Toward chemotherapy-reduced cure for *TCF3::HLF* B-cell acute lymphoblastic leukemia using CD19-directed immunotherapy

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In this issue of Haematologica, Wan and colleagues provide encouraging results from a monocentric phase II trial that included 16 children with relapsed/refractory *TCF3::HLF*-positive B-cell acute lymphoblastic leukemia (B-ALL) treated with dual CD19/CD22-directed chimeric antigen receptor (CAR) T-cell therapy.[1] *TCF3::HLF*-rearranged B-ALL is a rare and highly aggressive subtype, accounting for less than 1% of pediatric ALL cases that is defined by the t(17;19)(q22;p13) chromosomal translocation. This subtype is marked by profound resistance to conventional therapies even after consolidation with allogeneic hematopoietic stem cell transplantation (HSCT) in first remission, and thus universally recognized by major pediatric leukemia study groups as an ultra-high-risk subtype.[2]

The biology of *TCF3::HLF*-rearranged B-ALL is characterized by extensive transcriptional reprogramming and activation of gene expression programs reminiscent of fetal hematopoiesis, likely initiated in B-lymphoid progenitors.[3] The oncogenic fusion transcription factor binds enhancer positions to activate relevant target genes including MYC, BLC-2 and master regulators of hematopoiesis and cooperating factors including ETS family members.[3,4] Oncogenic activity depends on the co-factor EP300, which constitutes a possible therapeutic target.[4] BCL-2 is directly regulated by the fusion, conveying unique sensitivity to venetoclax. While mutations in *NRAS*, *KRAS*, and *PTPN11* are often present, they are typically subclonal and volatile, thus not a priority drug targets for this disease.[5] Venetoclax has shown potent activity in primary *TCF3::HLF*-positive samples, suggesting a particularly promising avenue for targeted intervention.

The rarity of *TCF3::HLF*-positive B-ALL and limited systematic reporting have hindered the development of standardized treatment guidelines. More than a decade ago, Martin Stanulla from the Berlin-Frankfurt-Münster (BFM) Study group suggested to us that the early use of CD19-directed immunotherapy may be beneficial for *TCF3::HLF*-positive ALL to prevent adaptation to treatment pressure. There is now strong evidence from a European case series of 19 patients treated with blinatumomab and HSCT demonstrating that durable remission is achievable with early CD19-targeted interventions (Table 1).[6] The results by Wan and colleagues indicate that similar disease control can be achieved with CAR T-cell therapy, in line with previous retrospective case reports of responses to CAR T in relapsed/refractory *TCF3::HLF*-positive B-ALL (Table 1). In this prospective study from the Shanghai Children's Medical Center, 16 children (median age ~11 years) received dual CD19 and CD22-targeted CAR T-cell therapy with a median follow-up of 15.5 months (range, up to 56 months). All patients achieved measurable residual disease (MRD)-negative complete remission by 2 months post-infusion, translating into a 6-month relapse-free survival (RFS) of 93% and a 12-month RFS of nearly 77%.

Longitudinal monitoring revealed durable CAR T-cell persistence by quantitative polymerase chain reaction in several patients beyond 6 months, with ongoing B-cell aplasia documented beyond 26 months in some cases. Only one of the four documented relapses was CD19-negative, indicating that other mechanisms of resistance will play a role for this subtype. Toxicities were largely manageable, with cytokine release syndrome (CRS) occurring in 13 of 16 patients (mostly grade 1-2; two grade ≥3 events) and transient ICANS in four patients. These compelling data highlight the feasibility and effectiveness of dual CAR T-cell therapy in this ultra-high-risk leukemia. The evidence whether dual CAR T provides advantages over CD19-directed CAR T therapy is still lacking. Of note ten of the 16 patients have received only the study treatment and did not relapse; however, the follow-up is still too short to draw definitive conclusions regarding long-term outcomes. The

Table 1. Summary of reported CD19-directed immunotherapy outcomes in *TCF3::HLF*-positive B-cell acute lymphoblastic leukemia.

