Post-CAR-T Cell Therapy (Consolidation and Relapse): Acute Lymphoblastic Leukaemia

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Role of consolidative allogeneic haematopoietic cell transplantation (allo-HCT) for B-cell acute lymphoblastic leukaemia (B-ALL) patients in minimal residual disease-negative (MRD) complete remission (CR) after CD19 CAR-T cell therapy.

The role of consolidative allo-HCT in B-ALL patients achieving MRD-negative CR after CD19 CAR-T cell therapy is still debated. At the last update of the ELIANA clinical trial, which investigated tisagenlecleucel in children and young adults with relapsed or refractory (R/R) B-ALL, the median duration of remission and overall survival was not reached (median follow-up, 24 months). The 24-month relapse-free survival probability in responders was 62%, with plateauing of the probability curves after 1 year (Grupp et al. 2019). Consolidation with allo-HCT was reported in only 9% of CR patients, suggesting that CD19 CAR-T cell therapy alone with tisagenlecleucel may be curative in a significant proportion of paediatric patients. In contrast, to date, the data do not suggest that CD19 CAR-T cell therapy is a definitive approach in most adults with R/R B-ALL. Across the main academic and industry-sponsored clinical trials of CD19 CAR-T cell therapy for adult B-ALL, the median durations of response ranged from 8 to 19 months, with important variations in the proportion of patients receiving consolidative allo-HCT in CR after treatment (35–75%) (Shah et al. 2019; Frey et al. 2020; Hay et al. 2019; Park et al. 2018). In our experience, we observed favourable outcomes in patients undergoing allo-HCT while in MRD-negative CR after defined-composition CD19 CAR-T cell therapy, with 2-year EFS and OS probabilities of 61% and 72%, respectively. After adjusting for previously identified prognostic factors for event-free survival (EFS; pre-lymphodepletion LDH concentration and platelet count, cyclophosphamide-fludarabine lymphodepletion), the hazard ratio for allo-HCT was 0.39 (95% CI

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0.13–1.15, $p = 0.09$), suggesting a beneficial effect on EFS. Based on these findings, our approach in adult patients is to recommend consolidative allo-HCT in adult patients with R/R B-ALL in MRD-negative CR after CD19 CAR-T cell therapy. Additionally, patient age and preferences, comorbidities, a history of prior transplant, and MRD must be taken into account. Investigators from the NCI/NIH (Lee et al. 2016) and Seattle Children's Hospital (Summers et al. 2018) reported a survival advantage in children and young adults consolidated with allo-HCT after CD19 CAR-T cell therapy. However, notably, to date, the available data rely on nonrandomized, retrospective analyses, and are potentially subject to important biases (Suisse 2007; Lévesque et al. 2010).

Management of Relapsed B-ALL After CD19 CAR-T Cell Therapy

CD19-Positive Disease After CD19 CAR-T Cell Therapy

If cryopreserved end-manufacturing CAR-T cells are available and the target antigen is still expressed, an attractive approach is to use the “left-over” cells to manufacture a second CAR-T cell product. We have shown that second CD19 CAR-T cell infusions are feasible and well tolerated, but in most cases directed at the murine single chain variable fragment (scFv) CAR domain, antitumour efficacy is limited by anti-CAR immune responses. We observed superior outcomes in patients who received cyclophosphamide and fludarabine lymphodepletion prior to the first CAR-T cell infusion and who received a higher CAR-T cell dose (10 times higher than the first CAR-T cell infusion). However, second CAR-T cell infusions achieved a CR in only 3 of 14 ALL patients (21%) (Gauthier et al. 2020). Efforts are underway to mitigate or circumvent anti-CAR immune responses using a CAR comprising humanized or fully human scFvs (Gauthier et al. 2018; Brudno et al. 2020). Maude et al. evaluated the use of the humanized scFv-bearing CD19 CAR-T cell product CTL119 in 38 children and young adults (Grupp et al. 2015). MRD-negative CR could be achieved in murine CAR-exposed patients (43%), although at a lower rate than in the CAR-naïve population (100%). The 12-month relapse-free survival probabilities in responding patients were 82% and 56% in the CAR-exposed and CAR-naïve cohorts, respectively. In another report, Cao et al. observed CR in 2 of 5 patients previously exposed to murine CD19 CAR-T cells (Cao et al. 2019). Further studies are needed to determine whether immunogenicity, poor CAR-T cell function or disease-related factors underlie the reduced efficacy of CD19 CAR-T cells employing fully human or humanized scFv in the murine CAR-exposed setting.

CD19-Negative Disease After CD19 CAR-T Cell Therapy

Encouraging results have been reported using CD22-targeted CAR-T cells, including in patients with CD19-negative B-ALL blasts after prior CD19 CAR-T cell therapy. Shah et al. reported their experience in 58 children and young adults with

R/R B-ALL, including 62% of patients who were previously treated with a CD19 CAR-T cell product (Shah et al. 2020). CD22 CAR-T cells achieved an MRD-negative CR in 61% of cases, with a median duration of response of 6 months (13 of 35 MRD-negative CR patients [37%] went on to receive allo-HCT). The MRD-negative CR rate in patients previously treated with CD19 CAR-T cells was 64%. In another report from Pan et al., CD22 CAR-T cells were administered to 34 children and adult patients. Prior failure of CD19 CAR-T cell therapy was documented in 91% of patients. CD22 CAR-T cells achieved MRD-negative CRs in 76% of patients. Responses were durable, with a 1-year leukaemia-free survival probability of 58% in CR patients (11 of 30 CR patients [37%] went on to receive allo-HCT) (Pan et al. 2019).

Key Points

- When feasible, allo-HCT should be offered to adult patients with R/R B-ALL in MRD-negative CR after CD19 CAR-T cell therapy.
- CD22 CAR-T cells are associated with high response rates after CD19 CAR-T cell failure, and the most durable responses are observed after consolidative allo-HCT.
- CD19 CAR-T cells with fully human or humanized scFv are under investigation to mitigate anti-CAR immune responses, potentially impeding the efficacy of repeat CAR-T cell infusions.

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