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Review Article

CAR-T Cell Therapy for Follicular Lymphomas

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Abstract. Follicular lymphoma is the second most diagnosed lymphoma in Western Europe. Significant advancements have considerably improved the survival of FL patients. However, 10-20% of these patients are refractory to standard treatments, and most of them will relapse. The treatment of follicular lymphoma patients with multiply relapsed or refractory disease represents an area of high-unmet needing new treatments with stronger efficacy. Chimeric antigen receptor (CAR)-T cell therapy targeting B-cell antigens, such as CD19 or CD20, is emerging as an efficacious treatment for R/R follicular lymphoma patients, particularly for those with early relapse and refractory to alkylating agents and to anti-CD20 monoclonal antibodies, resulting in a high rate of durable responses in a high proportion of patients.

Keywords: CAR T; Follicular lymphoma.

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Introduction. Follicular lymphoma (FL) is an indolent B-lymphoproliferative disease of transformed follicular center B cells, characterized by diffuse lymphadenopathy, bone marrow involvement, and splenomegaly. FL is the second most diagnosed lymphoma in Western Europe. At the molecular level, FL is characterized by the presence of a chromosomal translocation, t(4;18), resulting in the overexpression of the anti-apoptotic protein BCL-2; additional recurrent genetic alterations consist in mutations of chromatin modifying genes *KMT2D*, *CREBBP* and *EZH2*.

Significant advancements have been in the treatment of FL in the last two decades. Survival of FL patients has improved significantly due to the development of efficacious front-line treatments involving anti-CD20 antibodies combined with chemotherapy or lenalidomide. Furthermore, the treatment of FL patients with relapsed/refractory disease evolved during the last years, with the introduction of new classes of drugs, including immunomodulatory agents, phosphoinositide 3-kinase inhibitors, and epigenetic modulators, in addition to the standard treatments (cytotoxic agents, anti-CD20 antibodies and allogeneic hematopoietic stem cell transplantation).[1] However, the treatment of patients with multiple relapsed or refractory FL represents an area of high unmet need for which newer treatments with stronger efficacy or novel mechanisms of action are required. In this context, two novel T-cell engager therapies, namely bispecific antibodies and chimeric antigen receptor (CAR)-T cell therapy, have been recently introduced in the treatment landscape of FL patients with R/R disease.

CD19 CAR-T Cells Used in the Treatment of FL

Patients

Initial studies. Initial studies carried out using CD19-targeted CAR-T cells have involved treating a few non-Hodgkin lymphoma (NHL) patients and have shown high-rate responses, including complete responses.[2-4]

The Fred Hutchinson Cancer Research Center reported the results on a few FL patients treated with CD19 CAR-T on a 1:1 ratio of CD4/CD8$^+$ T-cells and the co-stimulatory molecule 4-1BB.[5] The phase I/II clinical trial using these cells reported a high rate of ORR and CR in patients with B-cell lymphomas, including FLs.[6] In fact, Hirayama et al. reported a clinical study on 21 patients with R/R FL (8 patients) and with transformed FL (13 patients); after lymphodepletion with cyclophosphamide and fludarabine, the patients were infused with 2x10^6 CD19 CAR-T cells per kilogram.[6] The CR rates were 88% for R/R FL patients and 46% for patients with histological transformation (tFL). All patients who achieved a CR remained in remission at a median follow-up of 24 months.[6] For tFL patients who achieved a CR, at a median follow-up of 38 months, the median PFS was 11.2 months.[6] No severe toxicity events related to CRS or neurologic events were observed.[6]

Tisagenleucel. The University of Pennsylvania reported initial results in FL patients using CTL 019 anti-CD19 CAR-CD3ζ-4-1BB lentiviral gene vector transfer (this vector will become tisagenleucel) in T cells of 15 R/R FL patients who have received multiple lines of therapy [7]. An update of these patients reported a five-year PFS of 43% in these patients.8

