Chimeric Antigen Receptor T-Cell Therapy in Aggressive B-Cell Lymphoma

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KEYWORDS

• CAR T-cell • Large B-cell lymphoma • Aggressive lymphoma • CAR T-cell toxicity • CAR T-cell resistance • Review • CD19

KEY POINTS

- Chimeric antigen receptor (CAR) T-cell therapy with axi-cel and liso-cel is approved for second-line treatment of large B-cell lymphoma (LBCL).
- CAR T-cell therapy with axi-cel, liso-cel, and tisa-cel is approved for the third-line treatment LBCL.
- Early CAR T-cell toxicity of cytokine release syndrome and immune effector cell associated neurotoxicity syndrome should be treated promptly with steroids and tocilizumab.
- Prolonged CAR T-cell toxicity includes persistent cytopenia and infection that can last more than a year postinfusion.

INTRODUCTION

Chimeric antigen receptor (CAR) T-cell therapy is a cellular therapy that uses an engineered T-cell receptor on the surface of donor T cells to kill cancer. The most common antigen targeted clinically in this context is CD19 which was chosen because of broad and high expression in leukemia and lymphomas.[1]

CAR T-cell therapy is increasingly an integral tool in the treatment of non-Hodgkin lymphomas (NHL). Though many initial clinical CAR T-cell studies debuted in leukemia,[2–5] the use of CAR has expanded dramatically in NHL in recent years where it is now approved as an early line of therapy in multiple lymphoma types. This review focuses on the clinical role of CAR-T cells in aggressive B-cell lymphoma including indications, determinants of outcomes, toxicities, and future areas of study.

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Section I–Indications for Chimeric Antigen Receptor T-Cell Therapy in Aggressive Lymphoma

Large B-cell lymphoma (LBCL) is the most common lymphoid malignancy. Though 5-year survival rates after first-line chemotherapy are 60%–70%, up to 50% of patients develop relapsed or refractory disease.[6,7] CAR T-cell therapy has revolutionized treatment of LBCL by using CD19 targeting chimeric antigen receptors expressed on the surface of genetically manipulated T cells to drive durable complete responses (CRs) in previously relapsed and refractory tumors.[1,8]

Currently, 3 CAR T-cell constructs are approved for the treatment of relapsed and refractory LBCL (**Table 1**): axicabtagene ciloleucel (axi-cel, brand name Yescarta),[8,9] lisocabtagene ciloleucel (liso-cel, brand name Breyanzi),[10,11] and tisagenlecleucel (tisa-cel, brand name Kymriah).[12,13] All 3 constructs involve use of autologous CAR-T cells to target the CD19 antigen with the single-chain monoclonal antibody FMC63[14,15] in a second generation[16] CAR T-cell construct. Axi-cel is engineered from a retroviral construct and uses a CD28 hinge, transmembrane, and activation domain. Liso-cel is a lentiviral construct engineered with a IgG4 hinge region, a CD28 transmembrane domain, and a 41BB transactivation domain. Tisa-cel is also a lentiviral construct engineered with a CD8 hinge and transmembrane domain with a 41BB transactivation domain (**Fig. 1**).

The axi-cel product is not balanced for CD4+:CD8+ T-cell ratio and is given at a standard dose of 2×10^6 CAR-positive viable T cells per kilogram. Liso-cel is given at a dose of 90 - 110 $\times 10^6$ CAR-positive viable T cells. The liso-cel apheresis product is sorted into CD4+ and CD8+ populations prior to transduction and the final CAR T-cell product is then infused as separate CD4+ and CD8+ CAR-T cells in a 1:1 ratio. Tisa-cel is also unsorted and given at a dose of 0.6 – 6 $\times 10^8$ CAR-positive vaiable T cells. Patients are typically treated with fludarabine and cyclophosphamide lymphodepleting chemotherapy generally starting on day minus 5 prior to cellular infusion. Recently, single-agent bendamustine has been successfully used as lymphodepleting chemotherapy in patients treated with tisa-cel,[17] and this may offer a less immune suppressive therapeutic option for other CAR T-cell vectors in the future.

All 3 constructs were initially approved for third-line treatment of relapsed and refractory LBCL. Axi-cel and liso-cel received additional approval for second-line treatment of patients with refractory disease or disease that relapsed less than 12 months from initial therapy after 1:1 randomization versus standard of care (SOC) autologous hematopoietic cellular transplant (HCT).

Axi-cel

Axi-cel was initially approved by the Food and Drug Administration in the United States on October 18, 2017. This approval followed the success of the pivotal phase 2 ZUMA-1 study[8,18,19] which targeted LBCL (including high grade B-cell lymphoma with MYC and BCL-2 or BCL-6 translocation, transformed follicular lymphoma, and primary mediastinal B-cell lymphoma) in the third line or later setting. This trial demonstrated an 82% objective response rate (ORR) with a 54% CR rate.[8] The median duration of response was 11.1 months, and the median overall survival (OS) was not reached after 27.1 months of follow-up.[19] Similar results were noted in consortium studies of patients treated in the SOC setting.[20]

