Highlights in CAR T-Cell Therapy from EHA2021: Paving the Way for Better Treatments

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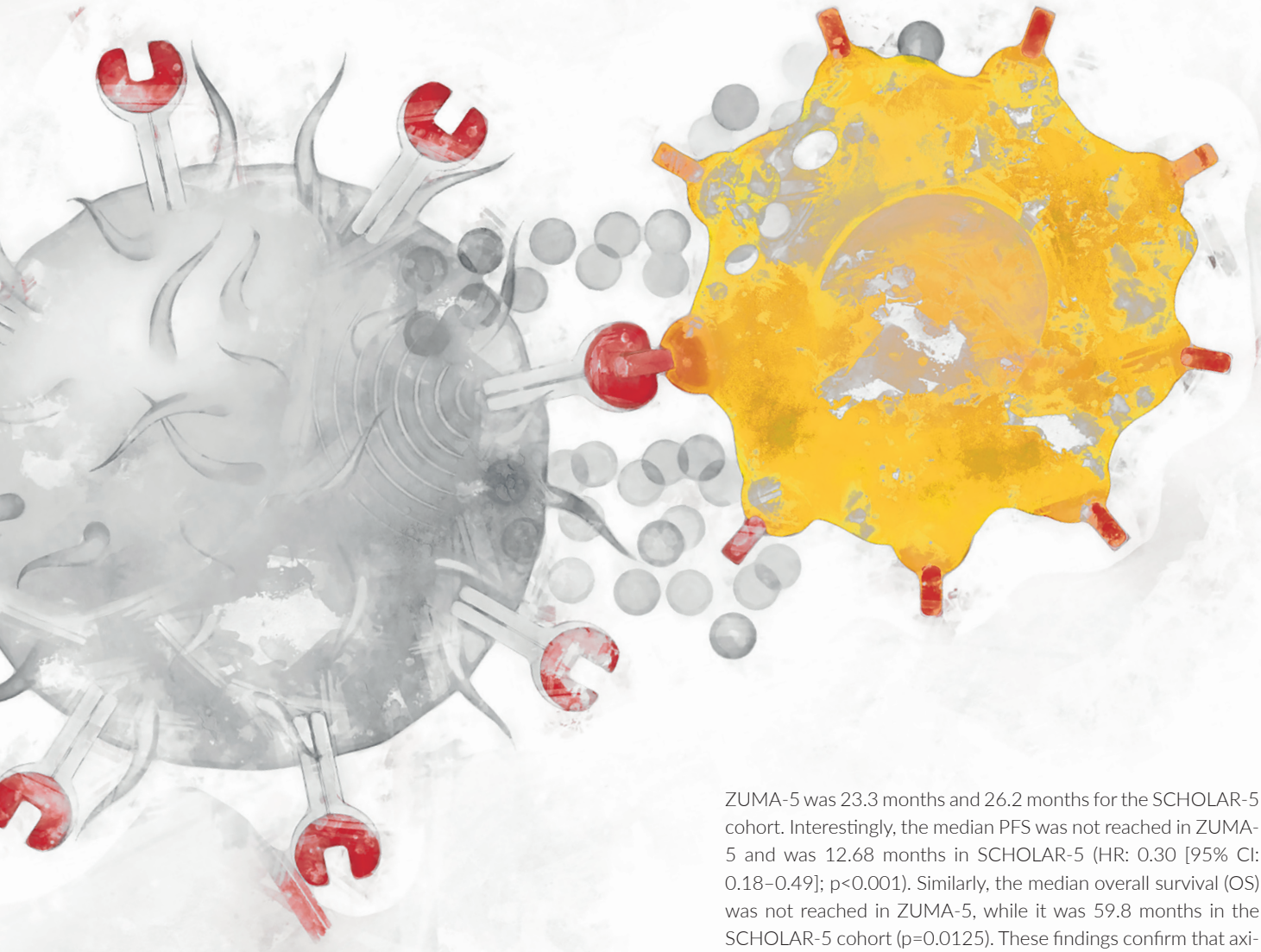
CAR T-cell therapy in DLBCL

