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CAR T-cell therapy for B-cell lymphoma

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Abstract

Chimeric antigen receptor-modified (CAR) T-cell therapy targeting CD19 has revolutionized the treatment of relapsed or refractory B-cell lymphomas. Based on unprecedented response rates and durability of response in high risk B-cell lymphoma patients, anti-CD19 CAR T-cell therapy was rapidly approved by the FDA for a variety of lymphoma subtypes. Anti-CD19 CAR T-cell therapy is now considered standard of care for patients with relapsed or refractory (R/R) aggressive non-Hodgkin's Lymphoma (NHL) after 2 or more lines of therapy. Three second-generation anti-CD19 CAR T-cell products have been FDA approved for R/R aggressive B-cell lymphoma and FDA approval has been obtained for Mantle Cell Lymphoma and Follicular lymphoma as well. This has ensured broad access to CAR T-cell therapy for patients with NHL and new real-world trials have helped confirm feasibility of CAR T-cell therapy for a broad patient population. The emergence of CAR T-cell therapy will likely provide a new patient population who is status post anti-CD19 CAR T-cell therapy. Investigation of mechanisms of failure of CAR T-cell therapy and clinical trials to study strategies to address this are thus required. Here we provide a thorough review on the use of the FDA approved anti-CD19 CAR T-cell products axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel in patients with indolent or aggressive B-cell lymphoma, and touch on mechanisms of failure of CAR T-cell therapy and potential approaches which are currently under investigation to address this.

Keywords

CAR T-cell therapy; Lymphoma; Hematologic malignancies; B-Cell lymphoma; Anti-CD19 CAR T-cell therapy; Cellular therapy; Cell therapy

Introduction

Non-Hodgkins B-cell Lymphoma (NHL) is a heterogeneous group of diseases that includes highly aggressive (ex. high grade B-cell lymphoma), aggressive (ex. Diffuse Large B-cell Lymphoma) and indolent disease (follicular B-cell lymphoma, marginal zone lymphoma).[1] Most patients with aggressive NHL will undergo induction with R-CHOP (rituximab,

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cyclophosphamide, doxorubicin, vincristine, and prednisone) or similar regimen. In DLBCL approximately two thirds of patients will achieve a cure with R-CHOP induction.[2] For patients with indolent B-cell lymphoma, bendamustine and rituximab/obinatuzumab has provided excellent up front response and durability, though patients are not typically cured with these regimens.[3,4] In relapsed or refractory (R/R) aggressive B-cell lymphoma, cure is still achievable in a subset of fit patients by utilizing salvage chemotherapy followed by autologous stem cell transplant with high dose chemotherapy conditioning.[5] In patients unfit for transplant or with relapse after auto transplant, overall response rate (ORR) to next line of therapy has traditionally been ~20%-30% with a median overall survival (OS) of ~6 months.[6–8] The advent of anti-CD19 Chimeric Antigen Receptor (CAR) T-cell therapy has therefore revolutionized treatment for B-cell malignancies.[9–11] Providing previously unprecedented response rates and durability in high risk B-cell lymphoma patients, anti-CD19 CAR T-cell therapy is now considered standard of care for patients with R/R aggressive NHL after 2 or more lines of therapy.[12] FDA approval of the commercial CAR T-cell products axicabtagene ciloleucel (axi-Cel; Yescarta Kite/Gilead), tisagenlecleucel (tisa-cel; Kymriah Novartis), and lisocabtagene maraleucel (liso-cel; Breyanzi Juno BMS)[13] have allowed for broad access to CAR T-cell therapy. More recent approval of brexucabtagene autoleucel (brexu-cel; Tecartus) for R/R mantle cell lymphoma and axi-cel for follicular lymphoma (FL) have broadened FDA approved indications for anti-CD19 CAR T-cell therapy. Here, we provide a broad review of the current data on the use of CAR T-cell therapy for B-cell lymphoma and also touch on mechanisms of failure and strategies to mitigate this to help inform treatment and management decisions for providers treating NHL.

