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The role of axicabtagene ciloleucel as a treatment option for patients with follicular/marginal zone lymphoma

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***Abstract*:** Chimeric antigen receptor (CAR) T-cell therapy with axicabtagene ciloleucel (axi-cel) continues to make its way in the treatment of B-cell lymphomas. Follicular lymphoma (FL) is the second most common non-Hodgkin's lymphoma. While its prognosis is usually good, the disease is considered incurable and patients still relapse. High-risk subgroups such as high FLIPI score or early relapses (POD24) face poor outcomes. Current treatment options with phosphatidylinositol 3-kinase (Pi3K) inhibitors or other novel agents have clinical activity but short remission with cures remaining elusive. The ZUMA-5 study of axi-cel has shown high response rates with durable remissions with manageable toxicities, particularly in poor risk FL, replicating the outcomes in smaller and earlier studies. Long-term follow up will demonstrate the real impact of axi-cel in relapsed FL.

Keywords: axi-cel, CAR-T, follicular lymphoma, marginal zone lymphoma

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Introduction

Follicular lymphoma

Follicular lymphoma (FL) is a mature B-cell malignancy derived from germinal centers B-cells. It is the second most common lymphoma in Western countries and the United States (US) and accounts for 20–25% of all lymphoid malignancies.[1,2] In 2016, approximately 14,000 new cases were diagnosed in the US.[3] The median age at diagnosis is between 60 and 70 years old. The majority of patients present with asymptomatic lymphadenopathy, do not have B symptoms, and do not require treatment urgently. In general, FL is considered an incurable lymphoma but very treatable.[2]

About 80% of FL patients carry the translocation (14; 18) which encodes the BCL2 anti-apoptotic protein, which is the hallmark molecular finding in FL.[1]Other genetic and epigenetic abnormalities are associated with the pathogenesis and progression of FL, such as chromatin modifying mutations (*KMT2D, CREEBP, EZH2*), immune evasion (*TNFRSF14*, *CREBBP*), and transcriptional regulation (*STAT6, BCL6, BCL2*) among others and that involve T-cell function and tumor microenvironment (TME).[4,5]

The prognosis of FL improved for patients of all ages after the addition of rituximab to chemotherapy regimens in early 2000.[6,7] A recent large French–American study showed a 10-year overall survival (OS) of 80% in FL patients treated with rituximab-containing regimens.[8] Multiple prognostic scores have been built, taking into account clinical (FLIPI, FLIPI2, etc.) and molecular (m7-FLIPI) characteristics of FL patients at the time of treatment, which have been helpful in categorizing patients into risk groups for the purpose of clinical trials.[9–12] However, all these schemas have fallen short in the identification of high risk FL with worse outcomes and short OS: patients that relapse within 2 years of completing therapy (5 year OS: 50%) and those with histologic transformation (5 year OS: 75%).[13,14]

Marginal zone lymphomas

Marginal zone lymphomas (MZL) are rare lymphoid tumors with heterogenous presentation

that account for approximately 5–15% of all non-Hodgkin's lymphoma (NHL) in the western hemisphere.[15] The main subtypes are: extranodal MZL (EMZL) of the mucosal associated lymphoid tissue (MALT) – the most common type (70% of MZL) – followed by splenic MZL (SMZL), and nodal MZL (NMZL).[1,15] These lymphomas are heterogeneous and have different clinical presentations, specific diagnostic criteria, genetic characteristics, and different prognoses that influence therapeutic decisions. The prognosis of MZL is dependent on the stage and specific diagnostic type, since some of the localized MZL may undergo curative interventions (antibiotic therapy, radiation therapy, or surgery). Specific MZL prognostic models such as the MALT-IPI in EMZL or the HPLL for SMZL have been developed, taking into account similar risk factors used in scores for the prognosis of FL.[16,17] As seen in FL, MZL patients with early relapse or POD24 or with transformation to high-grade lymphoma have inferior OS.[18,19]

