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CAR T cell therapy for B-cell lymphomas

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ABSTRACT

B-cell non-Hodgkin's lymphoma (NHLs)is a very heterogonous malignancy with diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) as the most common subtypes. Standard treatment with anti-CD20 based chemoimmunotherapy is usually very effective for disease control. However a significant proportion of patients with high-risk features (double hit lymphoma, transformed lymphomas or early relapses) will become refractory to standard therapies and will have limited alternatives for cure. Adoptive therapy with chimeric antigen receptor (CAR) T-cells is a new paradigm for effective treatment of poor prognosis lymphomas. Here we review the biology of poor risk DLBCL and FL, the rationale for CAR T-cell therapy in malignant lymphoma and the efficacy/toxicity profile of CD19 directed CAR T cell therapy for DLBCL and FL from early single center studies to multicenter/global clinical trial with different CAR T cell constructs.

1. Introduction

The use of chimeric antigen receptor (CAR) modified T-cells targeting CD19 expressing tumor cells have revolutionized the treatment of refractory B-cell lymphoid malignancies. Non-Hodgkin's lymphomas comprise a heterogeneous group of lymphoid malignancies that originates from B-cell lymphocytes, T-cell lymphocytes and natural killer (NK) cells. The revised World Health Organization (WHO) 2016 have re-classified many B-cell lymphoid malignancies entities based on a deeper understanding of genomics and molecular pathways [1]. The majority of lymphoid malignancies are of B-cell origin and almost invariably express CD19 protein on their cell surface. Thus, the use of CD19 directed CAR therapy has been subject of intense research for B-cell Non-Hodgkin's lymphomas (NHL).

2. Epidemiology of lymphomas

It is estimated that in 2015, there were 71,000 cases of NHL with approximately 19,700 deaths related to this disease. NHLs is the 7th leading cause of new cancer cases and accounts for approximately 3% of cancer-related deaths in the United States [2]. Of all NHLs, diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype with 32.5% of all newly diagnosed cases, followed by chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) with 18.6% and follicular lymphoma (FL) with 17.1% [3].

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3. Rationale for the use of CAR T cell therapy for B-cell non-Hodgkin's lymphomas

The basic anatomy of a CAR structure consists in an antigen-recognition domain, usually a single-chain variable fragment (scFv) derived from a monoclonal antibody targeting the selected antigen (ie: CD19); a hinge (usually derived from CD8 or Ig4 molecules) that links the recognition site to the transmembrane domain which bridges the membrane; and finally, the intracellular domain that typically contains CD3z chain critical for T cell receptor signaling. Second generation CAR molecules contain a second costimulatory signaling molecule, such as CD28 or 4-BB, that enhances T-cell activation and antitumor potency [4–8].

CD19 is a transmembrane glycoprotein that is involved in the regulation of the activation of B-cells in an antigen-receptor dependent manner. CD19 is uniformly expressed at all stages of B-cell differentiation and it is carried during B-cell malignant transformation [9]. CD19 is expressed in over 95% of B-cell malignancies such as chronic lymphocytic leukemia (CLL), B-cell NHL and B-cell acute lymphoblastic leukemia (ALL). Although CD19 is expressed on normal non-malignant B-cells, it is well established that cancer patients can survive without normal B-cells following chemotherapy or B-cell directed monoclonal antibodies; thus, it appears that there does not seem to be deleterious complications with long-term B-cell aplasia [10]. All these factors make CD19 an attractive target for immunotherapeutic approaches with several companies and academic institutions developing pivotal trials with anti-CD19 CAR T-cells [4,9].

4. Aggressive B-cell lymphomas

Aggressive B-cell lymphomas encompass a heterogeneous group of clinical and molecular diseases with DLBCL being the most common subtype. The WHO 2016 classification differentiated additional important subtypes such as high-grade B-cell lymphomas (HGBL) NOS and high-grade B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements, known as double (DHL) or triple hit lymphomas (THL). The prognosis of aggressive B-cell lymphomas is based on clinical, molecular and genetic factors as well as responsiveness to induction chemotherapy.

4.1. Clinical factors as predictive of poor prognosis DLBCL

Prognostic indices have been developed based on clinical factors that predict outcomes in DLBCL. They are commonly utilized in routine practice and in clinical trials. The commonly utilized clinically based scoring system, the International Prognostic Index (IPI), was updated with the Revised International Prognostic Index (R-IPI) which has since been validated in the rituximab era [11,12]. An enhanced scoring system, the NCCN-IPI score stratifies newly diagnosed DLBCL patients in 4 risk groups based on the same prognostic factors used in the IPI score. The NCCN-IPI score was able to better discriminate the low and high-risk subgroups than the IPI score [13,14]. Patients in the high-risk subgroup category per the R-IPI and NCCN-IPI scores have a 5-years overall survival (OS) of 54% and 33%, respectively; representing an unmet need in DLBCL. All scoring systems the IPI, R-IPI and NCCN-IPI can predict clinical outcomes accurately, and are used to different degrees in clinical practice.

