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LETTER

Chimeric antigen receptor T-cell therapy outcomes in T cell/histiocyte-rich large B-cell lymphoma and subsequent treatment strategies after disease progression: A GELTAMO/GETH study

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Chimeric antigen receptor T-cell therapy (CAR-T) is an effective approach for patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL). However, some rare variants do not seem to respond as well to this T-cell redirecting strategy. T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) is an infrequent subtype of LBCL which typically develops in young, male patients, characterized by an aggressive clinical course and chemo-refractory disease.[1,2] THRLBCL has unique biological characteristics and a inhibitory tumor immune microenvironment.[3,4] It is well-known that the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway is a key driver of immune escape;[5,6] this lymphoma subtype has been associated with PD-L1 gene alterations, such as PD-L1 copy gains and high PD-L1 expression on malignant B cells (often surrounded by abundant PD-L1–expressing macrophages and PD-1 + T cells). This distinct clinical behavior, together with its low incidence, have led to an underrepresentation of THRLBCL patients in most clinical trials, including those evaluating CAR T-cell therapy. Therefore, real-world data with this entity is highly anticipated. Taking all of this into consideration, we aimed to assess the safety and efficacy outcomes of THRLBCL after CAR T-cell therapy, outside of the clinical trial setting, as well as the efficacy of postrelapse approaches.

We carried out a retrospective, multicentre study including all adult patients with this diagnosis registered in the GELTAMO/GETH-TC database (Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea/Grupo Español de Trasplante Hematopoyético y Terapia Celular) from April 2019 to January 2024 who had received a CD19-targeted CAR T-cell infusion. The primary endpoint was overall survival (OS) and the secondary endpoints were response rate, progression-free survival (PFS), duration of response (DR), and subsequent therapy outcome. Twenty patients with R/R THRLBCL from 11 Spanish centers received CAR T-cell therapy from April 2019 to December 2023. If the patient had experienced disease progression after CAR-T, participating centers completed an additional database on subsequent treatments and their outcomes. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to the ASTCT consensus criteria.[7] Response assessment followed the Lugano recommendations.[8] OS and PFS were determined from CAR-T cell infusion for CAR T-cell outcomes and since the start of the first subsequent treatment for the following approaches. These were calculated using the Kaplan–Meier method and the Cox model to obtain hazard ratios (HR) with 95% confidence intervals (CI) and *p*-values. All reported *p*-values were two-sided, and statistical significance was defined at

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$p < 0.05$. Statistical analyses were performed using R software version 4.2.2.

In terms of baseline characteristics, median age was 50 years (interquartile range [IQR]: 40–64) and 16 patients (80%) were male. The International Prognostic Index (IPI) score at time of CAR-T was ≥3 in 55% of patients, and 52% had an Eastern Cooperative Oncology Group performance status (ECOG-PS) ≥ 1. Two patients (10%) received the CAR-T in the second line, 16 (80%) in third line, and 2 (10%) in fourth line. Considering the construct, 11 (55%) received axicabtagene ciloleucel (axi-cel), 8 (40%) tisagenlecleucel (tisa-cel), and 1 (5%) lisocabtagene maraleucel, which was administered in a clinical trial. Nineteen patients (95%) received bridging therapy (8 platinum-based regimens with Rituximab (R), 7 cyclophosphamide-R based regimens, 2 radiotherapy, 1 polatuzumab-bendamustine-R, 1 brentuximab monotherapy, 1 pembrolizumab monotherapy) (Supporting Information S1: Table 1).