Following the success of ZUMA-1, axi-cel was tested versus SOC HCT in the second-line setting in the ZUMA-7 trial.[9] In this trial, 180 patients were randomized to second-line CAR T-cell therapy versus 179 patients randomized to HCT. At a median of 24.9 months, the event free survival (EFS) was 8.3 months in the axi-cel arm and only 2 months in the SOC arm. Subsequent follow up also demonstrated an OS

Table 1
Overview of pivotal chimeric antigen receptor T-cell trials in large B-cell lymphoma

Product	Trial	Disease	Randomization	Bridging Therapy Allowed	Primary Endpoint	Objective Response Rate	Complete Response Rate
Axi-cel	ZUMA-1	3rd line LBCL	Single arm	No	Response rate	82%	54%
Liso-cel	TRANSCEND	3rd line LBCL	Single arm	Yes	Response rate	73%	53%
Tisa-cel	JULIET	3rd line LBCL	Single arm	Yes	Response rate	52%	40%
Axi-cel	ZUMA-7	2nd line LBCL vs SOC	1:1, open label	No	Event free survival (met)	83%	65%
Liso-cel	TRANSFORM	2nd line LBCL vs SOC	1:1, open label	Yes	Event free survival (met)	86%	66%
Tisa-cel	BELINDA	2nd line LBCL vs SOC	1:1, open label	Yes	Event free survival (not met)	46%	28%
Axi-cel	ZUMA-12	1st line high risk LBCL	Single arm vs historic control	Yes	Efficacy	89%	78%

CAR T-cell therapy has high response rates in relapsed and refractory LBCL.

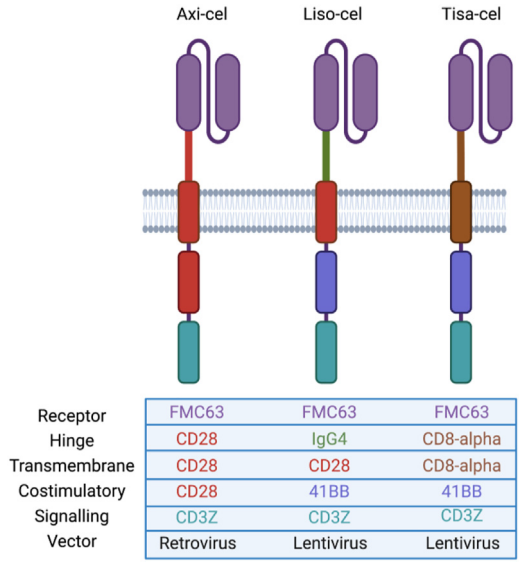

Fig. 1. Vector design of axi-cel, liso-cel, and tisa-cel, the 3 primary vectors used in LBCL. Axi-cel is a retroviral-based vector that relies on CD28 costimulation which liso-cel and tisa-cel utilize lentiviral vectors with 41BB costimulation.

difference favoring axi-cel (OS not reached in axi-cel vs 31.1 months in SOC).[21] Based on the success of the ZUMA-7 trial, axi-cel was approved on April 1, 2022 for second-line treatment of LCBL in patients who are refractory to first line treatment or who relapse before 12 months.

Finally, in the recent ZUMA-12 trial axi-cel was tested as a first-line treatment[22] for high-risk LBCL. In this phase 2, single-arm study patients with high-risk LBCL defined as high grade B-cell lymphoma (HGBCL) or LBCL with international prognostic index (IPI) score ≥ 3, were treated with axi-cel as part of risk adapted therapy in the first line. Patients with Deauville positive (Deauville 4–5) after 2 cycles of chemoimmunotherapy with anti-CD20 antibody and an anthracycline were recruited and the primary endpoint was CR rate (as determined by study investigators). The goal CR rate was 60% based on historic data from the Groupe d'Etude des Lymphomes de l'Adulte (GELA) study[23] and CALGB50303.[24] The result of the study was an impressive 78% CR rate which was substantially improved over historic controls. Though this study offers an excellent framework for considering CAR T-cell therapy in the first line, there is currently not approval for CAR-T cells in first-line LBCL.

Liso-cel

Liso-cel was initially approved for third line and beyond relapsed refractory LBCL on February 5, 2021 following results of the phase 2 TRANSCEND study.[10] This study demonstrated similar results to the ZUMA-1 study with an ORR of 73% and a CR rate of 53% in 256 patients evaluable in the efficacy set. The TRANSCEND study was followed by the phase 3 TRANSFORM study which, similar to ZUMA-7, randomized patients to receive either the CAR T-cell therapy or HCT in the second-line setting.[11] When comparing 92 patients treated with liso-cel with 92 patients receiving SOC, the EFS was significantly improved in the liso-cel group at 10.1 months versus 2.3 months in the HCT arm. There was no OS benefit in the CAR arm of the study

despite an excellent EFS benefit. In this case, the cross-over designed within the study may have confounded OS results. Based on results from the TRANSFORM study, liso-cel was approved by the FDA for second-line treatment of relapsed and refractory LBCL on June 24, 2022.