4.2. Molecular and genetic factors as predictive of poor prognosis DLBCL

Molecular studies play an important role in identifying DLBCL with high-risk features. Based on the cell of origin (COO) using gene expression profiling (GEP) studies, DLBCL can be classified into activated B-cell (ABC) subtype and germinal center B-cell (GCB) subtype (with 10% being molecularly unclassifiable). Each of these COO subtypes have distinct phenotypic, clinical characteristics and prognosis with ABC –DLBCL having worse outcomes, as compared to GCB – DLBCL, with standard upfront R-CHOP chemotherapy [15,16]. Similarly, next generation sequencing (NGS) studies showed that for GCB lymphomas, specific mutations such as BCL2, EZH2, KMT2D, S1PR2, and GAN13 have independent prognostic significance [17,18]. Widespread use of GEP or NGS remains limited due to cost and complexity, thus immunohistochemistry (IHC) methods continue to be more practical and feasible. The Hans classifier uses 3 markers CD10, BCL6 and MUM1/IRF4) that classifies DLBCL as GCB or non-GCB subtypes [18,19] by IHC. Other IHC based algorithms were developed with good concordance to GEP [20,21]. COO classification based on IHC algorithm is popular and less expensive then molecular techniques, however the predictive value of IHC methods has been questioned [22,23]. Alternative methodology includes RNA deep sequencing and limited set gene expression profile on formalin-fixed-paraffin-embedded (FFPE) tissue (NanoString Lymph2Cx) [24–26].

Another high-risk subgroup of DLBCL patients is characterized by the overexpression of the proto-oncogene MYC that promotes uncontrolled cell growth, associated with unregulated cell division and extranodal dissemination of lymphoma [27]. MYC aberrations and/or overexpression can be detected by band cytogenetics, interphase fluorescence in situ hybridization (FISH), genomic comparative hybridization (GCH) studies and IHC. MYC rearrangements are the most common partner IGH detected by FISH or cytogenetics, present in 3–17% of DLBCL, and can be associated with BCL2 and/or BCL6 rearrangements. When MYC rearrangements are present in conjunction with one or both BCL2 and BCL6 rearrangements it is termed double-hit lymphoma (DHL) or triple hit lymphoma (THL) [28]. About 60% of high grade B-cell lymphomas have MYC and BCL2 rearrangements, 20% have MYC and BCL6 and 20% are THLs with all three [29]. An aggressive course of disease with poor outcomes characterizes DHL and THL when treated with standard front-line chemotherapy [30,31]. Unfortunately, cytogenetics, FISH, or molecular exploration of MYC, BCL-2, and BCL-6 from diagnostic tissue is often not ordered or available. Alternatively IHC can be utilized for analysis of MYC protein overexpression in DLBCL and when found in conjunction with BCL-2 or BCL-6 protein overexpression it is called double-expressor lymphoma (DEL). While DEL represents a more heterogeneous disease than DHL, it has also been shown to be associated with poor outcomes across

studies [32–34]. Clinically, DHL and THL are characterized by advanced disease stage, very elevated LDH and CNS involvement(32, 35). The optimal treatment of DHL has not been well defined but it appears that front-line intensive regimens (such as dose adjusted-EPOCH-R with CNS prophylaxis) are associated with better outcomes than R-CHOP [35–37]. Similarly, the role of autologous stem cell transplantation (ASCT) is debatable, as DHL or DEL patients have inferior OS and PFS after ASCT as compared to non-DHL patients [38–41]. Thus, the best approach for MYC rearranged DLBCL remains unclear and represents an unmet need given its poor prognosis.

4.3. Response to therapy as prognostic indicator

The addition of rituximab to CHOP improved the OS of patients with DLBCL, however, approximately 30–40% of patients will relapse and become refractory to this regimen [42]. In the majority of cases, lymphoma recurrence occurs within the first 3 years from diagnosis with very few patients relapsing beyond 5 years [43]. In general patients with refractory disease (less than PR to initial treatment) or early relapse (relapse within a year from diagnosis or 6 months after the end of treatment) or progression within 2 years (EFS24) have poorer prognosis [44,45]. Salvage chemotherapy followed by ASCT is the current standard approach [44,46]. About 30–40% of patients with primary refractory disease or early DLBCL relapses will respond to salvage chemotherapy and will be able to undergo ASCT, however about 50% of these patients will ultimately relapse again and further approaches have limited efficacy [44,46,47]. The prognosis of relapsed DLBCL post ASCT is poor with a median OS of 10 months, and particularly worse for relapses within 6 months with a median OS of 5.7 months [48,49].

A retrospective international multicenter study (SCHOLAR-1) was carried out using data from 2 phase III randomized clinical trials (CORAL and CCTG LY.12 trials) and 2 observational studies (MD Anderson Cancer Center and University of Iowa/Mayo Clinic) that evaluated patients that at best achieved stable disease and progressive disease as best response at any point during chemotherapy or relapsed within 12 months of ASCT [50]. The results of this pooled analysis showed an overall response rate of 26% with a median OS of 6.3 months [50]. Another large retrospective study of 15 U.S academic institutions assessed risk factors of refractory DLBCL defined three groups: primary progression (PD with or within 6 weeks of CIT), residual disease (PR or stable disease [SD] after completion of CIT) and early relapse (relapse within 6 month of CIT and having achieved CR) with a 2-year OS of 18.5%, 30.6% and 45.5%, respectively [51]. Multivariate analysis demonstrated that ultra high-risk features (UHR) in refractory DLBCL patients were primary progression, MYC rearrangement present and intermediate-high or high NCCN-IPI score at the time of relapse [51]. The findings of these 2 studies will serve as benchmarking for clinical trials in poor risk refractory DLBCL.