Article	Key findings
Chen *et al.*, Blood 2021[2]	- 12 relapsed/refractory patients (mostly pediatric) received CAR T-cell therapy - 9 of 12 achieved complete remission and proceeded to HSCT - 1 patient relapsed before HSCT; 2 relapsed post-CAR T-cell therapy and were non-responders to re-infusion - no CD19-antigen loss was reported
Leahy *et al.*, Blood 2022[7]	- 4 pediatric *TCF3::HLF*-positive patients received CD19 CAR T-cell therapy - all achieved MRD-negative remission after infusion - 2 patients relapsed, 2 were in remission with a median follow-up of 26 months for the whole for the whole high risk cohort - one relapse was CD19 negative
Yao *et al.*, Annals of Hematology 2024[8]	- 9 relapsed *TCF3::HLF*-positive B-ALL patients (3 treated internally, 6 external); both children and adults - all 9 achieved MRD-negative complete remission after CD19 CAR T-cell therapy - 3 internal patients relapsed within 35–71 days; all relapses were CD19-positive - among external patients, data were incomplete: 4 relapsed, 2 remained in remission; outcomes and antigen status were partially missing
Wan *et al.*, Haematologica 2024[1]	- 16 pediatric relapsed/refractory patients received dual-target CD19/CD22 CAR T-cell therapy - all 16 achieved MRD-negative CR at day 30 post-infusion - 4 relapsed (3 $CD19^{+}CD22^{+}$, 1 $CD19^{-}CD22^{+}$); no dual-negative relapse observed - 14/16 were alive at median 15.5-month follow-up - CAR T-cells persisted beyond 6 months in several patients; B-cell aplasia >26 months in 1 case
Zeckanovic *et al.*, Haematologica 2025[6]	- 19 *TCF3::HLF*-positive patients (17 pediatric, 2 adults) treated with blinatumomab, mostly as bridge to HSCT - 17 of 19 achieved MRD-negative status, mostly after 1 cycle - 2 patients (ID 13, 19) were refractory to blinatumomab but responded to CAR T-cell therapy and proceeded to HSCT - 7 patients relapsed post-HSCT, most within 1 year - 3 patients received salvage CAR T-cell therapy after relapse; all developed developed consecutive relapses - 10 of 19 were alive at median 42-month follow-up - 2-year OS 63.1%, EFS 52.6%

CAR : chimeric antigen receptor; HSCT: hematopoetic stem cell transplantation; MRD: measurable residual disease; OS: overall survival; CR: complete remission; EFS: event-free survival.

role of consolidative HSCT in achieving long-term disease control remains open. Late relapses have been reported for *TCF3::HLF* B-ALL.[6]

Collectively, based on the reported evidence, there is a need to consider the early intervention with CD-19 directed immunotherapy already for the first treatment of *TCF3::HLF* B-ALL. As proposed by the AIEOP-BFM-ALL study group, we recommend bridging patients to immunotherapy with an induction regimen including venetoclax, given the rationale for a dependency on BCL2 in this leukemia subtype. This allows a rapid transition to CD19-directed immunotherapy, and subsequent HSCT.

Similarly, integration of immunotherapies, such as blinatumomab for lower-risk patients and CAR T-cell therapy for high-risk groups, offers a promising path to reduce treatment-related toxicity widely. A UK study of 105 chemotherapy-intolerant or -resistant children showed that blinatumomab achieved a 97% MRD response and comparable 2-year survival to standard chemotherapy, with significantly reduced toxicity.[9] Similarly, the ALL-MB 2019 pilot study (*clinicaltrials gov. Identifier: NCT04723342*), a single 28-day blinatumomab course after induction led to durable MRD negativity in nearly all 177 non–high-risk BCP-ALL patients, with 99.4% of children with evaluable MRD results, remaining MRD-negative during 12 months of maintenance.[10]

Our understanding of the impact of CAR T-cell therapy as a first-line treatment for high-risk B-ALL subtypes remain limited, but emerging evidence suggests it holds significant therapeutic potential. A large multicenter analysis of 231 children and young adults with relapsed/refractory $CD19^{+}$ B-ALL or lymphoblastic lymphoma treated with CD19-directed CAR T-cell therapies showed high overall complete remission rates (94%) across all cytogenetic risk groups, including high-risk subtypes such as *KMT2A*-rearranged, Ph^{+}, Ph-like, and *TCF3::HLF*, indicating that CAR T-cell therapy can induce durable remissions even in poor-prognosis cytogenetic subsets.[7] However, this evidence is limited to relapsed/refractory settings. Data on the frontline use of CAR T-cell therapy in patients with high-risk newly diagnosed B-ALL remain limited, with results from the CASSIOPEIA trial using tisagenle-

cleucel (*clinicaltrials gov. Identifier: NCT03876769*) still pending. The role and optimal timing of HSCT following CAR T-cell therapy in this ultra-high-risk setting also remain unresolved and warrant further investigation. There is an urgent need for retrospective analyses and prospective registries to inform clinical decisions. Ongoing efforts by the European CAR T Task Force of IBFM and ITCC aim to address these critical gaps in evidence and CAR T availability.

Disclosures

AZ has no conflicts of interest to disclose. JPB discloses consulting for SOBI. AB discloses consultancy for Astra Zeneca; honoraria from Amgen, Servier and Novartis; travel grants from Novartis.

Contributions

AZ and JPB wrote the manuscript. AB reviewed and contributed to the manuscript.

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