Structure, function, and manufacturing of CAR T-cell therapy

The idea of chimeric antigen receptor (CAR) T-cell therapy initially started with work by Eshhar et al in 1993.[14] Here they utilized a single chain variable fragment antibody domain (svFC) linked with a CD3 ζ signaling chain which was then inserted into a T-cell. This allowed for major histocompatibility complex independent activation of T-cells when presented with a specific target antigen recognized by the svFC.[14] This construct was known as a first-generation CAR. Initial studies using a first-generation CAR containing an svFC recognizing CD20 showed it promoted cytotoxic activity but had no real clinical efficacy.[15] In 2011, multiple groups published results evaluating the addition of costimulatory domains to the first-generation CAR Construct which led to increased CAR T-cell expansion, persistence, and pre-clinical efficacy.[16,17] Ultimately, these second-generation CAR constructs have proven to have unprecedented clinical efficacy, particularly against CD19 expressing B-cell lymphoma.

The preclinical and clinical development of axi-cel[18,19] and tisa-cel have been thoroughly described.[20,21] Axi-cel is a second-generation CAR construct composed of an svFC that recognizes CD19 and a transmembrane portion with a CD3ζ activation domain coupled to a CD28 costimulatory domain.[22] Tisa-cel is also a second-generation CAR construct; however, it contains a 4-1-BB costimulatory domain. The CD28 costimulatory domain has been postulated to provide increased expansion but decreased persistence compared to the 4-1BB costimulatory domain.[23] Liso-cel is composed of a second-generation construct with

4-1BB costimulatory domain and a defined CD4:CD8 cell ratio. In general, each CAR T-cell product comes with its own set of defining features which help physicians select a product. Considerations include average manufacturing time and manufacturing success rates, rates of adverse events including cytokine release syndrome (CRS), immune effector cell associated neurotoxicity syndrome (ICANS), and disease subtype indications.

Manufacturing of a CAR T-cell product starts with leukapheresis to obtain autologous peripheral blood mononuclear cells (PBMC's). After collection, the patients PBMCs are shipped to a centralized corporate GMP facility where they are enriched for T-cells and activated; typically using a combination of anti-CD3 and or CD28 antibody coated beads plus or minus stimulating cytokines. The target CAR gene is then transduced into T-cells utilizing a lentiviral vector. The now CAR expressing T-cells are then expanded to well above the target dose (most commonly 2×10^6/kg), viably cryopreserved, and then undergo quality control prior to shipping to the requesting hospital. Prior to infusion of CAR T-cell therapy, patients will undergo lymphodepleting conditioning chemotherapy, most commonly with cyclophosphamide and fludarabine.[24–26] Infusion of CAR T-cells most commonly occurs in the inpatient setting to ensure close monitoring for CRS and ICANS. However, institutional guidelines play a role and it is feasible to infuse products with lower rates of toxicity in the outpatient setting when accompanied by close monitoring.

Aggressive B-cell lymphoma

Axicabtagene ciloleucel

ZUMA-1 was a multicenter phase 2 study investigating the use of KTE-C19 (axi-cel) in patients with R/R aggressive B-cell lymphoma. This study enrolled 111 patients with DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma with R/R disease following at least two lines of prior therapy. Those with central nervous system (CNS) involvement were excluded. Axi-cel was successfully manufactured for 110 patients enrolled and administered to 101. The ORR was 82% and the CR rate was 54%. Importantly, there were no differences in response rates between higher risk subgroups including those with primary refractory and high grade disease and lower risk groups. With a median follow-up of 15 months, 42% of patients continued to have an objective response. OS at 18 months was 52%. The most common adverse events were neutropenia, anemia, and thrombocytopenia. Grade 3 or higher CRS and ICANS (described at the time as "neurologic events") occurred in 13% and 28% of the patients, respectively. Three patients died during treatment (1 from disease progression, 1 from sepsis after conditioning but prior to infusion, and 1 from multiple factors including multi-system organ failure and disease progression). Higher CAR T-cell levels in blood were associated with response.[9] Patients were followed up for a median of 27 months to evaluate for long term response. Median OS was not reached (NR) and the median progression free survival (PFS) was 5.9 months. No new treatment-related deaths occurred during the additional follow-up.[27]