Before the approval of the first chimeric antigen receptor (CAR) T-cell therapy for patients with diffuse large B-cell lymphoma (DLBCL) in Europe, treatment options after the first and second line were limited. Thanks to the approval of CAR T-cell therapies, there is a new set of options to treat patients with DLBCL. Currently, there are three CD19-targeted CAR T therapies approved in the United States for the treatment of patients with relapsed or refractory (R/R) DLBCL, namely tisagenlecleucel (tisa-cel)[1], axicabtagene ciloleucel (axi-cel)[2], and lisocabtagene maraleucel (liso-cel)[3]. Only tisa-cel[4] and axi-cel[5] are authorized so far for the treatment of this patient population in Switzerland. The approvals were based on the results of three pivotal trials, namely, JULIET[6], ZUMA-1[7], and TRANSCEND-001[8], which assessed the efficacy and safety of tisa-cel, axi-cel and liso-cel, respectively, in heavily pretreated patients with R/R DLBCL. Interestingly, the estimated progression-free survival (PFS) rate was approximately 40% in all three studies. However, further real-life studies are needed to investigate the effect of these CAR T-cell therapies in this patient population.

At EHA2021, the first results of DLBCL patients treated with CAR T-cells from the DESCAR-T registry, the French real-life database were presented.[9] In this multicenter, retrospective analysis, a total of 550 patients were treated with either tisa-cel (n=200) or axi-cel (n=350). So far, this is the largest reported data series in this patient population; however, with a limited median follow-up of 6.5 months, the long-term effect of the CAR T-cell treatment cannot be evaluated. At 6 months, the PFS rate (44.5%) was comparable with the previously reported results from the pivotal studies with tisa-cel[6] and axi-cel[7]. Due to the large size of the cohort, patients were stratified based on the remission status, a requirement of bridging therapy and progressive disease (PD) at the time of CAR T-cell injection. Of note, PD was clearly indicated as a predictor of poor outcome. Among patients who had PD at the time of treatment, a 38.2% 6-months PFS rate was observed in patients receiving axi-cel while 17.1% 6-months PFS was observed in those treated with tisa-cel.

Does allogeneic HSCT still have a place next to CAR T-cell therapy?

With the arrival of CAR T-cell therapy, the place for allogeneic hematopoietic stem cell transplantation (alloHSCT) in the treatment algorithm of DLBCL was increasingly questioned. Both treatment strategies have their advantages and inconveniences.[10] Importantly, several important differences exist in the treatment algorithm for these two different strategies: in particular, while the response to salvage therapy is required for alloHSCT; it is not required for CAR T-cell therapy. The long-term overall survival (OS) is similar for both therapies, with 40%–50% for alloHSCT and 35%–40% for CAR T-cell therapy. Both strategies are associated with specific toxicities like graft versus host disease (GVHD) for alloHSCT (~20%) and cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) in CAR T-treated patients (~5%). While the cost is currently much higher for CAR T-cell therapy, this could partly be ascribed to the novelty and may change in the future. Overall, both treatments show a satisfying ratio of immune versus lymphoma effects and are available as standard of care (SOC) in most countries, although alloHSCT could be especially beneficial in patients with DLBCL in regions where CAR T-cell therapy is not available. Importantly, both treatments are not mutually exclusive and can be combined: allogeneic HSCT could be an option in case of relapse after CAR T-cell therapy or in patients who have not achieved complete remission (<CR) or minimal residual disease negativity (MRD-), as well as in patients with poor bone marrow or with a therapy-related myeloid disorder.[11] In addition, allogenic transplantation could be essential for R/R DLBCL patients when there is manufacturing failure of CAR T-cells or a CD19-negative relapse.[11]



CAR T-cells in follicular lymphoma as a second indication for axicabtagene ciloleucel

Axi-cel has recently been granted approval by the Food and Drug Administration (FDA)[2] for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after ≥2 lines of systemic therapy; however, it is still not approved in Europe and Switzerland for this indication. The FDA approval was based on the results of the pivotal phase II ZUMA 5 trial, which showed that axi-cel, induced high rates of durable response in patients with indolent non-Hodgkin lymphoma (iNHL) who had failed ≥2 prior lines of therapy.[12] At EHA2021, Prof. Dr John Gribben presented the results from a weighted analysis using propensity score methods comparing clinical outcomes from the ZUMA-5 and SCHOLAR-5 trials in patients with R/R FL.[13] SCHOLAR-5, an international, multicenter external control cohort, aimed to provide comparative evidence in patients with R/R FL meeting ZUMA-5 eligibility criteria. The patients in the SCHOLAR-5 cohort were those who initiated a ≥3 line of therapy (n=118) and patients from the pivotal DELTA trial (n=25). Overall, the study included 86 patients from ZUMA-5 and 85 patients from the SCHOLAR-5 cohort. After propensity score weighting, all patient and clinical characteristics were well-balanced between the two groups of patients, except for Eastern Cooperative Oncology Group (ECOG) performance status (PS), with more patients in SCHOLAR-5 versus ZUMA-5 having ECOG PS of 1 at baseline (71% vs 40.7%). The median follow-up time for ZUMA-5 was 23.3 months and 26.2 months for the SCHOLAR-5 cohort. Interestingly, the median PFS was not reached in ZUMA-5 and was 12.68 months in SCHOLAR-5 (HR: 0.30 [95% CI: 0.18–0.49]; p<0.001). Similarly, the median overall survival (OS) was not reached in ZUMA-5, while it was 59.8 months in the SCHOLAR-5 cohort (p=0.0125). These findings confirm that axi-cel is a very promising treatment option for patients with R/R FL.