Tisa-cel

Tisa-cel was similarly approved on May 1, 2018 for the treatment of third line and beyond relapsed and refractory LBCL after the phase 2 JULIET study.[12] In this study, 93 patients were evaluated and 52% had ORR with 40% obtaining a CR. The 12-month relapse free survival was 65%. Similar to axi-cel and liso-cel, tisa-cel was also then compared to SOC HCT in the second line 1:1 randomized phase 3 BELINDA study.[13] In this study, 162 patients were randomized to the CAR group and 160 patients were randomized to the SOC group. There were no differences in median EFS which was 3 months in both groups.

The cause of the failure of the BELINDA study is unclear. Multiple factors likely played a role including (1) imbalance between groups as the CAR arm of the BELINDA had significantly more patients with HGBCL and higher IPI scores, (2) delays in care with a median of 52 days from apheresis to infusion compared to a median of 13 days in ZUMA-7 and 26 days in TRANSFORM, and (3) possibly the construct itself that may have less transactivation than other constructs.

The final possible cause of a weaker overall construct was recently supported in propensity matched study of 809 patients treated in the third line with SOC comparing tisa-cel with axi-cel.[25] In this study, patients were 1:1 matched and the axi-cel group demonstrated a best ORR/CR rate of 80% and 60% versus 66% and 42% in the tisa-cel group with 1-year progression free survival (PFS) and OS of 46.6% and 63.5% in the axi-cel group versus 33.2% and 48.8% in the tisa-cel group. All these differences were significant in the study potentially indicating improved outcomes in the axi-cel group when comparing constructs.

Whatever the cause of failure to meet the BELINDA trial endpoints, tisa-cel was not approved in the second line for LBCL which limits its clinical utility in aggressive lymphoma relative to axi-cel and liso-cel. The same SOC study[25] comparing axi-cel versus tisa-cel did demonstrate greater cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS), including high grade (grade $\geq$ 3) ICANS in the axi-cel group which possibly leaves open a role for tisa-cel in the third line for frail patients.

Bridging therapy

There is no clear consensus on the impact of bridging therapy or the best choice of bridging therapy prior to CAR T-cell therapy. In the original ZUMA trials patients requiring bridging therapy were excluded (see **Table 1**). The main goal of bridging is to temporally control tumor progression and preferably reduce tumor burden prior to CAR T-cell therapy. Such bridging could also provide additional time for CAR T-cell manufacturing, improve CAR-mediated responses, or provide for CAR T-cell eligibility by improving performance status.

Common forms of bridging therapy include chemotherapy, corticosteroids, targeted therapy such as ibrutinib or lenalidomide, and radiation.[20,26] More than 50% of patients reported in both trials and SOC studies received bridging therapy.[10,20,26,27] In general patients receiving bridging therapy have inferior outcomes[20,26,28] but this may vary by bridging therapy type with patients receiving systemic therapy bridging potentially having worse outcome, whereas those receiving radiation therapy bridging having similar or improved outcomes.[26] Given that patients requiring bridging therapy

are likely to have a higher overall disease burden prior to CAR, any notable adverse outcomes could be attributable to the difference in patient population rather than the bridging therapy itself. Because of these limitations in the retrospective setting, it is currently difficult to clearly establish any positive or negative overall impact of bridging therapy. Certainly, if a patient requires bridging therapy to maintain disease control while awaiting product, then it is appropriate to treat. Rapid referral to CAR T-cell centers may help abrogate the need for bridging therapy.

There is no standard bridging therapy regimen. Bendamustine likely should not be provided to patients prior to apheresis due to potential toxicity to the T-cell repertoire[29,30] which has led to our avoidance as a bridging therapy. Radiation therapy does offer good disease control with reduced systemic toxicity[31] but is only appropriate for localized disease. Steroid only bridging is frequently reported[20,26,27] but may not sufficient for patients with more rapidly progressive disease. Steroid-only bridging provides a reasonable short-term option that is unlikely to cause severe toxicity.

CD19 antibody–drug conjugate therapy such as loncastuximab and tafasitamab has not demonstrated subsequent loss of CD19 surface antigen or reduced response to subsequent CAR T-cell therapy in limited studies.[32,33] This is presumably due to the well described "bystander effect" associated with antibody–drug conjugates.[34] Despite this preliminary data, the number of patients in these reports is small and we do typically avoid these agents as a bridge to CAR due to CD19 co-targeting. The use of CD20 targeting bispecific antibodies[35–40] as a bridge to CAR is a novel possibility. However, these agents may represent a separate mechanism for long-term disease control making their sequencing in regard to CAR T-cell therapy unclear. Further, these therapies enjoy a rather long half-life similar to native antibodies and the impact of residual bispecific antibody on CAR function after infusion is unknown.

Ultimately if more aggressive systemic therapy is necessary, our practice is typically to use polatuzumab vedotin and rituximab (R-pola) which provides high ORRs with minimal toxicity.[41] We try to provide bridging after apheresis to minimize potential impact on T-cell fitness. Other standard salvage regimens such as rituximab with gemcitabine and oxaliplatin (R-GemOx) or rituximab with ifosphamide, carboplatin, and etoposide (R-ICE) are also options. Importantly, one goal of bridging therapy is to minimize systemic toxicity from the treatment itself so that the patient has sufficient performance status for CAR T-cell infusion. The clinical impact of bridging therapy is an area in clear need of additional research to improve outcomes and standardize care.