Treatment for indolent NHL

The standard frontline treatment of high tumor burden FL and MZL is chemoimmunotherapy, usually consisting of an alkylating agent-based regimen with anti-CD20 monoclonal antibody (rituximab or obinutuzumab), with the option to continue with anti-CD20 maintenance therapy for 2 years. This approach yields high response rates and durable remissions of more than 4 years, along with 8-year OS of over 80% regardless of the combination used.[20–24] Although some regimens have showed better progression-free survival (PFS), no single treatment has shown superior OS. Chemotherapy-free regimens are also an option as frontline therapy, specifically with the combination of lenalidomide and rituximab (R2) that elicited a complete response (CR) rates of 48% and 3-year PFS of 77%. These outcomes were comparable with those of chemoimmunotherapy in a phase III randomized clinical trial.[25] Although the R2 regimen is active in relapse MZL, it has not been formally tested in treatment-naïve patients.[26]

Relapsed/refractory FL/MZL

Patient with FL that have previously required treatment will eventually relapse and require further therapies. Responses to further therapies IN Relapsed/refractory (R/R) FL/MZL tend to be shorter and outcomes poorer, especially for those with short response to initial therapy.[13,27,28] For patients with rituximab refractory FL/MZL, the combination of bendamustine and the glycoengineered type II anti-CD20 antibody obinutuzumab (OB) demonstrated a superior PFS and OS over bendamustine.[29]

For patients with relapse FL that progress after 2 years, other effective options are available, including non-cytotoxic immunotherapeutic or targeted agents (Table 1).

The phase III AUGMENT trial in R/R FL and other indolent NHLs showed that lenalidomide and rituximab (R2) had a superior overall response rate (ORR) (78 *versus* 53%), PFS (39.4 *versus* 14 months) and 2-year OS (95 *versus* 86%) *versus* placebo and rituximab. Four different phosphatidylinositol 3-kinase (PI3K) inhibitors have been approved by the US Food and Drug Administration (FDA) for the treatment of R/R FL and have also proven to be effective in R/R MZL patients that have always been included, albeit in small numbers, in these trials. Idelalisib, duvelisib, copanlisib, and, most recently, umbralisib have been approved by the FDA for relapsed/refractory FL and MZL. The ORR and CR rates are between 45–60% and 5–10%, respectively, with a median PFS between 9.5 and 16 months.[31–34] While all these agents target the Pi3K pathway, and hence, similar drug class related toxicities, they differ somewhat in frequency and severity. The activity in MZL seem greater, specifically with copanlisib and umbralisib, with an ORR of 55–78% and PFS of 24.1 months and 12-month PFS of 71%, respectively.[38,39] The same is true for Bruton tyrosine kinase (BTK) inhibitors, which have poor results in FL, but excellent activity on MZL, with an ORR of 58% and a median PFS of 15.7 months.[35,36] Finally, the oral EZH2 inhibitor tazemetostat was studied in a single arm phase II trial for R/R FL patients with either mutated(mut) or wild-type (wt) EZH2 status. The ORR and median PFS for mut EZH2 and wt-EZH2 patients were 69 and 35%, and 13.8 and 11.1 months, respectively.[37]

Another option for high-risk fit patients, especially for those with early disease relapse, is the use of autologous hematopoietic stem cell transplantation (HCT). One large retrospective CIBMTR

Table 1. Selected trials in relapsed/refractory follicular lymphoma and marginal zone lymphoma.

