consolidation C). However, he was noted to have relapsed disease following consolidation cycle D with cytarabine and etoposide. At the time of relapse the patient was leukapheresed to obtain autologous T cells, and subsequently achieved a second remission following re-induction with a modified PEG-asparaginase, vincristine, and prednisone regimen. Upon recovery, the patient, as stipulated by the clinical trial, received lymphodepleting consolidation with high dose cyclophosphamide followed, 2 and 3 days later, by a split dose infusion of 3×10^6/kg autologous 19–28z$^+$ T cells, the lowest planned T cell dose on this trial. Over the next 2 weeks, FACS and Q-PCR detected gene-modified T cells in the peripheral blood. Significantly, over the next 5 weeks, despite recovery of neutrophils and T cells, the patient exhibited a persistent B cell aplasia consistent with CD19-targeted cytotoxic activity of the infused autologous 19–28z$^+$ T cells. The patient subsequently received an allogeneic stem cell transplant from a HLA-identical sibling effectively abrogating further analysis of modified T cell function. Despite this limitation, we conclude that following lymphodepleting chemotherapy, modified CD19-targeted T cells exhibit effective anti-CD19 cytotoxic activity, as demonstrated by the persistent B cell aplasia, in the clinical setting. These findings support the promise of this novel adoptive T cell therapy in patients with relapsed B-ALL.

Disclosures:

No relevant conflicts of interest to declare.

Author notes

* Asterisk with author names denotes non-ASH members.