Section II–Factors Impacting Chimeric Antigen Receptor T-Cell Efficacy in Large B-cell Lymphoma

There is limited data suggesting which factors limit efficacy after CAR T-cell treatment in aggressive lymphoma. Risk factors can be differentiated into patient-specific factors, tumor-specific factors, and CAR-specific factors (**Fig. 2**).

Chimeric antigen receptor specific determinants of efficacy

The major CAR specific determinant of function is the CAR T-cell vector itself which is described in detail above. Study of the CAR-T cell is a complex process that requires correlative analysis between the CAR-T cell and requisite patient data. Single-cell RNA (scRNA) study of CAR T-cell product has indicated that presence of CD8 T cells expressing memory signatures had improved outcomes, whereas T-cell senescence signals in the product were associated with inferior outcomes.[42] In a recently published companion study, the presence of post-infusion CAR T-regulatory cells was

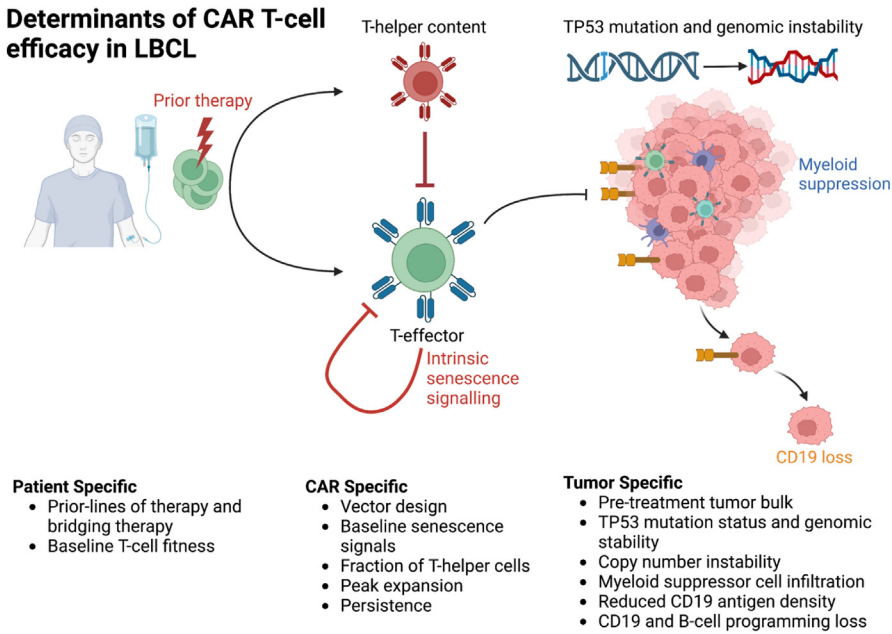

Fig. 2. Patient-specific, CAR-specific, and tumor-specific determinants of CAR T-cell efficacy described in LBCL. CAR T-cells are safe in many patient populations and there are few patient-specific determinants that are detrimental to CAR treatment. CAR-specific determinants have centered on the vector design itself and the ability of the CAR to expand and persist in some studies. Tumor-specific determinants of CAR T-cell efficacy are largely tumor bulk and the ability of the tumor to lose CD19 expression. Tumors with TP53 mutation and unstable genomes may also have worse outcomes. Traditional factors associated with poor outcomes such as HGBCL have not demonstrated worse outcomes in CAR T-cell therapy.

associated with worse outcomes possibly due to suppression of effector CAR T-cell populations.[43,44] Currently, there is no clearly dominant CAR T-cell population but identification of an "ideal" CAR-T cell may improve product development in the future.

One major focus of study within each vector is expansion of the CAR-T cell as an indirect measure of CAR T-cell fitness. CAR T-cell expansion occurs logarithmically after infusion and typically peaks between D7 and D14. CAR19 constructs with 41BB costimulatory molecules expand more slowly than those with CD28. So far there has not been clearly discerned differences in CAR T-cell expansion between tumor types, though additional persistence at later timepoints is notable in brexu-cel treatment of MCL in the ZUMA-2 trial,[45] and there appeared to be slightly higher peak expansion in marginal zone lymphoma relative to follicular lymphoma in the ZUMA-5 trial.[46]

CAR19 expansion is associated with limited impact on efficacy. There were greater CAR-positive cells noted by qPCR in patients with an objective response in the third-line ZUMA-1 study[8] though significant association between expansion and response was not reported in the ZUMA-7 study[9] or the ZUMA-12 study.[22] In independent analysis of third-line CAR T-cell treatment, there was an association between D7 axi-cel cell free DNA and EFS[47] as well as peak expansion and response by qPCR.[48] Similarly, there was increased liso-cel expansion noted in responders in the third-line TRANSCEND study but no relationship between liso-cel expansion and outcomes

was noted in the second-line TRANSFORM study.[10,11] In the third-line JULIET study, tisa-cel had increased persistence in patients with a response, but there was no difference in expansion in the first 28 days between responders and nonresponders.[12] Ultimately, the importance of CAR T-cell expansion and persistence remains indeterminate and may be variable based on line of therapy, method of CAR T-cell measurement, CAR vector, and pre-treatment tumor burden.