CAR T-cell therapy in multiple myeloma

In March 2021, FDA approved idecabtagene vicleucel (ide-cel), a B-cell maturation antigen (BCMA)-directed genetically modified CAR T-cell therapy for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) after ≥4 prior lines of therapy, including an immunomodulatory agent (ImiD), a proteasome inhibitor (PI) and an anti-CD38 monoclonal antibody.[14] The approval was based on results from the pivotal phase II KarMMa study evaluating the efficacy and safety of ide-cel in 128 heavily pretreated RRMM patients in this setting.[15] At EHA2021, Dr Albert Oriol presented an update on the KarMMa study which showed that ORR of 73%, including a complete response rate (CRR) of 33%, was achieved in ide-cel treated patients.[16] Despite these high response rates, PFS was limited to 8.6 months in this population. However, considering that these patients were heavily pretreated, the PFS is still promising. Several efforts are being taken to improve the PFS in RRMM patients by applying ide-cel earlier in the treatment algorithm; e.g., the phase III KarMMa-3 study which is comparing ide-cel to standard regimens in triple-class-exposed MM patients with 2–4 prior lines of therapy,[17] while the phase I KarMMa-4 study focuses on patients with high-risk newly diagnosed MM[18] and finally, the exploratory phase I/II KarMMa-7 study assesses ide-cel combination therapies in patients with RRMM[19].

Ciltacabtagene autoleucel (cilta-cel) is a second-generation BCMA-directed CAR T-cell therapy that has been investigated in the CARTITUDE-1 trial in RRMM patients (n=97) who had received ≥3 prior lines of therapy, with an ECOG PS ≤1, and had received a PI, an IMiD, and anti-CD38 therapy prior to treatment with cilta-cel.[20] The updated results of the CARTITUDE-1 trial presented by Dr Saad Z. Usmani showed that at a median follow-up of 18 months, ORR was 97.9% with a stringent complete response (sCR) rate of 80.4%.[21] Moreover, among MRD-evaluable patients (n=61), the great majority of patients (91.8%) were MRD negative (threshold: 10^{-5}). At a median follow-up of 18 months, the PFS was 66.0% and 18-months OS was 80.9%. Considering these very promising results, cilta-cel is currently under review for approval in the US and Europe.[22,23]

There are currently ongoing trials evaluating cilta-cel in lenalidomide refractory patients with progressive disease after 1–3 lines of MM therapy (CARTITUDE-2) and comparing cilta-cel with standard treatment in relapsed and lenalidomide-refractory MM patients (CARTITUDE-4).[24,25] Initial results from cohort A from the multicohort trial CARTITUDE-2 were presented at EHA2021 by Dr Mounzer E. Agha.[26] A total of 20 patients in cohort A of the CARTITUDE-2 trial received a single cilta-cel infusion. The primary endpoint of the study was MRD negativity ($<10^{-5}$ threshold). The secondary outcomes included ORR, duration of response (DOR), time and duration of MRD negativity and safety. At a median follow-up of 5.8 months, the ORR was 95%, with 75% of patients achieving a complete response (CR) or better and 45% achieving a sCR. The median time to first response was 1 month and the median time to CR or better was 1.9 months. At data cutoff, the median DOR was not reached. All patients evaluable for MRD (n=4) were MRD negative. Taken together, cilta-cel) led to early and deep responses in RRMM patients in this setting.

In conclusion, CAR T-cell therapy is, to use a metaphor employed by Prof. Cathrine Thieblemont at EHA2021, an additional stepping stone in the treatment of patients with DLBCL and RRMM. Hopefully, it can pave the path for patients with many other indications in the future, together with other available treatment approaches.

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