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## **The dilemma after chimeric antigen receptor T-cell therapy – to transplant or not?**

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has long been the definitive curative strategy for children and young adults with relapsed or high-risk acute lymphoblastic leukemia (ALL). Its anti-leukemic efficacy relies on both intensive cytotoxic conditioning and the graft-versus-leukemia effect<sup>1</sup>. The introduction of CD19-directed CAR T-cell therapy more than a decade ago transformed the treatment landscape of relapsed B-cell precursor ALL, by providing a targeted, immune-based option capable of inducing deep remissions in heavily pretreated patients. This led to the hope that durable disease control might be achievable without the long-term morbidity of HSCT<sup>2</sup>. However, real-world data have shown that relapse after CD19 CAR T-cell therapy occurs in nearly half of treated patients, and when consolidative HSCT is counted as an event, failure rates are even higher. Several factors have been associated with risk of failure post CAR T-cells, such as disease burden, rapid loss of B-cell aplasia, rising next-generation sequencing (NGS) minimal residual disease, and certain leukemia genomic features<sup>3</sup>. These have impacted decision making, despite lack of definitive data on when to intervene and what is the optimal intervention. In addition, the outcomes of relapse following CD19 CAR T-cells is dismal<sup>4</sup>.

The accompanying study by Myers et al. provides important insights by examining outcomes of 47 children and young adults undergoing first allo-HSCT after CD19 CAR T-cell therapy, either as pre-emptive consolidation or as treatment for post-CAR relapse<sup>5</sup>. The findings in the pre-emptive cohort are striking: a 3-year disease-free survival (DFS) of 90% and overall survival (OS) of 95%<sup>5</sup>. Inclusion of a child preemptively transplanted for rising NGS-MRD is notable, highlighting how ultra-sensitive detection of molecular recurrence may identify patients at high risk before overt relapse. These results underscore the potential benefit of pre-emptive transplantation in carefully selected individuals.

The outcomes of the post-CAR relapse cohort are similarly important. Achieving a 3-year DFS of 64% in patients transplanted predominantly in third or later remission represents a marked improvement over historical CR3 outcomes<sup>6</sup>. This finding is encouraging and supports allo-HSCT as a viable salvage strategy when deep remission can be re-established after relapse, in line with several additional studies from the contemporary era of T-cell engaging immunotherapy<sup>7,8</sup>.

However, we should take into account that the study design, starting from the endpoint of HSCT, underrepresents the full cohort of patients relapsing post CAR T-cells. In fact, this cohort represents only the subset of relapsed patients who responded to re-induction sufficiently to reach transplant in deep remission. Children with refractory relapse, persistent MRD, or significant toxicity after CAR T therapy are not included in this analysis, and continue to face poor outcomes. Thus, while these data highlight what is achievable in optimal circumstances, they do not describe the full post-CAR relapse population.

In addition, this cohort is composed entirely of transplant-naïve patients transplanted in deep remission, with all children MRD-negative by flow cytometry or negative/below the limit of detection by NGS. Additionally, the indication for preemptive transplant in 71% of patients was loss of B-cell aplasia (BCA), a known risk factor in CAR T-cells in ALL<sup>9</sup>. Recent work has described other interventions, such as maintenance therapy for such patients, showing similar

outcomes<sup>10</sup>. There is a need for prospective studies to evaluate whether HSCT is indeed required for patients losing BCA.

Taken together, this study provides valuable reassurance that allo-HSCT can achieve excellent results after CD19 CAR T therapy—whether used pre-emptively in high-risk patients or as salvage therapy for those who relapse but can achieve remission. These results therefore inform the efficacy of transplant in ideal candidates, but they cannot determine who should be transplanted, and whether alternative consolidations may also be beneficial. As the field moves toward increasingly personalized post-CAR strategies, integrating molecular monitoring, CAR kinetics, and patient-specific relapse biology will be essential. The work by Myers et al. brings us one step closer, defining a high standard for what post-CAR transplantation can achieve, and emphasizing the need for prospective studies to identify which children truly benefit from this intervention.

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