Patient-specific determinants of efficacy

In terms of patient-specific factors, CAR T-cell therapy has proven equally effective in patients who would typically have trouble tolerating high-risk therapy. In the ZUMA-1 study elderly (age >65 years) patients treated with CAR T-cell therapy had no difference in CAR T-cell expansion or difference in PFS relative to younger patients with similar toxicity.[49] This finding has been reproduced in single-center studies that also fail to find differences in efficacy in older patient populations.[50]

Another major pretreatment determinant of efficacy is prior therapies. Patients who have rapid tumor progression often require bridging therapy which is associated with worse outcomes and prolonged toxicity.[51] Patients who have lower peripheral T-cell counts at leukapheresis may also have inferior outcomes.[52] In particular, recent use of bendamustine prior to apheresis is associated with inferior outcomes.[29,30]

Finally, there is initial data suggesting that the fecal microbiota may impact CAR efficacy.[53] In this study, pretreatment exposure to antibiotics was associated with worse survival rates and increased toxicity. Subsequent analysis showed that specific gut microbiota composition is associated with improved responses, specifically the clostridial species *Ruminococcus* and *Bacteroides.*

The sum of this data suggests that though CAR T-cell therapy is safe and effective in frail patients, pretreatment T-cell fitness and other pretreatment parameters do play a role in outcomes. Additional study is necessary to understand which patients are at risk for CAR T-cell kinetic failure due to T-cell fitness at apheresis, or which patients who are at lower risk for kinetic failure could benefit from the use of less aggressive T-cell constructs or lymphodepletion regimens.

Tumor-specific determinants of efficacy

Tumor-associated factors are likely the major driver of treatment failure. The most commonly described mechanism of resistance to CD19-directed CAR T-cell therapy is loss of the CD19 cell surface antigen (**Figs 3**).[54–57] Mechanisms of antigen loss include downregulation of the CD19 antigen at the mRNA level and through alternate splicing[58] as well as mutation and copy number alteration at the DNA level.[47] Still loss of CD19 antigen has only been observe in 1/12 to 1/3 of cases in prior studies.[55,56,59] Other potential intratumoral mechanisms of resistance in LCBL include tumor microenvironmental characteristics such as tumor interferon response[60] and direct mutation of genes involved in B-cell identity such as PAX5 and genes involved in immune microenvironment modulation such as TMEM30A. Pretreatment tumor microenvironment enriched for cytokines that foster T-cell development is also associated with higher CR rates.[61]

One of the most frequently cited risk factors for poor outcomes is elevated lactate dehydrogenase (LDH)[20,43,47,62,63] which clearly carries a worse overall prognosis. LDH correlates with tumor burden and in keeping with this observation higher pretreatment ctDNA levels and increased metabolic tumor volume are noted in multiple studies to be major determinants of treatment failure.[47,64,65] High LDH may also have association with interferon signaling and myeloid suppressor cells in the tumor.[60]

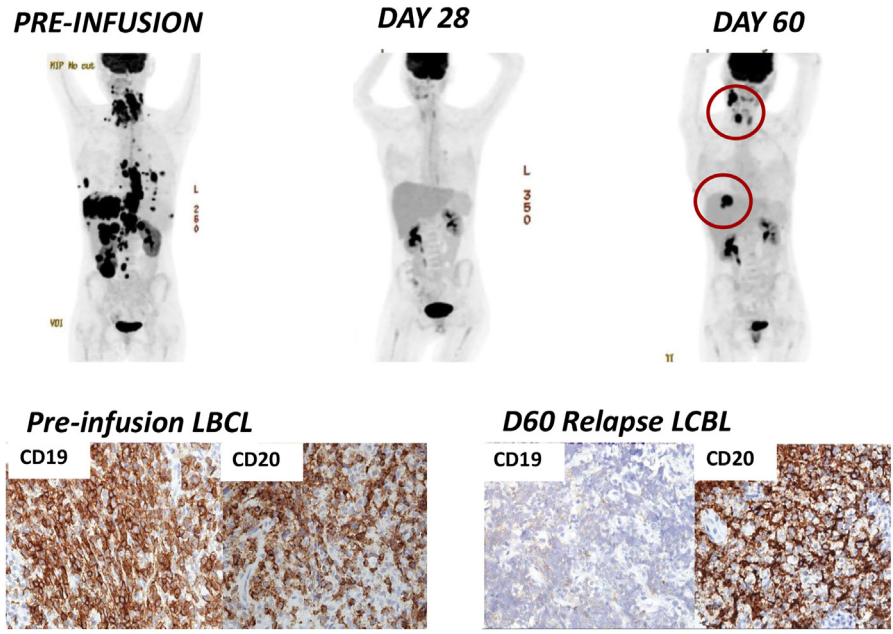

Fig. 3. Loss of CD19 is a common mechanism of LBCL resistance post CAR. The figure demonstrates loss of CD19 in a patient relapsing on D60 post-infusion with CD19 negative disease.