Study/phase	Type of lymphoma	Regimen	Number of patients	ORR%/CR%	PFS, months	OS, months
P III	FL/MZL	B+O; O maintenance	164 FL/28 MZL	69.1/11.2	25.8 months	41 months
Leonard *et al.*[30]/P III	FL/MZL	Rituximab plus Lenalidomide	147 FL/31 MZL	78/34	39.4 months	2 years OS = 95% FL 2 years OS = 82% MZL
Gopal *et al.*[31]/P II	FL/MZL	Idelalisib	72 FL/15 MZL	57/6	11 months FL 7 months MZL	20.3 months
Flinn *et al.*[32]/P II	FL/MZL	Duvelisib	83 FL/18 MZL	40/20 FL 66.7/0 MZL	9.5 mo.	28.9 months
Dreyling *et al.*[33]/P II	FL/MZL	Copanlisib	104 FL/23 MZL	58.7/20.2 FL 78.3/13 MZL	12.5 months 24.1 months	42.6 months 83% at 2 years
Zinzani *et al.*[34]/P II	FL MZL	Umbralisib	117 FL 69 MZL	53/12 FL 55/10.5 MZL	16 months 71% at 12 months	NR NR
Gopal *et al.*[35]/P II Noy *et al.*[36]/P II	FL MZL	Ibrutinib	110 FL 63 MZL	20.9/11 48/3	4.6 months 14.2 months	78% at 2 years 81% at 18 months
Morschhauser *et al.*[37]/P II	FL	Tazemetostat	45 EZH2 mut FL 54 EZH2 wt FL	69/11 35/3	13.8 months 11.1 months	

B, bendamustine; CR, complete response; FL, follicular lymphoma; MZL, marginal zone lymphoma; NR. not reported; O, obinutuzumab; ORR, overall response rate; OS, overall survival; PFS, progression free survival.

study showed that patients with relapse FL <1 year after frontline therapy showed a better 5-year OS for the patients treated with autologous HCT compared observation (73% *versus* 60%, respectively).[40] Other studies have also shown that autologous HCT may provide long disease remission but without a clear survival plateau.[41,42] Table 1 provides a summary of key studies in R/R FL and MZL.

Axicabtagene ciloleucel: structure and mechanism of action

The basic and clinical development of axicabtagene ciloleucel (axi-cel) has been extensively described.[43,44] The concept of CAR-T cells started with the earlier work by Eshhar *et al.*[45] using single chain variable fragment antibody domain (svFC) with single signal (without costimulation), known as first generation CAR, which promoted cytotoxic activity but limited clinical efficacy.[46] A major improvement in CAR-T cell design was the addition of a costimulatory signal (CD28, 4-1BB, etc.) that led to better CAR-T cell signaling strength, expansion, persistence, and pre-clinical and clinical efficacy.[47,48] Axi-cel (formerly KTE-C19) is a CAR construct with an extracellular portion, composed by a svFC domain that targets CD19; a transmembrane or hinge portion and intracellular (signaling) portion composed by a CD3zeta activation domain coupled with the costimulatory molecule, CD28 (CD19-CD28-CD3zeta).[49]

A central role of the immune system in cancer is the antitumor response, which is mediated mainly by T-cell activation and cytotoxicity upon activation of the T-cell receptor (TCR) – a process mediated by presentation of tumor peptides/antigens by the major histocompatibility complex (MHC). Several mechanisms, such as MHC downregulation, T-cell exhaustion, T-cell senescence, etc., impair these

antitumor responses. CAR-T cell therapy seeks to overcome this response by targeting tumor antigens in an MHC-independent fashion.[49,50]

A key role for CAR-T expansion and activation is provided by conditioning chemotherapy. In the case of axi-cel, the optimal conditioning regimen is the combination of fludarabine and cyclophosphamide. Conditioning regimen eliminates regulatory and inhibitory T-cells and likely suppressive myeloid cells. It also promotes the production of cytokines, such as interleukin (IL)-15 that favors the proliferation, activation and homing of CAR-T cells.[51,52]

Axi-cel manufacturing

Manufacturing of axi-cel starts with obtaining unmobilized peripheral blood mononuclear cells (PMBC) through a process called leukapheresis. After collection, PBMCs are transferred to a central cell processing laboratory where, in a closed system, cells are enriched and activated utilizing the anti-CD3 antibody IL-2. Then, the CAR gene is transduced into the activated T-cells using a gamma-retrovirus vector. Transduced T-cells (CAR) are then expanded to a target dose of 2×10^6/kg (maximum of 2×10^8 CAR-T cells), cryopreserved and tested (cell concentration and activation) prior to shipping to the requesting center. Prior to axi-cel administration, patients will undergo conditioning chemotherapy with cyclophosphamide at 500 mg/m^2 and fludarabine at 30 mg/m^2 given intravenously (IV) both for 3 days (Flu/Cy).[53,54] This process was studied initially in the National Cancer Institute (NCI) with the CD19-CD28-CD3zeta product and further developed in the first multicenter study that proved that central axi-cel manufacturing was feasible.[53,54]

