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

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Allogeneic hematopoietic stem cell transplantation (HSCT) has long been the definitive curative strategy for children and young adults with relapsed or high-risk acute lymphoblastic leukemia (ALL). Its antileukemic efficacy relies on both intensive cytotoxic conditioning and the graft-*versus*-leukemia effect.[1] The introduction of CD19-directed chimeric antigen receptor (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.[2] 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 after CAR T cells, such as disease burden, rapid loss of B-cell aplasia, rising minimal residual disease detected by next-generation sequencing, and certain leukemia genomic features.[3] 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 are dismal.[4]

The study by Myers e*t al*. published in this issue of *Haematologica* provides important insights by examining outcomes of 47 children and young adults undergoing first allogeneic HSCT after CD19 CAR T-cell therapy, either as pre-emptive consolidation or as treatment for relapse after CAR T cells.[5] The findings in the pre-emptive cohort are striking: a 3-year disease-free survival of 90% and overall survival of 95%.[5] Inclusion of a child pre-emptively transplanted for rising minimal residual disease detected by next-generation sequencing 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 disease-free survival of 64% in patients transplanted predominantly in third or later remission represents a marked improvement over historical third complete remission outcomes.[6] This finding is encouraging and supports allogeneic 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.[7,8] However, we should take into account that the design of the study by Myers *et al*., starting from the endpoint of HSCT, underrepresents the full cohort of patients relapsing after CAR T-cell therapy. 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 minimal residual disease, or significant toxicity after CAR T-cell 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 minimal residual disease-negative by flow cytometry or negative/below the limit of detection by next-generation sequencing. Additionally, the indication for pre-emptive transplant in 71% of patients was loss of B-cell aplasia, a known risk factor in CAR T-cell therapy in ALL.[9] Recent work has investigated other interventions, such as maintenance therapy for such patients, showing similar outcomes.[10] There is a need for prospective studies to evaluate whether HSCT is indeed required for patients losing B-cell aplasia.

Taken together, the study by Myers *et al*. provides valuable reassurance that allogeneic HSCT can achieve excellent results after CD19 CAR T-cell 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 consolidation may also be beneficial. As the field moves toward increasingly personalized post-CAR T-cell strategies, integrating molecular monitoring, CAR T-cell 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 T-cell transplantation can achieve, and emphasizing the need for prospective studies to identify which children truly benefit from this intervention.

Disclosures

No conflicts of interest to disclose.

Contributions

EJ and BB both wrote and approved the manuscript.

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