Two large consortia in the United States evaluated outcomes of axi-cel when given in a real-world setting. One group led by Jacobson looked at 122 patients from 7 medical centers in the U.S. treated with axi-cel. Seventy-six patients (62%) would have been ineligible for the ZUMA-1 trial. Median follow-up was 10.4 months. In the modified intention to

treat population, the best ORR and CR rates were 70% and 50%, respectively. Median PFS was 4.5 months in all patients however was NR in patients who achieved CR as best response. Median OS was NR in all patients and 1-year OS was 67%. Although response rates were similar in the ZUMA-1-eligible and ZUMA-1-ineligible groups (70% vs 68%), there was a statistically significant improvement in CR rate (63% vs 42%), median PFS (NR vs 3.3 months), and 1-year OS (89% vs 54%). Rates of grade ≥ 3 CRS and ICANS were 16% and 35%, respectively in all patients.[28] The other real-world group, led by Nastoupil, evaluated 275 patients who received axi-cel. 43% of patients would not have met ZUMA-1 eligibility criteria. Grade ≥ 3 CRS and ICANS occurred in 7% and 31%, respectively. Nonrelapse mortality was 4.4%. Best ORR and CR rates in infused patients were 82% and 64% respectively. At a median follow-up of 13 months the median PFS was 8 months and median OS was NR.[29]

The group at Stanford evaluated the long-term course of hematologic recovery, immune reconstitution, and infectious complications in 41 patients with DLBCL treated with axi-cel. They found that grade ≥ 3 cytopenias occurred in 98% of patients within the first 28 days postinfusion, with most resolved by 6 months. Only 40% of patients had detectable $CD19^+$ B cells by 1 year, and half continued to have a $CD4^+$ T-cell count <200 cells/μL by 18 months postinfusion. The majority of infections were seen in the first 28 days following infusion and a third of patients had an infection within the first 30 days. Receipt of corticosteroids was only factor that predicted risk of infection in a multivariate analysis (hazard ratio, 3.7). Opportunistic infections due to Pneumocystis jirovecii and varicella-zoster virus were seen up to 18 months postinfusion in patients who prematurely discontinued prophylaxis.[30] A similar retrospective study of 85 patients from Fred Hutch revealed similar findings.[31] These studies support the use of prophylactic anti-microbials and continuation of long-term immune surveillance post anti-CD19 CAR T-cell therapy.

Tisagenlecleucel

JULIET was an international, phase 2 study of tisa-cel in adults with R/R DLBCL who were ineligible for or had disease progression after auto transplant. A total of 93 patients received an infusion and were included in the efficacy analysis. The median follow-up was 14 months. Best ORR was 52% with a CR rate of 40%. Response rates were consistent across prognostic subgroups. At 12 months after the initial response, PFS was 65% (79% among patients with a CR). The most common grade 3 or 4 adverse events were CRS (22%), ICANS (12%), cytopenias lasting more than 28 days (32%), infections (20%), and febrile neutropenia (14%). Three patients died from disease progression within 30 days after infusion. No deaths were attributed to tisagenlecleucel, cytokine release syndrome, or ICANS.[10] In the long-term analysis of JULIET, at a median follow-up of 36 months, 60% of patients maintained their response.[32]

The Center for International Blood and Marrow Transplant Research analyzed tisa-cel in the real-world setting utilizing the national cellular therapy registry. Five hundred and eleven patients were enrolled from 73 centers, including 155 patients with NHL. NHL patients had a median follow-up of 12 months and best ORR was 62% with CR rate of 39.5%. Six-month PFS and OS rates were 39%, and 71%, respectively. Grade ≥3 CRS and

ICANS were reported in 12% and 8% of all patients, respectively.[33] GELTAMO reported a similar analysis in Europe of 91 patients at 10 Spanish institutions and outcomes were comparable.[34] Together, these real-world studies demonstrated similar efficacy and safety compared with those seen in the pivotal trials.

A sub-analysis of JULIET evaluated patient-reported health-related quality of life (HRQoL) scores. Two validated HRQoL instruments, Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) and Short Form-36 (SF-36) Health Survey, were used to measure HRQoL at baseline and months 3, 6, 12, and 18 postinfusion. Patients who achieved CR or PR sustained HRQoL improvement in all FACT scores at all time points and SF-36 instruments showed improvement on 5 of 8 subscales.[35]