Clinical experience with axi-cel

The NCI clinical experience with the CD19-CD28-CD3z CAR-T cells in B-cell NHL (which would become axi-cel) was initially documented in a patient with heavily pretreated FL. Based on this early success, the NCI protocol [ClinicalTrials.gov identifier: NCT00924326] was developed to treat patients with refractory diffuse large B-cell lymphoma (DLBCL) and indolent B-cell with this CAR-T cell construct. The study included 43 patients (DLBCL/PMBCL = 28, indolent NHL = 8 and chronic lymphocytic leukemia = 7). The ORR and CR were 81 and 58%, respectively.[53] Long-term follow up published recently reported that a significant proportion (51%) of patients had a duration of response (DoR) of more than 3 years, especially those patients who achieved CR.[55] Concentrations of CAR+ T cells peak and IL-15 level were correlated to CR rates and durable responses.[52,55]

The ZUMA-1 trial is the pivotal study that led to FDA approval of axi-cel for relapsed or refractory DLBCL. ZUMA-1 was a multicenter study that enrolled/apheresed 111 patients, successfully manufactured CAR-T cells in 110 patients (99%), and treated/infused 101 patients with axi-cel (95%). Patients were heavily pretreated with ⩾3 prior lines of therapy (69%), including primary refractory (26%), refractory to last therapy and relapsed post-autologous hematopoietic cell transplantation (auto- HCT; 21%). Axi-cel induced ORR and CR rates of 82 and 54%, respectively, which, in comparison with historical controls (such as SCHOLAR-1 data), was remarkable.[56] With a longer median follow up of 27.1 months, 39% and 37% of treated patients remained in persistent response and CR, and the PFS was 5.9 months.[57] Similar to the NCI experience, patients with ongoing responses (more than 2 years) had a significant CAR+ T-cells expansion in blood 7–14 days post CAR-T infusion.[57] All grades and grade >3 cytokine release syndrome (CRS) and neurotoxicity (NT) were documented in 93% and 13% and 64% and 32%, respectively.[56] Recent data of the ZUMA-1 (⩾4 years follow up) showed a 4-year OS of 44%. Interestingly, about 90% of patients had polyclonal B-cell recovery (including memory B-cells) and 60% of responding patients still had CAR+ T cells detected in blood, similar to the NCI experience.[58]

Rationale for axi-cel in FL

As mentioned above, the majority of patients with FL have a good outcome; however, a proportion of patients face a poor prognosis, especially those with early relapse, those who have received three or more lines of therapy and those relapsing after autologous HCT. The available FDA-approved novel agents for R/R FL, such as lenalidomide, PI3K inhibitors, and tazemetostat, have clinical activity but do not offer deep responses or long-term remission. Thus,

highly effective therapies with higher CR rates are needed.

Given the activity of CAR-T cell therapy in R/R DLBCL, and the fact that CD19 is also highly expressed in FL, a logical step is to evaluate this therapy in this type of lymphoma in a formal trial. As mentioned in the previous section, the first patient treated successfully with CAR-T cell therapy (in the NCI trial) had FL.[51] The NCI study included eight patients with indolent B-cell NHL (FL = 5, MZL = 1, indolent mantle cell lymphoma = 1 and unspecified indolent B-cell NHL = 1).[52,53,55] The ORR and CR for these patients were 100 and 67%, respectively, with a median follow up of 55 months and, at last follow up, 50% of the treated patients remained in remission. The median DoR and event-free survival (EFS) were 78 and 55 months, respectively. The median OS was not reached.[55]