4.4. Efficacy of CART therapy in aggressive B-cell lymphomas

4.4.1. Early studies in DLBCL

The initial studies of anti-CD19 CART cells for lymphoma were carried out in single institutions and included a diverse population of refractory B-cell NHLs, including DLBCL, FL, primary mediastinal B-cell lymphoma (PBMCL), marginal zone lymphomas (MZL) and transformed follicular lymphomas (TFL). Two early reports of anti-CD19 CART cells were in patients with indolent NHL (will be discussed below) [52,53]. The first study to include DLBCL patients utilized a first generation anti CD19z CART (without costimulatory domain) and second generation anti CD19-28z CART. While this study showed significant expansion of CART cells with CD28 costimulation (the nadir was reached at 4–6 weeks), there were no objective responses reported in DLBCL patients. It should be noted that patients received CART cells after at least 6 weeks from last chemotherapy and that there was no lymphodepleting regimen given [54].

The first CART cell study to demonstrate activity in DLBCL was conducted at the NCI using the CD3z-CD28 CART construct (later licensed by Kite pharma for development as axicabtagene ciloleucel). Nine patients with refractory aggressive B-cells NHLs were included: DLBCL [4], PMBCL [4] and DLBCL transformed from CLL [1] in whom CART cells were successfully manufactured at the first attempt. The conditioning regimen consisted of cyclophosphamide (total dose of 60 mg/kg) followed by fludarabine 25 mg/m^2 daily for 5 days [55]. There were five CRs and two PRs out of the seven evaluable patients. Three patients who achieved CR had ongoing remissions at the time of publication of the study [55]. In a long-term follow up of responding patients, there were still ongoing remissions and the duration of response ranged from 38 to 56 months [56], highlighting the durability of the therapy for large B cell lymphoma.

Another follow-up report from the NCI included 22 aggressive B cell lymphoma patients (DLBCL: 13, TFL: 2, PMBCL: 1, FL: 2, mantle cell lymphoma: 1 and RT: 1) and demonstrated that low dose conditioning chemotherapy (cyclophosphamide 300–500 mg/m2 and fludarabine 30 mg for 3 days) had effective lymphodepleting activity and was associated with less hematologic and non-hematologic toxicity [57]. In this study, the ORR and CR rates among patients with DLBCL (majority with refractory disease) were 68% and 47%, respectively. The median duration of remission was 12.5 months and the 12-month PFS was 63.3% [57].

Investigators at the Fred Hutchinson Cancer Research Center (FHCRC) developed CAR-T cells using a 4-1BB as costimulatory domain. A phase I clinical trial using this CAR construct, and a predefined 1:1 CD4:CD8 was conducted based upon strong pre-clinical data. Specifically, CAR T-cells manufactured using purified CD4$^+$ or CD8$^+$ central memory ($_{CM}$) or naïve ($_N$) T cells in a specific 1:1 CD4:CD8 ratio were more potent in eliminating CD19$^+$ tumor cells as compared to those manufactured from effector memory ($_{EM}$) T-cells in mouse models [58]. Thirty-four patients with various refractory or relapsed B-cell NHLs including de novo DLBCL [11], TFL [11], MCL [4] and FL [6] were treated [59]. Patients with relapse post-autologous HSCT and post-allogeneic HSCT were also included. This therapy had anti-lymphoma activity with an ORR and CR rates for the whole group of 63 and 33%, respectively; in the subgroup of aggressive lymphomas (DLBCL and TFL) the ORR and CR were 67 and 38%, respectively, and the CAR construct is now

Table 1
Patient characteristics in the three largest anti-CD19 multicenter studies CAR T-cells in aggressive B-cell NHLs.

Patients Characteristics	ZUMA-1 (Neelapu, 2017)	JULIET (Schuster, 2017)	TRANSCEND (Abramson, 2017)
No of patients enrolled	111 (101)	141 (85)	91 (67)
Median age, range	58 (23–76)	56 (24–75)	61 (29–82)
Age ≥ 65	24%	21%	17%
Lymphoma subtypes	DLBCL, TFL, PMBCL	DLBCL, TFL	DLBCL, TFL (CORE)[a]
Double hit lymphomas	NR	27%	27%
≥3 lines of therapy	69%	50%	50%
Primary refractoriness	26%	NR	NR
Refractory to > 2nd line	77%	NR	76%
Relapse post ASCT	21%	51%	44%

DLBCL: Diffuse Large B-cell Lymphoma, TFL: Transformed lymphoma, FL: Follicular lymphoma, ASCT: Autologous Stem Cell Transplantation, NR: Not Reported.

[a] The FULL cohort included: DLBCL transformed from CLL (Richter transformation) and marginal zone lymphoma (MZL), PMBCL and follicular lymphoma 3B

licensed by JUNO for development as JCAR017 [59].

Researchers at the University of Pennsylvania developed an alternate anti-CD19 CART also using 4-1BB as a costimulatory domain (called CTL019) with significant anti-lymphoma activity. Preliminary results presented at ASH 2015 confirmed its efficacy in patients with a variety of B-cell NHL, including DLBCL, FL and MCL [60,61]. In the updated analysis there were 38 patients enrolled but 10 patients did not receive treatment for a variety of reasons (rapid disease progression: 4, inability to manufacture CAR T cells due to low T-cell counts: 5, and 1 consent withdrawal) [62]. In the 28 evaluable patients at data cut-off (May 2017) the ORR was 64% and 57% of patients remained free of progression at a median follow up of 28.6 months [60,62]. In the 14 DLBCL patients, the ORR at 3 months and 6 months were 50% and 43%, respectively with no significant differences between GCB/non-GC, double hit status or transformation from FL subtypes [61,62]. The median duration of response was not reached with a 86% of responding DLBCL patients maintaining an ongoing response at last follow up [61,62].

