Editorial Commentary

Challenges in the treatment of pediatric acute lymphoblastic leukemia: insights from the pediatric real world CAR consortium regarding nonresponse and relapse post tisagenlecleucel

Peter Bader[#]^, Laura M. Moser[#]^

Division for Stem Cell Transplantation and Immunology, Department of Pediatrics, University Hospital, Goethe University Frankfurt, Frankfurt am Main, Germany

[#]These authors contributed equally to this work.

Correspondence to: Laura M. Moser, MD. Division for Stem Cell Transplantation and Immunology, Department of Pediatrics, University Hospital, Goethe University Frankfurt, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany. Email: moser@med.uni-frankfurt.de.

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Introduction

On May 10, 2023, Emily Whitehead, the first B-ALL patient ever treated with chimeric antigen receptor (CAR)-T cells, celebrated another year of being "cancer free" (1). Her annual images have been a powerful testament to the potential of CD19-targeting immunotherapy for pediatric ALL over the past decade (2). The emergence of this targeted approach has revolutionized pediatric ALL treatment, harnessing the immune system's power to combat cancer. However, a significant portion of patients still do not respond to or relapse after CD19-CAR-T cell therapy.

In their paper "Outcomes After Nonresponse and Relapse Post-Tisagenlecleucel in Children, Adolescents, and Young Adults With B-Cell Acute Lymphoblastic Leukemia", published in the *Journal of Clinical Oncology* (doi: 10.1200/JCO.22.01076), Schultz *et al.* analyzed data from the Pediatric Real World CAR Consortium and identified patients with CD19-negative relapse as a high-risk population (3).

CD19-CAR-T cell therapy and its success

Autologous T-cells engineered with a CAR targeting CD19 have been an FDA-approved treatment for patients under 26 years old with refractory B-ALL or second and later relapse since 2017. Clinical trials, such as the phase II ELIANA trial, and real-world cohort studies, have demonstrated a success rate of approximately 50–60% in treating these high-risk patients, with overall survival data reaching 36 months (4-9). However, there is limited data on non-response and relapse outcomes.

Insights from the reported cohort

In the analyzed cohort of 184 patients from the Pediatric Real World CAR Consortium, Schultz *et al.* identified 23 patients (12.5%) as non-responders assessed on day 28 after CAR-T application. Among these non-responders, 95% had a high disease burden, defined as ≥5% bone marrow blasts. During a median follow-up of 380 days post-infusion, 57 patients experienced relapsed disease,

^ ORCID: Laura M. Moser, 0000-0002-1241-5137; Peter Bader, 0000-0003-4554-0265.

resulting in a cumulative incidence of relapse of 37% (95% CI, 30% to 47%) at 12 months. High disease burden prior to infusion was associated with an increased risk of overall relapse, as well as a higher number of prior therapies. This finding supports previous experiences and suggests that a more aggressive leukemia and the autologous nature of CAR-T cell therapy may contribute to these challenges: Alterations in the T-cell repertoire due to prior therapies, including allogeneic hematopoietic stem cell transplantation (HSCT), may impact successful transduction, expansion, and *in vivo* persistence and functionality of CAR-T cells (10). Ongoing research is exploring various strategies to enhance T-cell fitness and persistence, such as using allogeneic effector cells, modified CAR signaling, and other approaches (11,12).

In the reported cohort, 41% (22 of 52) of relapsed patients had loss or down-regulation of CD19. There was no difference in median duration to relapse for $CD19^+$ *vs.* $CD19^-$ relapse. A higher number of pre-CAR relapses was associated with post-CAR loss or downregulation of CD19. However, in the reported analysis no further variables were significantly predictive of $CD19^-$ relapse. Loss or downregulation of CD19 was associated with significantly decreased overall survival rates, with a 12-month survival rate of 30% compared to 68% for CD19-positive relapse. Multivariate analysis confirmed that loss or downregulation of CD19 in relapse was associated with a greater risk of death.

Regarding antigen loss or downregulation, real-world data has come to show a difference to the reported data from the ELIANA study, where 15 out of 16 assessable patients relapsed with $CD19^-$ blasts (3 of whom went on to develop $CD19^+$ blasts) (4,9,13). Comparisons between study populations are hard to draw due to inconsistent measurement methods of $CD19^-$ status, as well as different criteria for study enrolment versus administration-approved indication for tisagenlecleucel. Notably, the ELIANA trial required a minimum of ≥5% blasts in the bone marrow, whereas only 61% of the reported cohort met this criterion. Therefore, the reported cohort likely represents patients with a lower disease burden.