CTL 019 represented the basis for developing the Tisagenleucel (Tisa-Cel) industrial product. Tisa-Cel is an autologous anti-CD19 CAR-T cell therapy with clinically demonstrated efficacy in patients with various B-cell malignancies. An initial pivotal study showed that 71% of R/R FL patients treated with Tisa-Cel achieved a CR. Based on this evidence, the phase II ELARA trial evaluated the safety and efficacy of Tisa-Cel in 97 R/R FL patients with two or more lines of prior treatments or relapsing after autologous HSCT[9] (**Table 1**). ORR was 86%, with a CRR of 69%.[9] Although cytokine release syndrome (CRS) and neurological events were frequently observed, these events were of mild entity, with only 0-3% of patients exhibiting grade ≥3 toxicity events.[9]

Since ELARA is a single-arm trial, a subsequent study performed a comparative effectiveness analysis to compare historical control data from a matched retrospective cohort of patients with R/R FL treated with standard care.[10] This analysis showed a better efficacy of Tisa-Cel with respect to standard care: ORR was 86% for Tisa-Cel compared to 64% for standard treatment; at 12 months, PFS was 70.5% for Tisa-Cel and 52% for standard care; 12-month OS was 97% for Tisa-Cel compared to 72% for usual care.[10]

Fowler et al. reported an analysis of healthcare resource utilization and hospitalization costs for the patients with R/R FL undergoing CAR-T cell therapy with Tisa-Cel, comparing inpatients (88% of total) to outpatients (12% of total).[11] The results of this analysis showed that the therapeutic efficacy of Tisa-Cel between these two groups of patients was similar; these findings support the view that Tisa-Cel can be safely administered to some R/R FL patients in the outpatient setting, thus reducing healthcare resource utilization and hospitalization costs.[11]

Axicabtagene Ciloleucel. Axicabtagene Ciloleucxel (Axi-Cel), previously known as KTE-C19, is based on three components: an extracellular domain with the svFc domain targeting CD19, a transmembrane or hinge domain and an intracellular signaling domain composed by a CD3zeta activation subdomain coupled with the stimulatory molecule CD28 (CD19-CD28-CD3ζ).

ZUMA-5 is a single-arm, multicenter, phase II trial that included 124 patients with R/R FL, mostly at stage IV (85%), with bulky disease (52%), and frequently pretreated with more than three lines of therapy (62%) or with progression of disease within 24 months of receiving chemoimmunotherapy (55%) or who failed to a previous ASCT (24%)[12] (**Table 1**). After conditioning lymphodepletion chemotherapy (cyclophosphamide and fludarabine), the patients received a single infusion of Axi-Cel (2x10^6 CAR-T cells per Kg).[12] Among 84 FL patients who were eligible for the primary analysis, the ORR was 94%, with 79% of patients achieving a CR.[12] According to the updated 3-year follow-up analysis of ZUMA-5, at a median follow-up of 40.5 months, the median duration of response (DOR) PFS and OS were 38.6, 40.2 and not reached, respectively. Long-term PFS rates were also high in patients with high tumor burden and >3 lines of prior therapy.[13]

A final report of the ZUMA-5 trial with a three-year follow-up was recently published. A ottal of 127 FL patients were evaluated, with an ORR of 94%, 79% of CR and 19% of PR; the median DOR was 38.6 months, with an estimate of 57% at 36 months; the median duration of CR was not reached, with 62% of CRs at 36 months; the median duration of PR was of only 4.9 months.[14] Importantly, all 13 patients retreated with Axi-Cel responded to the treatment, with a DOR of 5 months.[14] Median PFS was 40.2months, with a 36-months PFS rate of 54%.[14] Two events of disease progression and 10 deaths occurred >24 months after CAR-T treatment. The estimated cumulative PFS rate was 32%.[14] The median OS was not reached, with an estimated OF at 36 months of 76%; the 36-month cumulative incidence of lymphoma-specific death was 13%.[14] It is important to note that patients in ZUMA-5 who had recent exposure to bendamustine (within 6

Table 1. Main clinical studies of CAR-T cell therapy in R/R FL patients.