Concerning the safety profile, any (grade ≥3) CRS and ICANS rates were 85% (5%) and 50% (15%), respectively. One patient infused with tisa-cel died in the context of severe CRS and hemophagocytic syndrome. All other deaths in the analysis were due to disease progression. Regarding efficacy, the overall and complete response rate [ORR, CRR]) was 50% and 25%, respectively (Figure 1); all cases of CR occurred in axicel-treated patients. In the univariate analysis, factors associated with achieving CR versus other response were a lower pretreatment LDH level (median 182 vs. 682, $p = 0.03$), the use of axi-cel ($p = 0.05$), a low IPI score (IPI 0-2) at time of CAR-T ($p = 0.03$), and having received a prior autologous stem cell transplantation (ASCT) ($p = 0.03$). Regarding the risk of relapse, only a low IPI (I/II) pre-CART (HR: 1.73, 95% CI: 1.08–2.7, $p = 0.04$) and a prior ASCT (HR: 0.27, 95% CI: 0.08–0.9, $p = 0.03$) were significant. With a median follow-up of 25 months (95% CI: 13–NA) from CAR-T infusion, the median PFS and OS were 3.3 (95% CI: 1.4–11) and 9.2 months (95% CI: 6.1–NA), respectively. The 12-month PFS and OS were 23% and 43%, respectively (Supporting Information S1: Figure 1A,B). Supporting Information S1: Figure 1 shows the univariate analysis for responses, PFS, OS, and response. The median DR was 3.9 months (95% CI: 2–NA). In all cases, CAR-T expansion was observed. Of the 14 cases with persistence data, only in two cases the CAR-T did not persist at 6 and 12 months; however, in all cases, there was B cell aplasia at the time of the last follow-up. Eighteen (90%) patients experienced progressive disease (PD) after CAR-T-cell therapy, with a median OS since PD of 5.1 months (3.7, NR) and a 24-month OS of 24.2% (9.6–61.1). Ten (56%) of the 18 patients with PD after CAR-T received subsequent treatment, with a median PFS and OS of 3.6 (2.9–not reached) and 6.5 (3.0–not reached) months, respectively (Supporting Information S1: Figure 2C,D). This showed a clear trend towards improved survival compared to patients who only received best supportive care after CAR-T failure. in comparison to patients who only received best supportive care after CAR-T failure (Supporting Information S1: Figures 2 and 3). The median time from CAR-T progression to next therapy was 42.5 (IQR: 38–50.5; range = 4–57). In terms of the subsequent treatment outcomes, 5/10 patients achieved a response, using regimens based on checkpoint inhibitors (pembrolizumab, atezolizumab), polatuzumab, and tafasitamab-lenalidomide (Figure 1). Two patients achieved a CR, after radiotherapy ($n = 1$) and pembrolizumab monotherapy ($n = 1$). One patient treated with atezolizumab-glofitamab (a 1-year fixed-duration treatment) achieved a PR that is still ongoing after 2.5 years. No significant immune toxicities were observed in patients treated with CPI and/or BiAb after CAR-T. Only one patient underwent an allogeneic stem cell transplantation as consolidation after achieving a PR with four cycles of Tafasitamab-Lenalidomide, and maintains the response 6 months after the transplant.

CAR T-cell therapy is the standard of care for LBCL patients with an early (<12 months) relapse after frontline therapy or for patients after a second relapse, due to the high response rate, DR, and survival improvement, compared to alternative regimens.[9–13] Most of the pivotal trials included patients with diffuse large B-cell lymphoma, transformed follicular lymphoma, and high-grade B-cell lymphoma. However, THRLBCL was usually excluded due to its low incidence and distinct biological profile. In this study, we report one of the largest real-world cohorts of THRLBCL receiving CAR T-cells and provide a detailed analysis of subsequent treatment strategies.

Trujillo et al. published the first series of patients with THRLBCL treated with CAR-T ($N = 9$), with dismal outcomes after this T-cell redirecting strategy,[6] suggesting a potential refractory behavior in this patient population. They hypothesized that CAR T-cell failure in THRLBCL appeared to be related to acquired CAR T-cell dysfunction, rather than poor CAR-T cell expansion.[14] Recently, Pophali et al reported a 2-year PFS and OS of 29% and 42%, respectively, in