Molecular determinants of poor prognosis include TP53 genomic alterations[66] which may be associated with dysregulation of CAR T-cell-mediated cytotoxicity pathways. Notably, in this study patients who received CAR T-cell therapy with a CD28 costimulatory domain has improved survival relative to those that did not

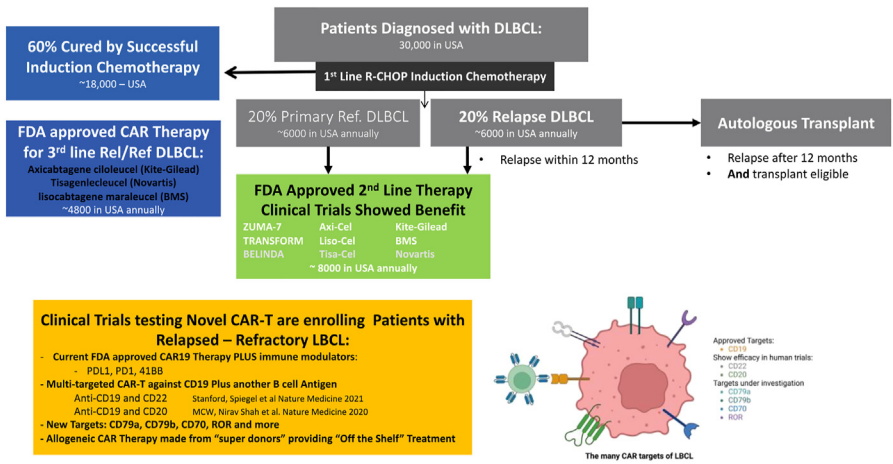

Fig. 4. Flow chart of CAR T-cell therapy in the new era. CAR T-cell therapy is approved in second line treatment of LBCL in patients with refractory disease or relapse before 12 months from the end of therapy. CD19-directed CAR T-cell therapy is the first of many potential cellular targets in LCBL indicating multiple new lines of therapy will become available in the future.

providing weak evidence that therapy could be risk stratified based on TP53 status. Additionally, using low pass whole-genome sequencing the presence of pretreatment copy number alterations were associated with inferior outcomes[67] though it remains unclear how these copy number alterations interact with tumor bulk and other markers of genomic instability such as TP53 mutation status. In a separate study tumor chromothripsis was associated with inferior outcomes as defined by whole genome sequencing.[68] Overall, these studies are strong evidence that genomic complexity is a mechanism of aggressive lymphoma resistance to CAR T-cell therapy.

Finally, there is limited data that antigen density of CD19 on the cell surface may impact CAR efficacy.[56,69] Increased activity along the more efficient immune synapse formed by CD28 co-stimulatory domains may help overcome resistance in tumors with low antigen density.[70] Prospective elucidation of higher risk molecular features such as TP53 mutation and low antigen density could lead to tailored CAR T-cell therapies directed against higher and lower risk to balance efficacy and toxicity.

Traditional factors associated with worse outcomes in LBCL include HGBCL which typically requires a MYC and BCL2 or BCL6 translocation (based on the WHO 2016 classification). More recently, more lymphomas with MYC and BLC6 translocations are not included as higher grade. CAR T-cell therapy has not demonstrated worse outcomes for HGBCL patients (reviewed in Ali and colleagues[71]). These findings are partially skewed by the fact that the comparator LBCL groups are so far by definition higher risk relapsed and refractory disease. Still the remarkable efficacy of CAR T-cell therapy on this traditionally difficult to treat histology may suggest that unique tumor resistance mechanisms underly resistance to CAR T-cell activity versus traditional chemoimmunotherapy.

Another common LBCL pathology that is traditionally difficult to treat is in primary and secondary central nervous system (CNS) lymphoma. Patients with CNS lymphoma so far have been excluded from major CAR T-cell trials. However, CAR-T cells do traffic to the brain and are easily discernable in the cerebral spinal fluid. Recently, a phase 1/2 trial of tisa-cel in primary CNS lymphoma demonstrated CR in 6/12 (50%) of patients with highly refractory primary CNS lymphoma. Of these, 3 had ongoing response at the time of data cutoff. CAR T-cell therapy is also effective in secondary CNS lymphoma with an 85.7% day 28 CR rate noted in one retrospective analysis.[72] Despite these promising results, there remains limited data on the efficacy of CAR T-cell therapy in CNS lymphoma though the available data do suggest that patients with a history of CNS lymphoma should not be excluded from SOC treatment if they also have systemic disease. Dedicated trials are necessary to further elucidate the impact of CNS involvement on efficacy.

Finally, Richter transformation is an additional tumor type with limited treatment options and a poor prognosis. Patients with Richter transformation were excluded from most early CAR T-cell trials excepting 5 transformed chronic lymphocytic leukemia/lymphoma (CLL) patients enrolled in the TRANSCEND study. Response assessment of Richter patients treated with CAR T-cell therapy are nearly absent from the literature. The minimal information available does indicate these tumors can response to CAR19 treatment[73–75] and should not be excluded from receiving CAR T-cell therapy if relapsed or refractory from standard therapy.[76] For Richter patients, we typically use liso-cel because (1) liso-cel is approved for LBCL in the second and third line, (2) transformed CLL was minimally included in the TRANSCEND study, (3) liso-cel has evidence in CLL alone,[77] and (4) the FDA label for liso-cel nonspecifically approves for transformed indolent lymphoma.