CAR-T cell product	Clinical study (phase)	Prior lines of therapy	Number of patients	ORR (%)	CRR (%)	PFS	OS	DoR	CRS (grade ≥3)	ICAN (grade ≥)
Axi-Cel	ZUMA-5 (II)	≥2	124	94	79	40.2 months	Not reached	38.6 months	78% (6%)	56% (18%)
Tisa-Cel	ELARA (II)	≥2	97	86	69	29.5 months	At 12 months 97%	NR	48.5% (0%)	23% (1%)
Liso-Cel	TRANSCEND (II)	≥2	101	97	94	12 months 81%	NR	12 months 82%	58% (1%)	15% (2%)

months) had shorter PFS after Axi-Cel, a phenomenon seemingly related to the immunosuppressive effects of bendamustine.[14] Longer follow-up will be required to assess the curative potential of Axi-Cel in FL patients. A phase 3 randomized trial was launched to evaluate the benefit of Axi-Cel compared to standard-of-care therapy for R/R FL patients (ZUMA-22; NCT 05371093).

A subsequent study compared the outcomes from ZUMA-5 with the International Scholar-5 cohort involving R/R FL patients treated with a third or higher line of standard therapy.[14] This comparative analysis showed a consistent improvement in outcomes related to Axi-Cel administration: the ORR and CRR were 50% and 30%, respectively, in Scholar-5 and 94% and 79%, respectively in ZUMA-5; the median OS and PFS in Scholar-5 were 59.8 months and 12.7 months, respectively, compared to not reached in ZUMA-5.[15] Thus, compared with available therapies, Axi-Cel showed a consistent clinical improvement in treating R/R FL patients after 3 or 4 lines of treatment.

A real-world study analyzed early outcomes in 151 R/R FL patients undergoing treatment with Axi-Cel: ORR and CRR were 93% and 84%, respectively; estimated PFS and OS at 6 months were 88% and 96%, respectively; grade ≥3 CRS and ICANS occurred in 2% and 13% of patients, respectively.[16] These findings supported the broad use of Axi-Cel for treating R/R FL.

Lisocabtagene maraleucel. Lisocabtagene maraleucel (Liso-Cel) is an autologous, CD19-directed, CAR-T cell product. Liso-Cel was approved by the FDA for second-line treatment of large B cell lymphoma.

The open-label, single-arm, multicenter phase II study enrolled patients with R/R FL who were at least 18 years of age, who had an ECOG performance status of 0 or 1, and who had previously received 2 or 3 lines of therapy and ≥2 prior combination systemic therapy, including an anti-CD20 antibody and an alkylator[17] (**Table 1**). Patients were treated with one single infusion of Liso-Cel ($100x10^6$ CAR-T cells) after lymphodepleting chemotherapy. 101 patients were suitable for analysis of efficacy. ORR was 97%, with a CR rate of 94%, 1 and 2-month DOR and PFS were 82% and 81%, respectively. The grade ≥3 CRS and neurologic events were very rare.[17]

Comparative Analysis of the Results Observed in ZUMA-5 and ELARA Trials. Mothy and coworkers have performed a comparative analysis of the results observed in the ZUMA-5 and ELARA trials. The ORR, CRR, and PFS were slightly better in ZUMA-5 (Axi-Cel) than in the ELARA (Tisa-Cel) trial: 92% vs. 86%, 76% vs. 69%, and 39.6 months vs. 29.5 months, respectively.[18] However, the ELARA study included more patients with advanced, bulky, and refractory disease compared to ZUMA-5 trial: ≥3 FLIPI 59.8% in ELARA and 44% in ZUMA-5; POD24 59.8% in ELARA and 55% in ZUMA-5; median number of prior therapies 4 in ELARA and 3 in ZUMA-5; prior autologous HSCT 36.4% in ELARA and 24% in ZUMA-%; patients with refractory disease 77.3% in ELARA and 68% in ZUMA-5.[18]

CD20 CAR-T Targeting in FL Patients. Some recent studies based on the treatment of a few R/R FL patients have provided evidence about the efficacy of CAR-T cells targeting CD20 or CD20 in combination with CD19.