Lisocabtagene maraleucel

The TRANSCEND-NHL 001 study was a seamless multi-center study evaluating liso-cel in DLBCL, high-grade B-cell lymphoma, transformed indolent lymphoma, primary mediastinal B-cell lymphoma, and FL grade 3B. Patients were assigned to one of three target dose levels of liso-cel, which were administered as a sequential infusion of CD4+ and CD8+ CAR T-cells in equal ratios. The primary endpoints were adverse events, dose-limiting toxicities, and ORR. Three-hundred and forty-four patients underwent leukapheresis, and 269 patients received at least one dose. Seven patients had secondary CNS involvement. Median follow-up for OS for all 344 patients who had leukapheresis was 19 months. Overall safety and activity of liso-cel did not differ by dose level. Of the patients evaluable for efficacy, ORR was 73% and 53% obtained CR. The most common grade 3 or worse adverse events were neutropenia, anemia, and thrombocytopenia. CRS and ICANS occurred in 42% and 30% of patients, respectively; grade 3 or worse CRS and ICANS occurred in 2% and 10% of patients, respectively.[13]

The impact of treatment with liso-cel on HRQoL and symptoms was evaluated as part of the TRANSCEND NHL 001 trial and similar to tisa-cel, clinically meaningful improvement was observed. HRQoL scores were generally higher for treatment responders than for nonresponders.[36]

Special considerations

Kittai et al evaluated the impact of pretreatment comorbidities on outcomes using the Cumulative Illness Rating Scale (CIRS). A retrospective chart review was performed at 4 academic institutions. On univariable analysis, Eastern Cooperative Oncology Group performance status at leukapheresis was associated with inferior PFS (hazard ratio [HR], $P = 0.03$) and OS (HR, 1.76; $P = 0.007$). Higher CIRS (CIRS ≥7 or CIRS-3+) was associated with inferior OS (HR, 2.12; $P = 0.03$). In multivariable analyses, CIRS ≥7 or CIRS-3+ and ECOG PS maintained independent prognostic significance.[37]

The impact of bridging therapy (BT) administered between leukapheresis and CAR T infusion for aggressive NHL is unclear. The US Lymphoma consortium study found an association between systemic BT and poorer OS.[29] Pinnix et al performed an evaluation of patients who received axi-cel and found that patients who received BT were more likely to have international prognostic index (IPI) score ≥3 ($P \leq 0.01$), bulky disease ($P = 0.01$),

and elevated lactate dehydrogenase (LDH; $P \leq 0.01$). One-year PFS and OS rates were not significantly different between BT and non-BT cohorts ($P = 0.06$ and 0.21, respectively). Compared with non-BT patients, 1-year PFS was inferior for patients bridged with systemic therapy ($P = 0.01$). Patients bridged with radiation alone had improved PFS compared those who received systemic BT ($P = 0.05$).[38] Prospective studies will be required to full define the effects of systemic vs. radiation based BT on CAR T outcomes.

The phase 1/2 clinical trials that led to the FDA approval axi-cel and tisa-cel excluded patients with CNS involvement. Dana Farber reported on 8 patients with CNS involvement who were treated with tisa-cel. All patients received prophylactic anticonvulsants and no patients required tocilizumab or steroid intervention for CRS nor ICANS. Best responses included 4 patient with PD, 1 patient with PR, and 3 patients with CR. 2 patients had ongoing CR at time of study analysis.[39] Further studies will be required to understand the utility of CAR T in CNS disease, though anecdotal reports such as these are promising.

Overall, the response rates to Anti-CD19 CAR T-cell therapy in R/R aggressive B-cell Lymphoma seen here were unprecedented. Further studies are ongoing to determine the optimal sequencing of Anti-CD19 CAR T-cell therapy in the management of R/R aggressive B-cell Lymphoma. The success here ultimately also led to the investigation of Anti-D19 CAR T-cell therapy in other B-cell lymphoma subtypes, including MCL and indolent lymphoma.

Mantle cell lymphoma

The majority of patients with MCL have aggressive features and typically undergo induction therapy followed by a recommendation for consolidative autologous stem cell transplant with high dose chemotherapy.[40] In general, MCL has typically felt to be incurable without the use of allogeneic hematopoietic stem cell transplant and relapse after initial therapy denotes a poor prognosis.[40] BTK inhibition (BTKi; ex. ibrutinib) has greatly improved outcomes in R/R MCL.[41] However, traditionally patients who relapse after BTKi still have a poor prognosis, with an ORR of 25-42% to next line of therapy and a median OS of ~6-10 months.[42]