These early single center studies showed significant anti-lymphoma activity in aggressive B-cell NHLs and led the design of multicenter studies that included several academic institutions in association with pharmaceutical companies.

4.4.2. Multicenter studies in aggressive lymphomas

Given the preliminary efficacy of CART therapy in single-institution studies, several CAR T cell constructs were licensed for development by pharmaceutical companies for development as therapy for lymphoma. Multicenter phase 1–2 pivotal studies were designed primarily targeting aggressive B-cell lymphomas. With some minor differences, all studies included poor prognosis DLBCL patients that had received, and remained refractory to, standard chemotherapy (Table 1). The ZUMA-1 study included patients with primary refractory DLBCL to front-line anthracycline based chemotherapy, with inclusion of patients relapsing after autologous HSCT.

The first multicenter trial to evaluate CAR T for DLBCL was the Phase I-II trial utilizing the NIH CD3 zeta/CD28 CAR construct with a streamlined closed manufacture process. The cell dose and conditioning chemotherapy previously tested at the NCI were confirmed safe in 7 patients with refractory DLBCL, as defined per SCHOLAR-1: best response as SD to last systemic therapy or progressed within 12 months of prior autologous transplant. The conditioning regimen consistent of cyclophosphamide 500 mg/m2 and fludarabine 30mg/m2 x 3 days followed by infusion of KTE-C19, now called axicabtagene ciloleucel (axi-cel) at a dose of 1–2x 10^6 CART cells/kg [50,63] was deemed safe. The objective response was 71% with 4 patient achieving CR (57%) at 1 month evaluation. Three patients had ongoing CR at 12 months post axi-cel infusion. Reversible grade 3 neurotoxicity and cytokine release syndrome (CRS) were reported among this cohort. One patient experienced grade 4 CRS and grade 4 encephalopathy and died of intracranial bleeding, which was considered unrelated to axi-cel. This patient had rapidly progressive disease associated with fevers and preplanned retrospective review of cytokine levels before conditioning chemotherapy demonstrated that the patient was already in an extremely inflammatory state prior to CAR T cell infusion. Prior to initiation of the phase 2 portion of the trial, safety criteria were included to check the CRP and delay CAR T cell infusion in patients with fever until appropriate work-up was completed.

The pivotal phase II portion of the ZUMA-1 trial [64] included similar eligibility criteria as the phase I, with two cohorts: cohort 1 for DLBCL and cohort 2 for PMBCL and TFL. The primary end point was objective response rate (ORR) in patients with more than 6 months follow-up post axi-cel infusion, as compared to historical controls. Secondary end points were duration of response (DoR), OS, safety and levels of CAR-T cells and cytokines. The CAR manufacturing success was 99%.

A total of 111 patients were enrolled, with a CAR manufacturing success rate of 99%. Ten patients could not receive axi-cel for various reasons (SAE prior to conditioning regimen: 5, non measurable disease: 2, no product available: 1 and SAE post conditioning regimen: 2).

The 101 patients that received the therapy were the pre-specified intent-to-treat (ITT) analysis cohort. The study met the primary endpoint compared to historical cohort (SCHOLAR-1) with an objective response of 83% and CR of 54% (in comparison to the a pre-specified ORR of 20%, $p < 0.0001$) representing a 8-fold higher CR rates in comparison to SCHOLAR-1. With a data cut-off of August 11th, 2017, the median follow-up time was 15.4 months (Table 2). The ongoing responses and CR were 42 and 40%, respectively for all patients treated on the phase 1–2 trial. Overall objective response rate and ongoing responses were consistent across key

Table 2
Multicenter studies with autologous anti-CD19 CART therapy for aggressive B-cell lymphomas.

Study	ZUMA-1 (Neelapu, 2017)	JULIET (Schuster, 2017)	TRANSCEND (Abramson, 2017)
No of patients enrolled (treated)	111 (101)	141 (99)	NR (91) 67 in CORE
Median age, range	58 (23–76)	56 (24–75)	61 (29–82)
Median follow-up	15.4 months	5.6 months	6.3 months
Costimulatory domain	CD28	4-1BB	4-1BB
Bridging chemotherapy	Not allowed	Allowed	Allowed
CART dose	2.0×10^6 cells/kg	Median, 3.1×10^8	DL1 5.0×10^7 cells[a] DL2 1.0×10^8 cells
Conditioning regimen	Flu 30 mg/m^2 x3d Cy 500 mg/m^2 x3d	Flu 25/m^{2}x 3d Cy 250 mg/m^2 x3d or B 90 mg/m^2 x 2d	Flu 30 mg/m^2 x3d Cy 300 mg/m^2 x3d
Efficacy			
%ORR (%CR)	82 (54)	59 (43)	84 (61)
3-mo %ORR (%CR)	44 (39)	45 (37)	65 (53)
mDOR	11.1 months	NR	9.2 months

NR: Not reported, mDOR: median duration of response, Flu: Fludarabine, Cy: cyclophosphamide, B: Bendamustine, ORR: Overall Response Rate, CR: Complete Response.
[a] Six patients received double dose of DL1.

covariates, including advanced stage, age, presence of bulky disease, high IPI score or refractory subgroups (R/R post auto HSCT or > 2nd line of therapy). The median duration of response was 11.1 months in all responders and was not reached in those achieving CR. The 18-month PFS and OS were 41 and 52%.