In sum, the overall tumor burden, pretreatment tumor characteristics such as TP53 mutation status, and tumor escape mechanisms such as CD19 loss work together to

drive relapse. Preinfusion patient characteristics limiting T-cell fitness may also contribute to kinetic failure of the CAR-T cell. Additional work in modeling which tumors are at highest risk may inform future trials such as use of less toxic CAR19 therapy for lower risk patients or using multiple infusions or CAR T-cell products directed against multiple antigens for higher risk patients. Additional molecular assessments of tumor burden such as ctDNA may help direct risk-adapted infusion strategies.

Section III–Chimeric Antigen Receptor T-Cell Toxicity

The success of CAR-T therapy makes thorough understanding of how the CAR-T cells work within the clinical setting of paramount importance. Despite their promise in treating patients with previously limited therapeutic options, CAR T-cell therapy suffers from novel toxicities such as CRS, ICANS, B-cell aplasia, prolonged cytopenia, and infection risk. This section will focus on known CAR T-cell toxicities.

Cytokine release syndrome and immune effector cell associated neurotoxicity syndrome

CRS and ICANS are the 2 hallmark toxicities of CAR T-cell therapy (**Table 2**). CRS is defined by the presence of fever with or without hypotension or increased oxygen requirement. CRS is typically the first CAR T-cell toxicity that occurs clinically with a median of onset of approximately 3 to 5 days. Initial studies focused on neurologic toxicity rather than the now more commonly used ICANS to define general neurologic impacts caused by CAR-T cells. ICANS itself is intimately associated with increased absolute CAR T-cell expansion in CD19 CAR T-cell vectors.[8,10,43,45] ICANS typically follows development of CRS but is much less common than CRS. The median onset of ICANS is approximately 6 days.

It is difficult to compare rates of CRS and ICANS across CAR T-cell vectors because of lack of head-to-head studies. That said the average rate of CRS in axi-cel constructs is 92% (ZUMA-1, ZUMA-7, ZUMA-12, ZUMA-5[46]) with an average of CRS greater than or equal to grade 3 of 9%. Average neurologic toxicity in the same group is 64% with 23% grade greater than or equal to 3. In the TRANSFORM and TRANSCEND trials an average of 42% of patients treated with liso-cel developed CRS with 2% having grade greater than or equal to 3 CRS; 21% developed neurologic toxicity with 7% developing grade greater than or equal to 3 neurotoxicity. Finally, the

Table 2
Overview of chimeric antigen receptor (CAR) T-cell mediated toxicities in CAR T-cell trials

CAR	Study	Pathology	CRS	CRS ≥3	Neurological	Neurological ≥3	N
Axi-cel	ZUMA-1	LBCL	93%	13%	64%	28%	101
Axi-cel	ZUMA-7	LCBL	92%	6%	60%	21%	170
Axi-cel	ZUMA-12	LBCL	100%	8%	73%	23%	40
Axi-cel	ZUMA-5	FL, MZL	82%	7%	59%	19%	148
Brexu-cel	ZUMA-2	MCL	91%	15%	63%	31%	68
Brexu-cel	ZUMA-3	ALL	89%	24%	60%	25%	55
Liso-cel	TRANSCEND	LBCL	42%	2%	30%	10%	269
Liso-cel	TRANSFORM	LBCL	49%	1%	12%	4%	92
Tisa-cel	JULIET	LBCL	58%	22%	21%	12%	111
Tisa-cel	BELINDA	LBCL	61%	5%	10%	2%	155

The axi-cel vector may have greater toxicity than the liso-cel and tisa-cel vectors based on limited cross-trial comparisons.

average rate of CRS in the JULIET and BELINDA trials was 60% with 14% grade greater than or equal to 3 and the rate of neurologic toxicity was 16% with 7% grade greater than or equal to 3.

Because of these numeric differences in the rate of CAR T-cell toxicity axi-cel is generally considered to have greater rates of severe ICANS which is also backed by propensity matched comparisons.[25] These differences are supported by initial observations suggesting increased toxicity in CD28 constructs,[78] increased cytokine signalling associated with CD28 transactivation in preclinical models,[79] and observed rapid increases in CAR T-cell expansion in CD28 constructs versus 41BB.[80] Consistent with these findings, high blood expansion of CAR T-cells is clearly associated with development of ICANS.[8,10,43]

Cytopenia

Currently, cytopenia after CAR has been defined relative to infusion as early (<30 days after infusion), prolonged (30–90 days after infusion), and late (>90 days after infusion).[81] Lymphodepleting chemotherapy is frequently associated with the development of early grade 3 cytopenias. In the ZUMA-1 trial, neutropenia occurred in 84% of patients with 78% grade greater than or equal to 3, thrombocytopenia occurred in 58% with 38% grade greater than or equal to 3, and anemia occurred in 66% with 43% grade greater than or equal to 3.[82] The TRANSCEND study had similar results of neutropenia in 63% of patients and 60% grade greater than or equal to 3, 31% had thrombocytopenia with 27% grade greater than or equal to 3, and 48% of patients had anemia with 37% grade greater than or equal to 3.[10] Results were similar in the ZUMA-7, ZUMA-12, and TRANSFORM studies. Close monitoring is required in the immediate postinfusion period while lymphodepleting chemotherapy takes effect and until counts have an opportunity to recover.