Anti-CD19 directed CAR-T therapy thus has now been established as a key therapeutic option for R/R MCL. Brexu-cel (Tecartus, formerly KTE-X19, Kite/Gilead) is a second-generation anti-CD19 CAR T-cell product containing a CD28 costimulatory domain. Brexu-cel differs from axi-cel in that its manufacturing process includes a step for ex-vivo removal of CD19 expressing cells in order to limit contamination by circulating malignant cells and B-cells. This process is hypothesized to mitigate clinically significant T-cell activation and exhaustion of infused CAR T-cells in response to CD19+ cells during the manufacturing process. Brexu-cel was studied in patients with R/R MCL in the pivotal phase two ZUMA-2 trial.[43] In this study, 74 patients were enrolled and underwent leukapheresis and manufacturing of product and 68 ultimately received infusion of CAR T-cells. Of the 74 patients who underwent leukapheresis, three patients failed manufacturing. Two patients did not receive brexu-cel due to disease progression and one due to the development of atrial fibrillation.[43] All enrolled patients had two or more prior lines of MCL directed

therapy including prior treatment with a BTKi such as ibrutinib. A sizeable proportion of treated patients had other high risk features, including Ki67 proliferation index ≥ 30% in 82% of patients, intermediate/high risk MCL-IPI (MIPI) in 56% of patients, disease that was refractory to the last line of treatment (40%), and blastoid or pleomorphic histology (31%). The ORR among all enrolled patients was 85% including a 59% CR rate, and among treated patients with at least 7 months of follow-up an ORR of 93% with a 67% CR rate was demonstrated. The 12-month PFS was 61% with an OS of 83%. Notably, in subgroup analysis high risk groups appeared to have a similar likelihood of objective response as well as PFS. This includes patients with blastoid or pleomorphic histology, high Ki67 index, *TP53* mutated disease, or refractory disease to prior therapy which traditionally all have denoted poor prognosis. Toxicities among treated patients were comparable to those seen with axi-cel in ZUMA-1 and in real-world studies. CRS of any grade was seen in 91% of patients (15% grade ≥ 3). Any grade of ICANS was seen in 63% of patients; Grade ≥ 3 ICANS was observed in 31% of patients. Grade 3 or greater cytopenias were common, occurring in 94% of patients. Longer-term follow-up has been presented in abstract form at ASH 2020, with a 15-month estimate of PFS of 59% after a median of 17.5 months of follow-up.[44]

Liso-cel is also currently under investigation for R/R MCL in the dose expansion phase of the TRANSCEND NHL 001 study. Preliminary results from the MCL cohort of TRANSCEND were reported at ASH 2020, with 41 patients with R/R MCL having undergoing apheresis and 32 having received liso-cel.[45] Prevalence of high risk features was similar to ZUMA-2. Of note, CNS was not exclusionary for this study, and at least one patient with CNS disease was noted to have achieved an objective response. The ORR at time of preliminary analysis was 84% including a 59% CR rate. A similarly high ORR (75%) was reported among patients with blastoid morphology. Reported toxicities included ICANS of grade 3 in three of 26 and grade 4 CRS in one patient (no grade 3 CRS observed). Hematologic toxicities included ongoing grade ≥ 3 cytopenias at day 29 in 11 patients (34%). There were two reported grade 5 AEs including one patient with tumor lysis syndrome and one patient with cryptococcal meningoencephalitis. Overall, similar to brexu-cel, high response rates were seen with liso-cel in R/R MCL. The toxicity profile of liso-cel appears to differ from axi-cel or brexu-cel.[9, 13, 43] If preliminary results from TRANSCEND are confirmed in the completed study, liso-cel may offer a good second CAR-T option for MCL patients with a lower expected incidence of CRS and ICANS.

Overall, the rate and depth of response to Anti-CD19 CAR T-cell therapy in R/R MCL was unprecedented, particularly in high risk populations and those who had failed BTKi. On the basis of the ZUMA-2 results, brexu-cel was granted accelerated approval by the FDA (Tecartus) for the treatment of adult patients with R/R MCL. Subsequently this has vaulted brexu-cel to become the preferred therapy for patients with R/R MCL who have progressed after BTKi. That being said, further follow-up is required in order to assess long term clinical outcomes with CAR-T in MCL to assess whether a subset of patient can achieve durable remission. *TP53* mutation and blastoid morphology typically predict for poor outcomes with chemo-immunotherapy or BTKi in MCL[46–48]; however, these patients had equally high response rates to CAR T-cell therapy in ZUMA-2. Thus, sequencing of

CAR-T therapy in earlier lines of treatment is of interest in high-risk groups and further prospective studies in these settings are anticipated.