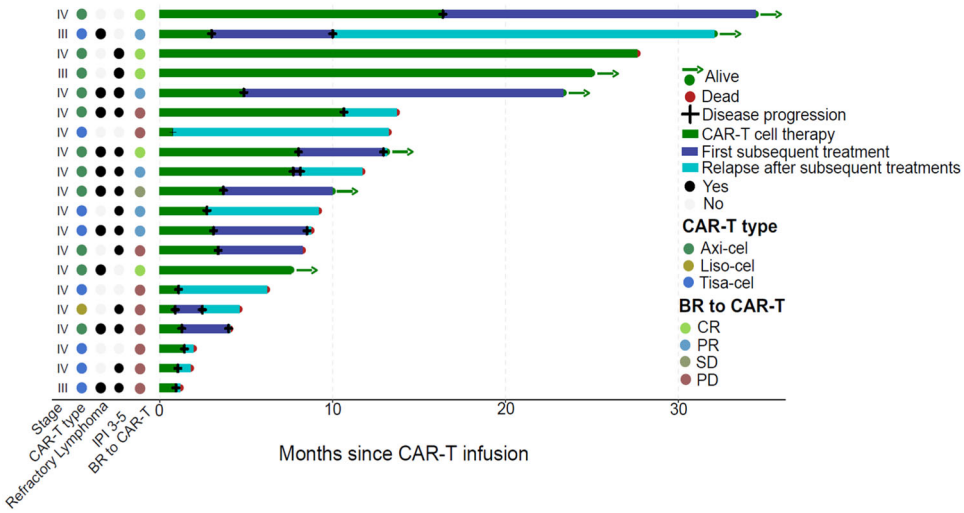

FIGURE 1 **Outcome of patients treated with CAR-T therapy, highlighting the lymphoma stage, type of product, lymphoma risk, response obtained, relapse, and current situation.**

58 R/R THRLBCL patients treated with CAR T-cells;[15] in this study, ECOG-PS was the only factor with an impact on survival. However, beyond these intriguing data, there have been very few studies focused on the clinical characteristics and response patterns to CAR-T therapy in this infrequent disease entity.

Similar to these series, patients in our study had poor outcomes, with a median PFS and OS of 3.3 and 9.2 months, respectively. Interestingly, the patients achieving CR were those with a low LDH, early stage and low-risk IPI at time of CAR-T cell therapy. However, regardless of the response to CAR-T, 18 out of 20 patients experienced disease progression, in syntony with the previously mentioned studies. Strikingly, our long-term OS for the patients rescued after CAR-T relapse was very similar to that reported by Pophali et al., with 40% of patients alive at 2 years. Considering the high relapse rate, effective subsequent strategies seemed to be the underlying reason for these long-term outcomes. In our dataset, among patients receiving treatment after CAR-T relapse ($N = 10$), 2-year OS was 44%, even though most were early relapses (30% <3 months, 70% <6 months), significantly higher in comparison to other reports including outcomes of R/R LBCL patients with an early relapse post-CAR-T.[16] Patients receiving PD1-blockers and bispecific antibodies presented better outcomes, supporting the hypothesis that THRLBCL could be responsive to PD-1 blockade therapy in light of the exceptionally high numbers of PD-L1-expressing tumor-associated macrophages and PD-1 + T cells that surround the malignant B cells.[5]

Concerning toxicity, incidence and severity of short-term adverse events, such as CRS and ICANS, were similar to the pivotal trials and real-world DLBCL data.[17,18]

The main limitation of our study is the small sample size, as well as the lack of centralized pathology review. However, despite this drawback, we report long follow-up after CAR-T infusion and provide insight into subsequent treatment strategies, which remain an important knowledge gap in this particular setting.

In conclusion, the efficacy of CAR T-cell therapy was significantly lower for THRLBCL patients in comparison with LBCL patients. However, response rates to subsequent treatment were encouraging. In light of the results with checkpoint inhibitors or bispecific antibodies in the post-CART scenario, the development of clinical trials focused on this patient population exploring combination strategies with CAR-T is highly anticipated.

AUTHOR CONTRIBUTIONS

Mariana Bastos-Oreiro and Gloria Iacoboni designed research, performed research, collected, analyzed and interpreted data, and wrote the paper. Víctor N. Garcés performed the statistical analysis. Ana C. Caballero, Javier Delgado, Aitana Balaguer, Mi Kwon, Sonia Gonzalez de Villambrosia, Ana Jimenez-Ubieto, Rebeca Bailen, and Alejandro Martín García-Sancho collected data and performed research. Pere Barba designed research, conceptualized, and supervised the study.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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