The increasing availability, high clinical response rates and clinically manageable toxicity of CAR-T cell products might also contribute to a changing patient selection and puts CD19-CAR-T cell therapy earlier in the line of treatment, which might favor $CD19^+$ relapses. Higher tumor burden has been shown to be associated with CD19- relapse, possible due to singular CD19- leukemic blasts evading standard flow-cytometric detection prior to, but proliferating after CD19-CAR therapy, when bulk $CD19^+$ blasts have been diminished (9,13). Non-response to prior CD19-targeting therapy with blinatumomab (a bi-specific T-cell engager), has also been shown linked to CD19-loss or downregulation after CD19-CAR treatment (9).

The timing of relapse emerges as a crucial variable in determining overall survival probabilities. The median time from CAR-T cell infusion to relapse was 101 days (range, 30–645 days). Although the timing of relapse when analyzed categorically (0–60, 61–180, or >180 days after infusion) did not significantly affect overall survival after relapse, a landmark analysis of patients with a minimum follow-up of 6 months showed that early relapse within 6 months of treatment was associated with a significantly increased risk of death [hazard ratio (HR) =4.75 (95% CI, 1.86 to 12.1)]. Among patients with early relapse, 38% (9 of 24) died, whereas patients who survived more than 6 months without relapse exhibited excellent overall survival rates of 92% (95% CI, 86% to 99%) at 18 months after CAR-T therapy.

Other studies also show that early relapse after CAR-T cell therapy, especially when performed after an allogeneic HSCT is associated with a dismal prognosis (8,14). In the reported cohort 11 patients had received a prior HSCT, 10 of whom experienced relapse.

Regarding the post-relapse treatment, the authors comment on the heterogeneity of applied treatments, with lacking unified strategies and variable reporting limiting the scope of their analysis. Of the relapsed patients, 88% received salvage therapy, with chemotherapy being the most commonly used first-line salvage therapy, followed by inotuzumab (an antibody-drug conjugate targeting CD22) and second CAR-T cell application. Among patients who received first-line salvage therapy, 56% (20 of 36) achieved remission. Additionally, 15 patients received a second CAR-T cell therapy, most commonly using the same CAR construct, while others participated in clinical trials with different CAR constructs. Among these patients, 67% (10 of 15) achieved complete remission (as determined by flow cytometry), highlighting the feasibility of subsequent CAR-infusions to reinstate remission.

However, overall survival analysis after second CAR-infusions cannot be unequivocally interpreted as 9 of 15 patients went on to receive subsequent therapies. 19 patients of the whole relapse-cohort were successfully bridged to transplant, with 9 of them receiving allogeneic HSCT after a second CAR-T cell infusion.

Longer follow-ups and larger cohorts are needed to

assess the outcome of HSCT in the setting of CD19-CAR relapse. The best approach to sequencing allo-HSCT and CD19-CAR-T cell therapy in high-risk ALL patients has yet to be established, particularly since the non-random assignment to consolidative HSCT limits the interpretation of the benefits seen with HSCT.

Future directions and conclusion

The variability in available treatment options and indications, as evident in real-world data from the reported cohort, highlights the differences in treatment strategies influenced by local experience, access to clinical trials, and other factors.

Various strategies can be employed successfully to achieve remission in the setting of tisagenlecleucel-relapse. However, overall survival for patients experiencing relapse after CD19-CAR therapy remains low, with an overall survival rate of only 52% at 1 year in the reported cohort. Schultz *et al.* emphasized that relapse with antigen loss or downregulation of CD19 is associated with an even worse overall survival of only 30% after 1 year, underscoring the need for further research and therapeutic advancements to help these patients.

Numerous products are currently under assessment in clinical trials, as the fields of immunology and genetic engineering synergize to create smarter and safer treatment options (11).

In conclusion, Schultz *et al.*'s featured report highlights the paradigm shift in the treatment of high-risk B-ALL patients since the introduction of CD19-CAR-T cell therapy. However, their findings on the still dismal prognosis after relapse serve as a cautionary reminder of the urgent need to discover consistent and effective salvage therapies. Although significant progress has been made, the overall survival rates for relapsed patients remain low. More research is warranted to improve outcomes and provide better support for these patients.

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