# Prolonged remission using CD19 chimeric antigen receptor-T cell therapy followed by haploidentical transplantation in a 5-month-old patient with infantile acute lymphoblastic leukemia

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**Abstract**

Tisagenlecleucel offers promise to children with relapsed/refractory (r/r) acute lymphoblastic leukemia (ALL). However, there is limited experience with and data supporting the use of tisagenlecleucel in infants. We describe our successful experience using tisagenlecleucel followed by a haploidentical donor hematopoietic stem cell transplantation in an infant with r/r KMT2A-rearranged ALL, the youngest infant to survive and achieve prolonged remission using this approach.

## INTRODUCTION

Infants younger than 6-months of age diagnosed with precursor B-cell acute lymphoblastic leukemia (ALL) have a rare and aggressive form of leukemia associated with inferior outcomes, especially if associated with KMT2A gene rearrangements (KMT2A-r).[1-4] Dismal outcomes are observed despite intensive therapies including allogeneic hematopoietic stem cell transplantation (HSCT).[1,5-9] While a therapeutic advantage exists for early HSCT in a subset of high-risk infants with KMT2A-r ALL transplanted in a first complete remission, early disease recurrence, refractory or progressive disease often limits this approach.[6,8-12] Those who do proceed to HSCT frequently relapse without curative treatment options.[6, 13]

Tisagenlecleucel, an autologous anti-CD19 chimeric antigen receptor T-cell (CAR-T) agent, offers promise to patients with relapsed or refractory (r/r) ALL, demonstrating remission rates as high as 81% in both children and adolescents.[14-16] However, there is limited experience utilizing CAR-T in infants resulting from the exclusion of children <1 year of age from initial clinical trials.[1] The approach has been limited due to an infant's smaller size and blood volume; concerns include cellular collection safety, the timing of autologous T-cell harvest during a patient's treatment course, the optimal infusion dose, and the management of post-infusion toxicities.[10,17-19] There are inherent difficulties in obtaining sufficient autologous T-cells in infants to generate a suitable CAR-T product.[17-21] Whether CAR-T therapy alone is satisfactory to achieve durable long-term remissions remains under investigation for all recipients with little information in the setting of aggressive infantile ALL. Failure following CAR-T therapy is frequently secondary to antigen escape.[14,22] Multiple reports demonstrate superior outcomes and sustained remissions in pediatric and adult patients with r/r ALL receiving CAR-T as a bridge to allogeneic HSCT;[10,14,15] however, there is a dearth of data supporting the use of CAR-T therapy in infants.[18]

Here we present our experience in a high-risk infant with r/r KMT2A-r ALL who successfully received the CD19 CAR-T cell therapy, tisagenlecleucel, in tandem with haploidentical donor HSCT. This is the youngest infant to survive and achieve prolonged remission following CAR-T therapy and subsequent HSCT.[18]

## CASE DESCRIPTION

Our patient is an African American female diagnosed at 6-weeks of age who presented for evaluation of persistent vomiting, lethargy and an unusual skin rash after several weeks of concern for failure to thrive. Initial white blood cell (WBC) count was 834x$10^9$/L with 98% circulating lymphoblasts. Flow cytometry performed on peripheral blood revealed ALL with 98% of total cells expressing CD19. Cytogenetic analysis revealed a t(11;19)(q23.3;p13.3) translocation and flouresent *in situ* hybridization analysis confirmed a KMT2A-r ALL. Cerebrospinal fluid (CSF) analysis revealed central nervous system (CNS) involvement. The patient underwent leukoreduction and subsequently initiated treatment as per the Interfant-06 standard protocol (clinigaltrials.gov: NCT00550992).

End of induction assessment demonstrated clearance of the extra-medullary disease and a bone marrow morphologic remission but flow cytometric evidence of minimal residual disease of 0.36%. Three months after diagnosis she relapsed with confirmed ALL detected in the bone marrow and CSF with chloromatous skin lesions following a period of delayed blood cell count recovery from consolidation therapy. She received high-dose methotrexate (HD-MTX) (3.3gm/$m^2$) with 6-mercaptopurine (6MP) and intrathecal methotrexate/hydrocortisone (IT MTX/HC) that resulted in clearance of peripheral blood and CSF lymphoblasts and resolution of chloromas.

She underwent autologous CD3 lymphocyte apheresis using the CMNC program in the Spectra Optia automatic apheresis system for CAR-T generation over a course of 3 collection days at the age of 5-months and weighing 6.8kg. The device was primed with whole blood which was reinfused to her at the completion of the procedures. Absolute lymphocyte count (ALC) at the start of collection was 0.88x$10^9$/L. On day 1 the product output was poor with a total nuclear cell count (TNC) of 0.14x$10^9$/L and a CD3 count of 0.02x$10^9$/L cells.