Indolent lymphoma

Follicular Lymphoma (FL) and Marginal Zone Lymphoma (MZL) are the two most common variants of indolent NHL.[1] Most patients only require treatment when indications (ex. symptoms or cytopenias) are present and patients respond well to less intense therapies such as bendamustine and rituximab/obinatuzumab.[3,4] However, the disease course in indolent lymphoma is one of remissions and relapses and patients can develop chemotherapy-refractory status or transformation into a more aggressive histology. Early use of autologous stem cell transplant with high dose chemotherapy conditioning can be considered for high-risk patients who experience early failure of chemoimmunotherapy (< 2 years), however this approach is typically only curative in rare cases and 5 year OS for all patients with early failure is ~50%.[49] Refractory patients or those with frequent relapses who have run out of lines of therapies have traditionally required consideration of allogeneic stem cell transplant to achieve cure. Many patients in this setting are not good candidates for donor transplant, and their prognosis is poor.[50] Given Anti-CD19 CAR T-cell therapy's activity in aggressive lymphoma, evaluating CAR T-cell activity in indolent B-cell lymphoma was a logical next step.

ZUMA-5 was a phase two, multicenter, single-arm study of axi-cel in patients with R/R indolent NHL. Patients had either indolent FL (Grade 1-3a) or MZL. At the time of the primary analysis reported at ASH 2020,[51] 146 patients with indolent lymphoma had been treated (124 with FL and 22 with MZL). 86% of patients had stage III/IV disease, 47% had a FL-IPI (FLIPI) Score ≥ 3, 49% had bulky disease, 64% had ≥ 3 prior lines of therapy, and progression of disease within 2 years of first chemoimmunotherapy was present in 55% of patients. With a median follow-up of 17.5 months, the ORR was 92% and CR was achieved in 76% of 104 evaluable patients. In 84 patients with FL, the ORR was 94% with a CR rate of 80%. In 20 evaluable MZL patients, ORR was 85% and CR rate was 60%. For FL, 64% of patients had ongoing response at the time of this primary analysis and the median OS and PFS were not reached for any cohort. CRS of any grade occurred in 82% of patients, and ICANS of any grade in 60% of patients. Grade ≥ 3 CRS occurred in 7% of all patients, Grade ≥ 3 ICANS occurred in 19% of patients. Grade 3 cytopenias occurred in 83% of patients. Based on the results of ZUMA-5, on March 5, 2021, the FDA approved the use of axi-cel in R/R FL following at least 2 lines of therapy. Accrual for the MZL arm of ZUMA-5 remains ongoing.

This primary analysis of axi-cel in indolent lymphoma demonstrated that axi-cel can provide exceptional response rates and survival outcomes even in poor risk and refractory FL. Continued close follow-up will be required to determine durability of the response in this population. It also remains to be seen how anti-CD19 CAR T-cell therapy will be sequenced in terms of treatment for indolent lymphoma. There are many novel targeted therapies with clinical activity including four PI3 Kinase inhibitors, one EZH2 inhibitor, and lenalidomide which can be sequenced to provide long term survival. However, in certain high risk populations and in those who have run out of treatment options, anti-CD19 CAR

T-cell therapy appears to be an ideal option to provide high response rates and potentially durable remissions.

Clinical trials evaluating the use of other anti-CD19 CAR T-cell products in FL are underway. The preliminary analysis of the ELARA trial, studying the use of tisa-cel in FL, showed an ORR of 82% and CR rate of 65% in a similarly high risk group of patients.[52] Though median follow-up was only 6.5 months at time of analysis, the median DOR, PFS, and OS curves appear to be comparable to those seen in ZUMA-5. As expected with tisa-cel, toxicities rates were lower with any grade CRS occurring in 48% of patients (0% ≥ Grade 3). ICANS occurred in 10% of patients (2% grade ≥ 3). Liso-cel is currently being assessed in the TRANSCEND Follicular Lymphoma study (NCT04245839). Ultimately, we expect a range of anti-CD19 CAR T-cell products to become FDA approved for the use in FL (and eventually MZL). This will then allow for the consideration of different products based on rates of manufacturing success and turnaround times, patient and disease characteristics, and treatment goals.