The JULIET trial is a phase II multicenter study in patients with refractory DLBCL utilizing CTL019, the anti CD19 CAR construct with a 4-1BB costimulatory domain created at the University of Pennsylvania. Interim results were presented at the American Society of Hematology 59th Annual meeting in 2017 [65,66]. CAR T cells were manufactured centrally, however in contrast to ZUMA-1 cryopreserved apheresis products was utilized and bridging chemotherapy was allowed in order to prevent rapid disease progression. The lymphodepleting chemotherapy consisted of fludarabine 25 mg/m^2 and cyclophosphamide 250 mg/m^2 for 3 days or bendamustine 90 mg/m^2 for 2 days. Key eligibility criteria included aggressive B-cell lymphoma (DLBCL or TFL), relapse after autologous HSCT or ineligible for HCST, or refractory after 2 lines of therapy. Similar to the ZUMA-1 trial, the primary endpoint was ORR.

141 patients were enrolled, however 42 patients were unable to receive CTL019 infusion due to: change in patient status (rapid disease progression in 28 patients, AE in 1 patient, investigator decision in 2, withdrawal in 1 and 1 case of protocol deviation) and inability to manufacture CART cells in 9 cases. . Thus, 99 patients received CTL019 infusion with 81 patients having completed more than 3 months follow up at the time of the analysis with a data cutoff of March 8th, 2017. With a median follow up time of 5.6 months, eighty-nine out of 99 infused patients received various bridging chemotherapy regimens. The median dose of CTL019 was 3.1×10^8 ($0.1–6.0 \times 10^8$) cells. With an objective response of 53% (CR 40%), the JULIET study met its primary endpoint ($p < 0.0001$ [95% CI, 44–72]). The 3- and 6-months ORR (CR) rates were 38% (32%) and 37% (30%). The median OS and DoR were not reached in responders. The relapse-free survival at 6 months was 74%. If patients were in CR at 3 months, they continued with ongoing CR at data cutoff. Outpatient infusion of CTL019 was feasible and was given to 26 patients and 20 (77%) of those remained as outpatient more than 3 days. No deaths were attributed to CLT019, but 3 patients died within 30 days of infusion (all due to disease progression).

The TRANSCEND-001 study is testing JCAR017 construct, with 4-1BB costimulatory molecule, using a defined CD4:CD8 T-cell ratio [67]. In this trial the inclusion criteria was broader than ZUMA-1 or JULIET: refractory/relapsed DLBCL, TFL, FL grade 3B, mantle cell lymphoma and PMBCL. Patients with CNS involvement, Richter transformation, transformation from marginal zone lymphoma (MZL) and relapsed post-allogeneic HSCT were also included in the study. There were three dose-levels (DL) in this study: DL-1S was 5×10^7,and DL-2S was 1×10^8. A small cohort of patients received double dose of JCAR017 at 5×10^7 that was administered 14 days apart (currently suspended). The conditioning regimen consisted of fludarabine 30 mg/m2 and cyclophosphamide 300 mg/m2 daily for 3 days. Bridging therapy was allowed for disease control. With a data cutoff of July 17th, 2017, the median follow-up was 6.3 months, The investigators labeled the “FULL” study cohort to include 91 patients and the pivotal population of 67 patients, the “CORE” portion of DLBCL, TFL, and high grade B-cell lymphoma. Although the number of enrolled patients (and those who did not receive the product for various reasons) was reported in the preliminary analysis presented at the ICML-2017, but not reported at the recent ASH 2017 meeting [68,69]. The full cohort analysis data reported an ORR and CR rates of 75 and 56%, respectively. In the CORE data set the best ORR (CR) rates, 3-month and 6 month were 75% (56%), 65% (53%) and 57%(52%) with 55 patients that had more than 3 months follow up. There was a trend towards a dose-dependent improved activity of JCAR017 with a 3-month ORR (CR) rates of 63% (58%) and 40% (27%) in DL2 and DL1, respectively (CORE). The activity of JCAR017 was not different across different high-risk DLBCL groups including double and triple hit lymphomas. In patients achieving CR the median DoR was 9.2 months in the FULL and not reached in the CORE datasets, respectively and the median OS was 13.7 in the FULL and NR in the CORE subgroups [69]. This trial also showed the feasibility and safety of outpatient administration in a small cohort of patients, with CRS and neurotoxicity rates not significant different from inpatient treatment and reducing the duration of hospitalization by 40% [70].

5. Indolent B-cell lymphomas

Indolent NHLs comprise a heterogeneous group of B-cell lymphoproliferative disorders characterized by a slow disease progression and a pattern of relapses over the course of the disease. Diseases that are considered in this category are: follicular lymphoma (FL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL) and small lymphocytic lymphoma (SLL). Although patients with indolent lymphomas can live for many years, they are considered incurable with few exceptions (i.e., limited stage disease or allogeneic stem cell transplantation).

Follicular lymphoma is the most common indolent lymphoma and represents about 35% of all NHLs. There has been an important improvement in the outcomes in FL with median survivals approaching 2 decades, mainly due to the introduction of anti-CD20 monoclonal antibodies (rituximab) in combination with standard chemotherapy [71–74]. Given the favorable outcomes of majority of patients with iNHL and FL and durable remissions with available chemoimmunotherapy, PFS and OS may not be adequate to estimate efficacy of new interventions due to long follow up needed, particularly in the front-line setting. Thus, models/prognostic markers that predict outcomes have been developed using clinical and/or molecular factors and/or responsiveness to initial therapy.