Shadman and coworkers reported the development of MB-106, a third-generation CD20-targeted CAR-T with both 4-1BB and CD28 co-stimulatory domains.[19] A first pilot clinical study explored the safety and effi cacy of MB-106 in 11 R/R B-cell NHL, including 3 FL patients: 2/3 FL patients displayed a CR, while the third patient showed a PD.[19]

The Mustang Bio Inc. developed an industrial procedure for the generation of MB-106 CAR construct. A recent report was recently presented at the 17th International Conference on Malignant Lymphoma, Lugano 2023, involving 20 R/R FL patients treated with MB-106 in a single institution.[20] The median age of these patients was 63 years and 75% of these patients had POD24 (progressive disease within 24 months), 20% had prior history of histological transformation and 5% had prior treatment with a CD19 CAR-T; median prior lines of treatment was 4.[20] ORR was 95% and CRR was 80%; patients who received the highest MB-106 doses had ORR of 100% and CRR of 91%; the patient who received prior CD19 CAR-T cell therapy achieved a CR.[20] No grade ≥3 CRS or neurologic events were observed in these 20 patients.

Other studies have explored bispecific CAR-T targeting both CD20 and CD19 in patients with R/R B-

cell NHLs.[20-21] These studies included a limited number of R/R FL patients and provided initial evidence about a consistent clinical efficacy of these bispecific CAR-T.[21-22]

A recent study reported a novel CD19/CD20 bispecific CAR-T construct transduced into autologous naïve (TN) and memory cells (MEM); CAR-T cells engineered using this CAR-T construct were able to induce a high rate of responses in 10 R/R N/R NHL patients at low dosages, not inducing toxicity-related events.[23] The 3 R/R FL patients, all in the category of POD24 high-risk patients, included in this study, achieved a CR. These observations showed that CART19/20 TN/MEM cells are safe and effective in patients with R/R NHL, and particularly in FL patients, with durable responses achieved at low dosage levels.[23]

Conclusions and perspective. In the third-line setting, the treatment opportunities for R/R FL patients are highly heterogeneous, reflecting the lack of a standard therapy. Standard treatments involve immunochemotherapy, anti-CD20 monotherapy or combined with lenalidomide, PI3K inhibitors and HSCT; usually, high response rates to these therapies are observed, but of short duration.[24] Particularly limited responses are observed in patients with high FLIPI (follicular lymphoma international prognostic index) and refractory to alkylators.[24]

CAR-T cell therapies represent an additional tool to the armamentarium of R/R FL patients, achieving high rates of responses in heavily pretreated patients and with acceptable side effects. The results so far obtained support the view that in the third-line setting, particularly for patients refractory to alkylating agents and anti-CD20 monoclonal antibody and early relapse patients, CAR-T cell therapy can be proposed as a part of the standard care armamentarium, considering its high efficacy and its capacity to induce long-lasting remissions. However, some problems remain for the widespread utilization of CAR-T. They are fundamentally the high cost, the not prompt availability, and the side effects.

Two points need to be explored in future studies. First, longer follow-up is required to assess the durability of responses and overall survival induced by CAR-T cell therapy more carefully. Second, prospective studies are needed to compare CAR-T versus available therapeutic options, standard or experimental.

Actually, a recent trial utilizing Mosunetuzumab, a CD20 × CD3 T-cell-engaging bispecific monoclonal antibody that redirects T cells to eliminate malignant B cells, induces the belief that this approach also merits consideration and further studies, having a similar efficacy.[25]

The response rates in the current study are more similar to those observed in studies evaluating chimeric antigen receptor (CAR) T-cell therapies in patients with relapsed or refractory follicular lymphoma and two or more lines of therapy, in which high objective response rates (86–94%) and complete response rates (60–79%) were reported, along with durable remissions at relatively short follow-up.[23-25]

With a median follow-up of 18·3 months, responses in the current study of mosunetuzumab were also durable and maintained for 18 months or longer in 70·2% of complete responders and 56·9% of all responders. Both CAR T-cell therapies and bispecific antibodies are likely to have essential roles in the future management of relapsed or refractory follicular lymphoma. Of note, however, mosunetuzumab is an off-the-shelf immuno-therapy that avoids many of the logistical challenges associated with current CAR T-cell therapies, including the need for leukapheresis, lymphodepleting chemo-therapy, and centralized manufacturing with an extended lead time (median 17–29 days). Furthermore, the typical side effects of T-CAR cells, the Cytokine release syndrome, and neurological adverse events seem very rare during the therapy with mosunetuzumab. Neutropenia was the most common hematological adverse event, with no febrile neutropenia and manageable with growth factor support. No grade 5 (ie, fatal) adverse events due to infection were reported.

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