Mechanisms of anti-CD19 CAR T-cell failure and salvage strategies

Approximately ~60% of patients with R/R aggressive NHL who undergo anti-CD19 CAR T-cell therapy will progress during the initial treatment period, or achieve a response and then subsequently relapse.[9–11] In patients with DLBCL who fail after anti-CD19 CAR T-cell therapy, it has traditionally been felt that allogeneic hematopoietic stem cell transplant would remain only curative option. However, many of the patients who fail anti-CD19 CAR T-cell therapy cannot achieve the response necessary nor are fit enough to undergo allogeneic stem cell transplant. By understanding the mechanisms of failure of CAR T-cell therapy, we can develop rational strategies to mitigate failure up front and improve outcomes after failure of Anti-CD19 CAR T-cell therapy.

Failure of CAR T-cell therapy encompasses progression during the initial treatment period, or response and subsequent relapse. The mechanisms for initial resistance/progression to CAR T-cell therapy and relapse after initial response to CAR T are diverse and are not exclusive of one another. Mechanisms of failure include tumor or disease intrinsic factors, CAR T-cell specific mechanisms of failure, and CAR T-cell/host interactions resulting in failure.

Tumor intrinsic mechanisms of failure

Tumor intrinsic factors leading to CAR T-cell failure include the loss or mutation of the CD19 extracellular epitope though a variety of mechanisms.[53, 54] In ZUMA-1, eleven patients who experienced axi-cel failure were able to provide biopsy specimens of their lymphoma tissue. In 3/11 of these patients (27%), the CD19 antigen was found to have been lost on evaluation by IHC and/or flow cytometry.[9] Also in ZUMA-1, out of the 52 patients with CAR T-cell failure, nine were re-treated with a second infusion of axi-cel. Five out of nine of these patients had a response, two of which were CR and three which were PR's who ultimately progressed. Gauthier et al also reported their findings after a second infusion of anti-CD19 CAR T-cell therapy in 21 patients with B-cell lymphoma.[55] They found an ORR of 39% and a CR rate of 20%.[55] Thus, though retreatment with anti-CD19 CAR T-cell

therapy was feasible, responses were not optimal, likely due in some part to loss/mutation of the CD19 antigen.

Alternative strategies to address failure of CAR T-cell therapy secondary to antigen loss are currently in development. In acute lymphoblastic leukemia (ALL), Shah et al showed that anti-CD22 directed CAR T-cell therapy used in patients with relapse after anti-CD19 directed immunotherapy provided CR rates of 70%.[56] In NHL, CD22 expression ranges from 91% to 99% in the aggressive and indolent populations, respectively.[57] CD20 expression is near ubiquitously expressed in DLBCL.[58] Clinical trials investigating single antigen anti-CD22 and anti-CD20 CAR T-cell therapy in DLBCL after failure of anti-CD19 CAR T-cell therapy are underway. However, single antigen alternative CAR T-cell therapy does not address if the disease is CD22 or CD20 low expressing nor does it address if antigen loss again occurs. Studies investigating novel vectors combining multiple antigens on a single CAR (ex. CD19/22 and/or CD19/20/22) to address these issues are under way.

CAR T-cell specific mechanisms of failure

CAR T-cell specific mechanisms of failure can result in poor CAR T-cell expansion and function ultimately resulting in poorer clinical outcomes. Etiologies can include inadequacy of manufactured product resulting from manufacturer error or poor quality donor T-cells.28 Pre-clinical work evaluating novel culture conditions for the creation of CAR T-cell therapies with improved phenotype profiles and less exhaustion are underway. Studies looking at optimal bridging therapy and evaluating the use of chemotherapy vs. radiation vs. combined therapy are also required to ensure optimal donor cells are provided for product manufacturing.

Tumor/host and CAR T-cell interactions as mechanisms of failure

The tumor microenvironment (TME) is comprised of an immunosuppressive milieu of both tumor and non-tumor immune cells.[59] Interactions of the TME with CAR T-cells can result in decreased CAR T-cell expansion and increased exhaustion.[60] Host systemic inflammation and tumor burden can contribute as well.[61] In DLBCL, peak expansion of CAR T-cells correlates with response rates at 12 months,[51] particularly when peak expansion is correlated to tumor burden.[61] In MCL, peak CAR T-cell expansion correlates directly with response.[43] Retrospective studies quantifying risk factors for CAR T-cell failure have identified extranodal disease sites ≥2, increased CRP, and high metabolic tumor volume at the time of treatment.[62] Thus addressing causes of CAR T-cell expansion is a critical to mitigating CAR T-cell failure.