5.1. Clinical factors as predictors of outcomes in FL

The Follicular Lymphoma-IPI or FLIPI (age > 60, stage III/IV, elevated LDH, > 4 nodal sites and hemoglobin < 12 g/dl) and FLIPI-2 (age > 60, hemoglobin < 12 g/dl, increased B2 microglobulin, bone marrow involvement, largest lymph node > 6 cm in size) scores was able stratify FL patients into three risk categories: low risk (10-year OS of 71%) intermediate risk (10-year OS of 51%) and high risk (10-year OS of 36%) [75,76].

5.2. Response to therapy as a high-risk indicator for indolent NHL

There have been several studies seeking surrogates of FL survival other than OS and PFS. A large pooled analysis of 13 randomized clinical trials in FL showed that CR rate at month 30 from front-line therapy for FL was predictive of PFS, regardless of the inclusion of rituximab in the regimen [77]. Another strong predictor of survival is the duration of response. The National Lymphcare Study (NLCS) studied the outcomes of FL patients treated with R-CHOP as a front-line regimen. The study identified that event-free survival at 24 months (EFS24) was associated with poor outcomes in comparison to those who did not experience early relapse (5-year OS of 50% and 90%, respectively) [78], and the surrogate endpoint was since validated in other analysis [79–81]. Patients not achieving EFS24 remain as an unmet need in FL and constitute as a primary endpoint in clinical trials for FL (and other iNHL).

5.3. Biological and molecular predictors

Follicular lymphoma is graded based on the number of centroblasts per high-power field from grade 1 to grade 3a/3b. Whilst there are no differences in clinical outcomes between grades 1 – 3a and treatment decisions are not affected, grade 3b FL is considered a distinct disease and usually approached as an aggressive lymphoma (similar to DLBCL) and treated with anthracycline based chemotherapy, with a probability of cure of about 40% [82].

The FL tumor microenvironment (TME) has been extensively studied with different methodologies, most commonly using gene expression profiling techniques of non-neoplastic cells. Immune interactions between TME and neoplastic FL cells seem to be prognostically relevant [83]. $CD4^+$ T-cells including FOXP3+ regulatory T-cells (Treg) and follicular helper cells (Tfh), and their interaction with TME, may influence response to therapy and antitumor immunity [84,85].

The mutational landscape of follicular lymphoma is characterized by the presence of several gene alterations, with the majority involving epigenetic regulators and chromatin modifiers but also involving the B-cell receptor pathway genes [86–89]. These mutations are believed to promote FL lymphomagenesis by interacting with p53, BCL2 and BCL6 but also resistance and short response to therapy [88].

The m7-FLIPI score was developed incorporating 7 gene alterations known to be recurrently mutated in FL: *CREBBP*, *ARID1A*, *EZH2*, *EP300*, *FOXO1*, *MEF2B* and *CARD11*. The m7-FLIPI score was better to discriminate high-risk subgroups than traditional FLIPI with a 5-year failure free survival (FFS) and OS of 25% and 42% in the high-risk category [90]. Additionally, the m7-FLIPI score was able to identify better patients in high risk of not achieving EFS24, however was able to qualify only 50% of FL patients with early progression [91].

5.4. CAR-T cell studies in indolent non-Hodgkin lymphomas

To date the majority of NHL patients that have received anti-CD19 CAR T-cells were aggressive B-cell NHLs (mainly DLBCL), some of the first NHL patients to receive this therapy were indolent NHLs. The first FL cases reported no response to first generation anti-CD19 CAR T-cells without costimulation [52]. The first lymphoma patient successfully treated with anti-CD19 CAR T-cells with CD28 as co-stimulatory domain was reported by the NCI and this patient achieved long-term remission [53]. A subsequent report included 5 patients with indolent NHL (4 FL and 1 MZL) that were treated with CAR T-cell single infusion followed by several doses of IL-2 [92]. Patients received a conditioning regimen consisting of cyclophosphamide 60 mg/kg x 2 days and fludarabine 25 mg/m^2 x 5 days. Although all patients achieved a response (PR) there were no patients who achieved CR with 75% of FL patients having ongoing response at the time the study was reported [92].

In the 32 patients included in a FHCRC study (with various NHL histologies) that used a 1:1 ratio CD4/CD8 to manufacture CAR T-cells, there were 6 FL patients (there were no other indolent NHL subtypes). In evaluable FL patients the ORR and CR rates were 80% [4/5] and 40% [2/5] [59].

Results of the Phase IIa trial using the CTL019 CAR construct at the University of Pennsylvania included 14 patients with refractory FL that had relapsed within 24 months of initial diagnosis and/or remained refractory to least 2 lines of therapy [60,93]. Patients received a variety of conditioning regimens such as bendamustine 70 mg/m2 x 2 days, cyclophosphamide, radiation plus cyclophosphamide and fludarabine-cyclophosphamide. This trial included FL patients with poor prognosis features including prior multiple therapies (median of 5), relapsed post-autologous HCT (21%) and allogeneic HCT (1 patient). The updated analysis showed a 3-month ORR and CR of 79% [11/14] and 50% [7/14], respectively. The median PFS was not reached and at the median follow u of 28.6 months 70% of patients were disease free [62,93].

