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Advances in cellular therapies

In this article we review 2 studies on CD19 CAR-T cells, which were presented at the annual meeting of the European Hematology Association (EHA) 2024 in Madrid, Spain. The first study investigates the efficacy and safety of CD19 CAR-T cell therapies in ≥75 years old patients. The second trial explores if CD19 CAR-T cells expressing interleukin-10 (IL-10) are more resilient to exhaustion and ultimately show a better response rate in DLBCL or B-ALL.

Chimeric antigen receptor T-cells (CAR-T cells) are targeted cellular therapies, commercially available for less than a decade. CAR-T cells are manufactured on an individual basis from the patients own T-cells: First T-cells are collected by leukapheresis, then transduced with a vector bearing the CAR construct and finally expanded for later reinfusion in the patient. The CAR construct converts the recognition of an antigen of choice into an activating signal, resulting in a cytotoxic response of T-cells (1). The first commercially available CAR-T cells express chimeric antigen receptors targeting CD19+ cells. CD19-CAR-T cells are currently available for therapy of diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and B-cell acute lymphoblastic anemia (B-ALL)(1,2).

CD19 CAR-T cell therapy in ≥75-year-old large B-cell lymphoma patients (Abstract S242)

CD19 CAR-T cells offer a curative therapy for relapsed or refractory patients with DLBCL (3). DLBCL patients ≥75-years (yrs) have been poorly studied so far. B. Goffroy et al. used the DESCAR-T registry, that includes patients receiving commercially available CD19-CAR-T cells in France (4), to comparatively study patients below versus (vs) above 75 yrs.

The two major concerns in elderly patients include a potentially lower efficacy as a result of immunosenescence on the one hand and higher treatment associated toxicity resulting from a higher comorbidity burden on the other hand. In total 1524 adult patients from 31 French centers were included. 1399 patients were <75 yrs and 125 patients ≥75 yrs. Neither the overall response rate indicated as median (95% CI): 78.0% (75.7% - 80.2%, 95% CI) in <75 yrs vs 74.8% (65.8% - 82.4%, 95% CI) in ≥75 yrs (p=0.425) nor the complete response rate 60.8% (58.1% - 63.4%, 95% CI) in <75 yrs vs 62.6% (53.1% - 71.5%, 95% CI) in ≥75 yrs patients (p=0.699) differed significantly. The progression free survival (PFS) was not significantly different either with 6.1 months (m) (5,7 m - 7,4 m, 95% CI) in <75 yrs vs 8.2 m (4.1m - 11.3m, 95% CI) ≥75 yrs patients (p=0.733). The overall survival (OS) showed no significant difference with 24 m (20.4m - 31.6m, 95% CI) in <75 yrs vs 18.3 m (9.4 m - 32.0m, 95% CI) in ≥75 yrs old patients (p=0.116). Non relapse mortality (NRM) was higher in ≥75 vs <75 yrs old patients: 19.5% vs 8.1%, respectively (p<0,0001), whereas early NRM < 28 days post-infusion was not statistically different in ≥75 versus <75 yrs old patients. Subsequent analysis has revealed that the differences in the late NRM are mainly the result of infections, cytokine release syndrome (CRS) and other causes but not Immune effector cell-associated neurotoxicity syndrome (ICANS).

In summary, CD19-CAR-T cell therapy in DLBCL patients ≥75 yrs is not less effective than in younger patients, as indicated by a comparable PFS. NRM is, however, higher in the patient population ≥75 yrs. These patients suffer more often from CRS and infection after CAR-T cell therapy and they may also suffer from health problems unrelated to CAR-T cell therapeutic side effects. Taking together, these data suggest that CD19 CAR-T cell therapy is also a feasible therapy in patients ≥75 yrs.

First in human IL-10 CD19 CAR-T cells (Abstract S281)

Despite the success of CD19 CAR-T cell therapy for B-cell malignancies, refractoriness and relapse remain a problem. Exhaustion and dysfunction of the CAR-T cells have been identified as possible reasons (5). Previous work demonstrates, that IL-10 stimulation of terminally exhausted CD8+ tumor infiltrating T-cells resulted in enhanced proliferation and effector function (6). IL-10 expressing CAR-T cells may display increased resilience towards exhaustion and are more efficient in eradicating malignancies. Wang et al. provided insight into the ongoing first-in-human study of IL-10 expressing CD19 CAR-T cells in patients with either DLBCL or B-ALL in the study. As of the time point these results were reported, 9 patients suffering from DLBCL and 8 patients with B-ALL were included. The complete remission rate was provided at the following time points after infusion: 1m 17/17 patients, 3m 10/10 patients, 6m 6/7 patients. One patient with B-ALL suffered from a relapse after 4.6m. No relapse was observed in patients with DLBCL. In patients with DLBCL, the median peak of CAR-T cell expansion was after 12 days (d) (range 10-22d) and reached 41.1% (range 6.9 – 85.7%) of total lymphocytes. In B-ALL the peak of CAR-T cells was after 11 d (range 8-15d) expanding to 47.7% (range 20.2 – 70%) of total lymphocytes. All patients showed CRS, while one patient suffered from grade 3 CRS. One patient had ICANS. Early Immune effector cell–associated hepatotoxicity (ICAHT) was observed in 15 patients and late ICAHT in one patient. In summary, the data available up to the present time point is encouraging. While only one relapse of a B-ALL was recorded so far, no relapse in the DLBCL patient group was found. However, these data are still preliminary. If the low relapse rate holds true for a longer observation interval and a larger patient cohort, IL-10 producing CD19 CAR-T cells may constitute an impressive improvement in CD19 CAR-T cell therapy. □

Author: Dr. med. Dr. phil. II Laurent Schmied, Department of Hematology, University Hospital Basel.
Mentor: Prof. Dr. med. Gabriela M. Baerlocher, Clinic for Hematology and Oncology, Hirslanden Zürich

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