Other CAR constructs were studies in indolent B-cell NHLs. The Fred Hutchinson Cancer Research Center (FHCRC) reported data in FL using their CAR-T cell construct, which consisted of a anti CD19 CAR-T cell on a 1:1 ratio of CD4+/CD8+ T-cells and the costimulatory molecule 4-1BB.[59,60] This phase I/II study included eight patients with a median age of 53, heavily pretreated (median prior regimens of 4) including prior auto-HCT and prior anthracycline exposure in 38 and 88% of cases, respectively. Patients received a CAR-T cell target dose of 2×10^6 CAR cells/kg with prior conditioning chemotherapy with Flu/Cy at different dosing regimens. The therapy was highly effective with ORR and CR of 100 and 88%, respectively. With a median follow up of 24 months, the median PFS and OS were not reached.[60]

The University of Pennsylvania (UPenn) also reported their experience using the anti CD19 CAR-CD3zeta- CD137 (4-1BB) lentiviral genevector transfer or CTL019 (which eventually become tisagenlecleucel). The study included 15 FL patients, median age of 62, heavily pretreated (5 median prior regimens), prior auto-HCT in 20%. The ORR and CR rates were 79 and 71%, respectively.[61] The initial report with a median follow up on 27 months showed a median DoR, PFS, and OS that were not reached.[61] The 5-year follow up showed that 43% of patients were progression free.[62]

Although these reports had small number of patients, the clinical activity and durability of responses were consistent across studies and with different products. These earlier experiences justified the launch of large and dedicated studies in indolent B-cell NHL.

ZUMA-5 clinical trial

Based on the earlier results of axi-cel in the ZUMA-1 study in large B-cell lymphoma, the most logical step is to assess its efficacy in other CD19+ B-cell lymphomas such as indolent B-cell NHLs. Thus, ZUMA-5 was launched. The ZUMA-5 is a phase II, multicenter study of axicabtagene ciloleucel for indolent B-cell NHL [ClinicalTrials.gov identifier: NCT03105336]. Patients were eligible if they had FL or MZL (nodal or extranodal) and had received at least two prior lines of therapy including an alkylating based regimen (single agent anti CD20 based antibody was not considered a line of therapy). Patients with prior autologous HCT, POD24 status, prior Pi3K inhibitor treatment were allowed. Patients with splenic MZL, small lymphocytic lymphoma (SLL), Waldenstrom macroglobulinemia (WM), and prior allogeneic HCT were excluded. Screened and enrolled patients underwent leukapheresis for axi-cel manufacturing, received conditioning chemotherapy with FluCy IV for 3 days (per ZUMA-1 specifications) and received axi-cel infusion on day 0 at 2×10^6 CAR+ cells/kg. The primary endpoint was ORR and secondary endpoints were CR rates, DoR, PFS, and OS.[63]

The ZUMA-5 trial enrolled 151 patients and infused 146 with axi-cel (FL = 124, MZL = 22). Five patients were not eligible for infusion (DLBCL transformation = 1, ineligible = 3 and 1 patient with trial unrelated death). The median age was 61 (between 34 and 79). Patients had high-risk features: POD24 (55%), high FLIPI score (47%), bulky disease (49%), prior PI3K inhibitor (29%), progression within 6 months from the most recent therapy (68%) and prior auto HCT (23%). The manufacturing time from apheresis to axi-cel infusion was 17 days, similar to what it was seen in the ZUMA-1 trial.[56]

By an independent review committee (IRC) assessment, axi-cel showed high responses with an ORR and CR rates of 92 and 76%, respectively.