Anti-CD19 CAR therapy for indolent lymphomas seems well tolerated with expected toxicity and appears to provide long-term remission in some cases, thus it may have a curative potential. Although a majority of trials include also aggressive lymphoma, however there are studies dedicated to indolent B-cell NHLs with axi-cel (NCT03105336). To date we do not have enough data to predict which indolent lymphoma patients might benefit from the therapy and characterization of the clinical and molecular prognostic factors is warranted on trial.

6. Toxicities of CAR T-cell therapy in lymphomas

The toxicities related to CAR-T cell therapy were well described in early studies in B-cell lymphomas and acute lymphoblastic leukemia (ALL) [55,59,94,95]. There are two main categories of toxicity: cytokine release syndrome (CRS) and neurotoxicity. which can be accompanied by organ damage (renal failure, cardiac dysfunction, liver dysfunction, etc) [96,97]. A more specifically defined criteria for quantification of neurotoxicity, known as CAR-T cell-related encephalopathy syndrome (CRES), was recently developed [96]. The vast majority of CAR T-cell related toxicities resolve within few weeks, and are reported in both single-center and pivotal multicenter studies [55,59,92]. While, the symptoms and signs of each type of toxicities may overlap, it is important for the clinician to recognize these potential complications as they could be life threatening and, in certain circumstances, lead to death. The diagnosis and management of CRS and CRES have been extensively discussed in other manuscripts [96–98].

There are clinical factors that correlate with the development of CRS such as disease burden (specifically in ALL) and levels of CAR T-cells administered [55,59,94,95]. Increased levels of tumor necrosis factor (TNF-alpha), IL-2R, IL-6, interferon (IFN)-gamma, IL-10, IL-15, and ferritin have been shown to be associated with severity of CRS [55,59]. Neurotoxicity seems to be cytokine driven as well [55]. Peak C-reactive protein (CRP) has been shown to be related to CRS severity and can be used as surrogate for early treatment/supportive care [94].

These toxicities have been also reported in the multicenter studies ZUMA-1, JULIET and TRANSCEND trials, with variable frequency and severity, apparently due to differences in patient population, disease subtypes (and clinical presentation), use of different toxicity grading systems and differences in CAR-T cell constructs. The Lee criteria was used to grade CRS in ZUMA-1 and TRANSCEND while the U Penn Criteria was used for severity stratification of CRS in the JULIET trial. Table 3 describes the frequency and features of CART related toxicities in the 3 multicenter studies in NHL.

Table 3
Toxicities in the three largest multicenter studies with anti CD19 CAR T-cell therapy for aggressive B-cell lymphomas.

Study	ZUMA-1 (Neelapu, 2017)	JULIET (Schuster, 2017)	TRANSCEND[a] (Abramson, 2017)
No patients enrolled (treated)	111 (101)	141 (85)	NR (91)
Cytokine release syndrome			
Time to onset, median, range	2 days (1–12)	3 days (1–9)	5 days (1–14)
Duration, median, range	8 days (NR)	7 days (3–34)	5 days (NR)
Grade (All)	93%	58%	36%
Grade 3˚ 4	13%	23%	1%
Use of tocilizumab	43%	15%	12%
Use of vasopressors	17%	6%	24%
Use of steroids	27%	11%	16%
Admission to ICU	NR	24%	NR
Infections			
All Grades	35%[1]	27%	NR
Grade 3 or 4	31%[1]	13%	NR
Neurotoxicity			
Time to onset, median, range	5 days (1–17)	NR	10 days (3–23)
Duration, median, range	17 days (NR)	NR	11 days (NR)
All Grades	64%	21%	21%
Grade 3 or 4	28%	12%	15%

NR: Not reported, ICU: Intensive care unit. [1] Febrile Neutropenia.
[a] Reported from the FULL cohort data.

7. Expansion/persistance of CAR T cells

In vivo expansion and persistence of CAR T cells has been shown to be associated with clinical outcomes in hematological malignancies and particularly in lymphomas [57,59,95]. The ZUMA-1 study CAR T cells peaked within 14 days of the infusion and were still detectable in majority of patients by day 180. CAR T cells levels by day 28 (area under the curve [AUC $_{0\text{-}28}$] was 5.4 times higher in those in CR versus non responders ($p < 0.001$) [99]. In the TRANSCEND study higher concentrations and AUC $_{0\text{-}28}$ levels of CAR T cells expansion were also associated with clinical and durable responses, as well as with higher tumor burden, peak cytokines, CRS and NT; however, there were no differences in detectable CAR T cells (persistence) in responding and non responding patients in this study a fact that is supported by the long term NCI data that showed non clonal CD19$^+$ B-cell recovery in patients with durable remissions [56,100]. The UPenn data showed that CTL019 CAR T cells were detected at a median of 24 months in 14 out 16 patients who had CR. Recovery of CD19$^+$ B-cells occurred in 50% of responding patients and was not associated with disease relapse [62].

A critical component is the conditioning regimen that leads to lymphodepletion. The most commonly used agents are low dose cyclophosphamide and fludarabine [55]. Others such as bendamustine and low radiation have been utilized. The rationale of inducing lymphodepletion prior to adoptive cell therapy include enhancement of the antitumor activity by decreasing regulatory T-cells (T regs), creating a peritumoral inflammatory milieu by tissue damage and increased activation of antigen-presenting cells [101,102]. A key homeostatic cytokine that promotes T-cell proliferation and activation, IL-15, is increased in the setting of lymphodepletion and has been associated with peak CAR T cells and clinical response. All these factors create a favorable environment for CAR T cell survival and persistence after appropriate lymphodepletion [57,103].