Adjustments were made for collection on days 2 and 3. On day 2, the TNC obtained was 1.4x$10^9$ and the CD3 count was 0.42x$10^9$ cells. Day 3 yielded 2.64x$10^9$ TNC and 0.31x$10^9$ CD3 lymphocytes. The procedure totaled 4.18x$10^9$ TNC and 0.76x$10^9$ CD3 cells over 3 days. Despite her small size, the cellular goals for apheresis were the same as for an adult and were appropriately met without any complications.

CNS and peripheral blood lymphoblasts re-emerged following chemotherapy with high dose cytarabine and pegaspargase but cleared following HD-MTX (3.75gm/$m^2$), 6MP, dexamethasone, vincristine and IT MTX/HC. Lymphodepleting therapy with a 2-day course of cyclophosphamide and fludarabine was administered 7 days prior to tisagenlecleucel infusion. The total cell viability in the final CAR-T product was 85.4% with 2.7% CAR positive viable cells, below the 3% threshold required by the Food and Drug Administration (FDA) for product release. However, the overall number of chimeric antigen receptor (CAR) viable transduced T-cells was 2.3x$10^6$ cells/kg, meeting the clinical specifications required for commercial use.[23] As the final product did not meet all the required specifications, she received the manufactured cells on compassionate use exemption at 7-months of age.

Figure-1 summarizes her WBC count, lymphoblast count, C-reactive protein, ferritin, fibrinogen, maximum daily temperature and clinical course following CAR-T infusion. Her course was complicated by grade 2 cytokine release syndrome (CRS) in conjunction with the emergence of confirmed CD19 lymphoblasts detected in peripheral blood on day 7. CRS was manifested by persistent high fevers, tachycardia, tachypnea and grunting. She received two doses of tocilizumab on days 7 and 10. She developed tumor lysis syndrome (TLS) and subsequent acute kidney injury manifested by an increase in creatinine from 0.32mg/dL to 0.61mg/dL. She subsequently developed *Klebsiella pneumoniae* bacteremia, disseminated intravascular coagulation and unexplained hypoglycemia. Full recovery from TLS and CRS occurred following the clearance of peripheral lymphoblasts by day 13. She was discharged home on day 26 in remission confirmed by morphologic and flow cytometric assessment of bone marrow.

At 9-months old she proceeded with a planned myeloablative (busulfan/cyclophosphamide) haploidentical allogeneic HSCT from her 14-year old sister. Tacrolimus and mycophenolate mofetil were used for graft-vs-host-disease prophylaxis. She developed reversible hyperbilirubinemia, transaminitis and hepatomegaly. Complications included *Klebsiella pneumoniae* bacteremia, mucositis, hypertension and pericardial effusion.

She was discharged on day 34 in remission confirmed by CSF evaluation and morphologic and flow cytometric analysis of her bone marrow. She is now 12-months post-HSCT and remains in a remission.

## DISCUSSION

This case highlights that apheresis for CAR-T cell generation can be done safely and successfully in an infant. Secondly, use of a product with modified CAR-T parameters can result in remission. Despite not meeting the FDA's percent of CAR positive viable cell specifications, our patient's manufactured CAR-T product was equally capable of expansion and leukemia targeting with no evidence of greater safety risk.

Lastly, our patient's ongoing remission status cannot be stressed enough. The availability of tisagenlecleucel provided an opportunity to control very chemotherapy resistant disease prior to HSCT. Pre-transplant remission status following second-line therapy significantly impacts survival following HSCT in patients with r/r KMT2A-r ALL;[3,8] the added benefit of tisagenlecleucel facilitated a deeper remission prior to receiving HSCT, thereby providing an opportunity for maximal long-term survival in an infant who previously had a dismal prognosis. With her being approximately 12-months in remission post-HSCT, she is now beyond the greatest risk period for relapse.[3] Future clinical investigations using CAR-T therapy prior to HSCT for infants with r/r KMT2A-r ALL offers the potential for improved survival in a disease where little progress has been made in treatment outcomes.

### Conflict of Interest Statement

The authors have nothing to disclose.

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## Figure Legends

**Figure 1:** A, Time course of patient's WBC count versus lymphoblast count post-tisagenlecleucel infusion; B, Time course of patient's CRP versus maximum daily temperature post-tisagenlecleucel infusion; C, Time course of patient's ferritin versus maximum daily temperature post-tisagenlecleucel infusion; D, Time course of patient's fibrinogen versus maximum daily temperature post-tisagenlecleucel infusion. CAR-T, chimeric antigen receptor-T cell; CRP, C-reactive protein; WBC, white blood cell.