For FL and MZL, the ORR (CR) were 94% (80%) and 85% (60%), respectively. Reponses were consistent regardless of several factors such as age, stage, FLIPI score, tumor burden, prior numbers of therapies, or POD24 status. With a median follow up of 17.5 months, the DoR, PFS, and OS were not reached. The 12-month PFS and OS was 92.9% and 73.7%, respectively. The median PFS for FL and MZL were not reached and 11.8 months, respectively.[63]

Regarding key toxicities, CRS occurred in 82% of cases with grade ⩾3 CRS in 7%. Median time onset and duration of CRS was 4 and 6 days, respectively. Patients required steroids (17%) and tocilizumab (49%). There was a patient death from multiorgan failure while having CRS. Neurological toxicity (NT) also occurred with all grades and grade >3 in 60 and 19%, respectively. The median onset and duration were 7 and 14 days, respectively. There were no grade 5 neurological events.

CAR-T cell peak and expansion occurred with a median time of 9 days. Higher CAR+ T-cells expansion were associated with ongoing responses at 12 months as well as with the severity of CRS and NT. In FL, higher peak levels of IL-1R, IL-6, IL-10, IFN-gamma, tumor necrosis factor alpha, GM-CSF, and CLL2 were associated with grade ⩾3 NT. These findings were similar to what it was shown in the ZUMA-1 study.[56,63] Table 2 lists the most important highlights of the ZUMA-5 trial.

Future directions: deciphering the role of axi-cel in indolent lymphomas

The primary analysis of ZUMA-5 demonstrated that axi-cel is highly active poor risk refractory FL, including heavily pretreated patients, POD24, refractory to the last therapy, and post autologous HCT. This includes patients previously treated with Pi3K inhibitors and IMiDs. A median DoR and PFS that are not reached is very remarkable in the third-line setting. Given this data, the approval of axi-cel for FL is imminent.

A still unanswered question pertains to the best and most appropriate sequence of therapies for indolent NHLs, given all available options (four Pi3K inhibitors, one EZH2 inhibitor, and one IMiD). Several factors should be taken into account, such as the efficacy rates when compared with other alternatives, side effect profiles and tolerability, logistics, and duration of therapy. In lieu of different treatment alternatives with novel agents for R/R indolent B-cell NHL, the exact role and place of axi-cel in this setting it is not well defined; however, it will continue to evolve, especially once long-term follow up data for axi-cel become available. These and other factors and clinical experiences can help inform individualized treatment decisions for physicians treating patients with R/R FL. So far, initial ZUMA-5 data show high CR rates along with durable responses and non-reached PFS and OS, which is remarkable and compares favorably with other approved novel agents that, in general, have low CR rates and median PFS between 9 and 16 months. CAR-T cell therapy is also a one-time therapy, as oppose to novel agents for which patients need to continue treatment indefinitely. The remarkable responses seen in earlier studies (prior to ZUMA-5) in FL suggest that patients receiving axi-cel for indolent NHLs likely will have long-term benefit.[55,60,62]

High tumor burden has been associated with CAR-T-related toxicities and less durable responses.[55,64] Since novel agents seem to be less toxic and immunosuppressive than traditional chemotherapy, they can offer an optimal bridging treatment in order to reduce tumor burden prior to CAR-T cell therapy. Additionally, novel agents may not affect quantity and quality of lymphocytes, needed for successful CAR-T manufacturing, as oppose to cytotoxic chemotherapy, which may have deleterious effect.[65] Recently, it has been shown that ibrutinib and idelalisib may improve the T-cell composition and hence the final CAR-T cell product, thus potentially increasing its efficacy.[66,67]

Other cell therapies such as autologous and allogeneic HCT play an important role in R/R FL. While the efficacy and long-term benefit has been demonstrated, having a chemosensitive disease is a prerequisite to achieving long-term benefit. Other disadvantages of allogeneic HCT include the need for a matched-donor, the relatively high treatment-related mortality (TRM), and the fact that it is limited to younger patients.[68,69] In addition, autologous and allogeneic HCT for FL remain underutilized in the US; thus, with the approval of axi-cel for these conditions, it is unlikely that transplants will play an increased role in FL.[27]

Table 2. ZUMA-5 clinical trial highlights.