Tumor microenvironment and CAR T cells trafficking into the tumor seem to be associated with clinical activity. In the TRANSCEND-001 study patients who achieved CR had an increased CD8$^+$ CAR T cells concentration in the tumor area [104].

8. Other targets/approaches for cellular therapy in lymphomas

Despite the success of anti-CD19 CARs in B-cell NHLs, relapses do occur. One of the hypothesized mechanisms is CD19 immunological antigen escape; especially since CD19 negative B-cell malignancies relapses have been reported [103]. Failure to express CD19 in some B-cell NHLs and/or epitope/antigen loss of the CD19 through splicing mechanism have been described as resistance mechanism or relapse in patients receiving CD19 directed therapy (such as CARs or bispecific antibodies) [105]. Thus, developing CAR T-cells against alternative lymphoma targets is actively being pursued.

Given the success of anti-CD20 therapy for B-cell NHL in the last decade with the use of monoclonal antibodies, a logical CAR target is the CD20 antigen. Earlier studies showed the feasibility of this approach with modest activity [52,106]. When costimulation with 4-1BB was added to the anti-CD20 CAR T cells, the ORR and CR rates were 80–83% and 17–50% in 2 different trials, respectively [107,108]. Anti-CD20 CAR T-cells with CD28 and 4-1BB as costimulation ("third generation CAR") was feasible with clinical efficacy and tolerable toxicity profile [108].

Studies with CD22-speficic CAR showed potent activity in CD22$^+$ B-cell leukemias but it also has anti-lymphoma activity in preclinical studies [109]. Most of studies reported are focusing on CD22$^+$ B-ALL but there ongoing trials for refractory CD22$^+$ B-cell NHLs (NCT02315612 and NCT 02794961) [110].

One of the most common complications of anti-CD19 CAR T-cell therapy is B-cell aplasia with associated hypogammaglobulinemia that is associated increased frequency of infections. One way to prevent this complication is by targeting on light chain type of the immunoglobulin. One study has showed promising activity of anti-kappa light chain CAR in NHL [111].

Another attractive target is the tyrosine kinase like-orphan receptor 1(ROR-1) that is present in neoplastic cells but no in B-cells, thus preventing B-cell aplasia. ROR-1 specific CAR-T cells are currently being studied mostly in CLL [112,113].

Immune escape is a postulated mechanism of CAR resistance, thus targeting more than one antigen is a proposed approach in order to prevent this immunological event. Bi-specific CARs targeting CD19 and CD20 antigens for B-cell malignancies has been developed (CD19-OR-CD20 CAR) with significant pre-clinical activity, even in CD19 negative tumor cells [114]. Bi-specific CARs targeting CD19 and CD22 are also in development and feasible in preclinical studies, and although majority of the trials focus on B-cell ALL CD22$^+$, some include B-cell NHLs (NCT03287817 and NCT03233854) [115].

Development of immunogenicity of CARs, especially against the epitopes of the murine derived scFvs portion, has been linked to decreased persistence and activity of CAR T-cells once infused [116]. In order to reduce scFv immunogenicity, fully human CAR T-cells with human derived scFv has been developed and showed interesting preclinical profile with potential for clinical use [117].

9. Conclusions and future directions

CAR T cell therapy has emerged as a treatment option for difficult to treat refractory B-cell non-Hodgkin lymphoma. From early reports to multicenter and global studies the clinical efficacy has been consistent in refractory patients including poor risk B-cell lymphomas. With the FDA approval of axicabtagene ciloleucel, the imminent approval of other CAR T-cell constructs for lymphoma is expected.

Further efforts will be directed towards improving efficacy of CAR T cells by understanding mechanism of CAR T failure and improving safety. As up-regulation o PD-1/PD-L1 pathway is a well-known mechanism it is expected that combination therapy with PD-1 inhibitors may enhance CAR T cell activity [118]. Targeted agents such as ibrutinib and idelalisib could also have a role in improving the CAR T cell efficacy by increasing its proliferative capacity and reversing T-cell dysfunction [119,120]. Utilization of next generation CAR T-cell products such as third generation CAR T cells or bi-specific CAR T cells represent another approach of

improving CAR T cell therapy efficacy.

Finally, as the role of CAR T cells in refractory B-cell NHL is becoming standard, it will be important to evaluate the potential role in different settings. Clinical trials testing CAR T cell therapy in primary induction failure for DLBCL, comparing CAR T cell therapy to salvage chemotherapy and autologous HCT, or even testing the therapy for high risk patients in the frontline setting.

Practice points

- CAR T cell therapy fills a previously unmet need to for refractory non-Hodgkin's lymphoma
- Several anti-CD19 CAR T cell constructs have been studied in multicenter pivotal studies without enough data to compare efficacy
- CAR T cell related toxicity remains a clinical challenge. This therapy should be limited to specialized center with experience in cell therapies and high-risk immunotherapy.

Research agenda

- New CAR T cell products in order to improve efficacy are currently being tested
- The addition of drugs that target inhibitory immune mechanisms (PD-1/PD-L1), restore immune dysfunction or target the tumor microenvironment will be investigated
- The role CAR T cell therapy as a second line agent and as up-front therapy for high risk disease may challenge current standard of care approaches

Conflicts of interest

Julio C. Chavez: Kite Pharma (Advisory Board, Speakers Bureau), Novartis (Advisory Board), Genentech (Speakers Bureau), Frederick F. Locke: Kite Pharma (Scientific Advisor), Cellular Biomedicine Group (Consultant).

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