Targeted agents for salvage therapy and as conditioning prior to CAR T-cell therapy to address the interactions of tumor/host and CAR T-cell driven mechanisms of failure

Lenalidomide is one agent that may be useful as a salvage containing regimen post CAR T-cell therapy failure. Lenalidomide derives its efficacy from both anti-tumoral and immunomodulatory effects including increased T-cell activation and disruption of TME induced immunosuppression.[63] Lenalidomide enhances the anti-tumor function of CAR T-cells by changing receptor expression on tumor cells, via alteration of the TME landscape, and via direct effects on CAR T-cells.[63] Lenalidomide has been shown to potentiate CAR

T-cell activity in low-antigen and immunosuppressive environments, increase CAR T-cell number, delay the onset of functional exhaustion[64] and restore the T-cell immune synapse.[65] Thieblemont et al evaluated early lenalidomide as salvage with progression post Anti-CD19 CAR T-cell therapy. They found early initiation of lenalidomide allowed 7/11 relapsed patients to recapture a response they initially had obtained with CAR-T, and 4/11 patients obtained CR. Patients receiving early lenalidomide also had higher CAR T-cell expansion compared to other progressing patients including those treated with lenalidomide at later time points.[66] Multiple abstracts evaluating lenalidomide containing salvage regimens post CAR T-cell failure in a retrospective manner are expected to be presented at ASH this year. Future prospective studies evaluating optimal timing and patient populations who may benefit from lenalidomide as salvage post CAR-T failure are required.

BTKi initiated prior to leukapheresis in CLL has been shown to improve expansion of CAR T-cells, improve their function, decrease T-cell exhaustion[67] and improve rates of cytokine release syndrome (CRS).[68] BTKi appears to function by improving T-cell exhaustion by TME modulation including reduced PD1 and CLTA4 expression, inhibition of Tregs and downregulation of chemokines on B cells thus potentially disrupting tumor cell adhesion/homing.[69] Here at the Ohio State University Comprehensive Cancer Center, we have had relative success by utilizing ibrutinib prior to CAR T-cell therapy in a series of patients with DLBCL with antecedent CLL. Nine patients received axi-cel for their DLBCL with antecedent CLL. Seven out of nine patients remained on BTKi through leukapheresis and prior to CAR T-cell infusion. Five patients achieved CR and 4 of these remained disease free at time of analysis.[70] More selective BTK inhibitors like zanubrutinib have been shown to specifically improve the antitumor potency of Liso-cel.[71] Liu et al evaluated the use of BTKi as a salvage regimen post failure of anti-CD19 CAR T-cell therapy and prior to a second infusion of Anti-CD19 CAR T-cell therapy. They found response could be recaptured with BTKi as salvage and also found that responses to a second infusion of Anti-CD19 CAR T-cell therapy while on BTKi were improved compared to prior reports of second infusion of an Anti-CD19 CAR T-cell therapy. Peak expansion of CAR T-cells for patients receiving ibrutinib prior to infusion was also increased.[72]

In patients who fail targeted salvage therapy post failure of CAR T-cell therapy and in certain patients for whom targeted salvage therapy is not optimal, consideration can be given to chemoimmunotherapy followed by allogeneic stem cell transplant. Clinical trials investigating new therapies are also recommended to be given strong consideration.

Conclusion

Anti-CD19 CAR T-cell therapy for R/R NHL has revolutionized how we treat our patients. Across the spectrum of NHL including aggressive and indolent disease, CAR-T has resulted in unprecedented response rates and durability of responses in traditionally very high risk populations. In aggressive NHL, mantle cell lymphoma, and follicular lymphoma FDA approval of current products and imminent approval of future products will likely lead to further studies investigating the optimal sequencing of these products in earlier lines of treatment. With this, treating patients who are status post anti-CD19 CAR T-cell therapy will

likely be the new normal. Investigating mechanisms of CAR-T failure and novel strategies to address this will be critical to the optimal care for these patients in the future.

Conflict of Interest:

Nathan Denlinger: No COI. **David Bond:** Kite/ Gilead- advisory board. **Samantha Jaglowski:** Novartis—advisory board, research funding; Kite—advisory board, research funding; Juno/BMT—advisory board; Takeda—advisory board; CRISPR therapeutics—advisory board.

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