Product	Axicabtagene Ciloleucel (axi-cel): - Autologous anti CD19 CAR-T cell - Antibody fragment derived targeting CD19 - CD3- zeta and CD28 costimulatory intracellular domains
Patients	Enrolled/leukapheresed: 151; Infused: 146 (FL: 124, MZL: 22)
Key inclusion/exclusion criteria	Inclusion: - Relapse/refractory FL (grade 1–3a) and MZL to at least 2 lines of therapy. Must have progressed within 1 year from last therapy. - Must have had an anti-CD20 antibody and an alkylating agent.
	Exclusion: - SLL, WM, splenic MZL, FL grade 3B or any prior transformation to DLBCL. - Prior allogeneic HCT.
Manufacturing	Median time from apheresis to delivery is 17 days
	Manufacturing success: 100%
Conditioning regimen and dose of axi-cel	Fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/$m^2 \times 3$ days IV
	Axi-cel dose: 2×10^6 CAR-T cells/kg
Key population characteristics	Median age: 61 years (34–79)
	FLIPI $\geqslant$3: 47%
	Bulky disease: 49%
	Median prior therapies: 3 (1–10)
	POD24: 55%
	Prior HCT: 23%
Efficacy	ORR: 92% (FL: 94%, MZL: 85%)
	CR: 76% (FL: 80%, MZL: 60%)
	DoR: NR (FL: NR, MZL: 10.6 months)
	PFS: NR (FL: NR, MZL: 11.8 months)
Toxicity	CRS - Any grade: 82%, grade >3: 7% - Time to onset: 4 days (1–15)
	NT - Any grade: 60%, grade >3: 19% - Median time to onset: 7 (1–177)

CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; FL, follicular lymphoma; HCT, hematopoietic cell transplantation; IV, intravenous; MZL, marginal zone lymphoma; NR, not reached; NT, neurotoxicity; ORR, overall response rate; POD24, progressive disease within 24 months; SLL, small lymphocytic lymphoma; WM, Waldenstrom macroglobulinemia.

The toxicities (CRS and NT) of CAR-T cell therapy, and particularly axi-cel, are unique and will be a factor when counseling this option for patients with FL. Practitioners should be aware of, and trained in regards to, these toxicities when considering this therapy. Since the approval of CAR-T cell therapy in 2017, significant experience has been gained, including the development of specific guidelines by experts in the field.[70–72] Non-academic centers are becoming more familiar with CAR-T cell therapy and may be able to offer this therapy safely to patients.[73]

Bi-specific antibodies are promising and have also shown significant high response rates. Interestingly, the reported median PFSs with mosunetuzumab and odronextamab are 11.8 and 11.4 months, respectively.[74,75] Although it seems that CAR-T cell therapy seems to compare favorably, a longer follow up is needed in order to confirm these findings.

Finally, other autologous anti-CD19 CAR-T cell products, which are FDA-approved for R/R DLBCL, are becoming available for FL.[76,77] The preliminary analysis of the ELARA trial [tisagenlecleucel (tisa-cel) for R/R FL] encouraging data with an ORR (CR) of 82.4% (65.4%) in evaluable patients and with a median follow up of only 6.5 months. Remarkably, the median DoR, PFS, and OS were similar to those of ZUMA-5.[78] Toxicities rates were somewhat lower with CRS in 48% (all grades 1–2) and NT in 10% (2% grade $\geqslant$3). Lisocabtagene maraleucel (liso-cel) is currently being evaluated in the TRANSCEND FL study [ClinicalTrials.gov identifier: NCT04245839]. It appears that either tisa-cel and liso-cel will become available for FL as well, and the choice of CAR-T product will be determined by manufacturing success, reliability, toxicity profile, and familiarity.

Conclusions

Axi-cel has demonstrated to be highly active in poor-risk FL patients, including those with early relapse (POD24), heavily pretreated (including prior Pi3K inhibitors and IMiDs), and autologous transplantation. Axi-cel has been associated with expected toxicities such as CRS and neurological events, which were manageable with standard approaches. In the era of several treatment options with novel agents, it will be important to develop appropriate sequencing in order to achieve the best benefit for patients.

Conflict of interest statement

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