An unexpected but significant toxicity after CAR T-cell therapy in aggressive lymphoma is persistent cytopenia.[83] Early studies indicate that cytopenias can frequently persist for 1 year or longer postinfusion.[84,85] In the ZUMA-1 extended cohort 17% of patients maintained grade 3 or worse cytopenia 3 months after infusion.[82] Though neutrophils typically recover to normal levels, B-cell aplasia post-CAR, presumably due to on-target but off-tumor activity of the CAR T-cell itself, can persistent for longer periods of time. In CLL CAR T-cell persistence with associated B-cell aplasia has followed for over 10 years.[86] In axi-cel treated patients, CAR-T cells and B-cell aplasia frequently persist for multiple years post-infusion as well.[9,82] The relationship between CAR persistence and persistent cytopenias is unclear, though persistent CAR is likely associated at least with persistent B-cell aplasia. Consequent with these cytopenias, patents are at a high risk for infection after CAR T-cell therapy.[83,85,87–90]

Predictive scoring mechanisms for prolonged cytopenia in LBCL post-CAR are developed,[91] and pre-infusion predictive factors increasing the risk of developing post-CAR prolonged cytopenia include low platelet count, low absolute neutrophil count, low hemoglobin, high C-reactive protein, and high ferritin. These studies suggest patients with increased inflammatory markers and pretreatment cytopenias are at greater risk for additional cytopenia. It is difficult to use this data clinically as CAR T-cells are often the only reasonable line of treatment for patients no matter the ultimate toxicity, but with increased research and new anti-cancer agents these scoring systems may improve toxicity response or therapeutic choice.

In sum, post-CAR cytopenias are a durable consequence of CAR T-cell infusion and are likely multifactorial related to prior treatments, lymphodepleting chemotherapy, and the CAR T-cell itself including the inflammatory impact of initial CAR T-cell expansion and the on-target but off-tumor effect of persistent CAR T-cell targeting of CD19.

These toxicities are difficult to avoid and providers should be considered infectious prophylaxis and close immune surveillance. There are not clear differences in the rates of cytopenias between vectors. A separate article of this review covers post-CAR toxicity management in detail. Treatment of CAR T-cell-related toxicity and toxicity mechanisms is reviewed in detail by Neelapu and colleagues[92] and Siegler and colleagues.[93] Management of post-CAR cytopenias is discussed in Hill and colleagues[94] and Jain and colleagues.[81]

Secondary malignancy

Several recent studies suggest there is increased potential for development therapy related myeloid neoplasms (t-MN) after CAR T-cell therapy.[95,96] The most comprehensive of these studies indicates reduced latency between CAR T-cell treatment and development of t-MN post CAR. An additional study demonstrated that clonal hematopoiesis of indeterminate potential (CHIP) was present in 34% to 48% of patients prior to CAR T-cell therapy.[97,98] A separate study did associate the presence of CHIP mutations prior to infusion with increased severity of ICANS.[99] The presence of CHIP in this context was associated with increased response rates in one study, but none of these studies described differences in long-term outcomes in patients with CHIP mutations prior to infusion. The known prolonged cytopenias associated with CAR T-cell therapy which often recover over time combined with the often-substantial pretreatment chemotherapy received by patients prior to CAR infusion make the causative factor in the development of myeloid malignancies after CAR difficult. Further study into secondary malignancy after CAR T-cell therapy is warranted, but must be balanced by careful discrimination versus other causes of cytopenia in the setting of a patient population that is known to have a high prevalence of CHIP mutations and prolonged cytopenias that are likely not attributable to myeloid neoplasms.

Section IV–Novel Chimeric Antigen Receptor T-Cell Constructs and Bispecific T-Cell Engagers

Novel chimeric antigen receptor T-cell constructs

Despite the remarkable success of autologous CD19-directed therapies in LBCL, the high relapse rate after CD19-directed therapy necessitates additional tumor-directed therapies in up to half of treated patients. Multiple new CAR T-cell constructs are currently in clinical trials. Recently, the first CD19-22-directed bispecific CAR-T cell was published though this therapy unfortunately was met with high rates of CD19 antigen loss and relapse, possibly without substantial CD22-directed activity.[56] Similarly a CD19-20 bispecific CAR demonstrates anti-tumor activity in humans without antigen escape.[100] Promising single targets against CD22 are also in production and have recently been granted accelerated approval based on successful phase 1 trial results.[101] Notably, the development of multiple single target CAR-T cells raises the possibility of tandem[102] or cocktail[103,104] infusions in the future that may abrogate tumor-mediated antigen escape. In initial trials, these therapies have demonstrated response rates up to 90% highlighting the promise of multi-antigen targeting. Despite this promise, larger trials are necessary to more clearly define the safety and efficacy of combining constructs. Finally, multiple additional autologous targets are under investigation. These include CD79ab,[105,106] CD70,[107] and ROR1.[108]

Another important development in the CAR T-cell field is generation of allogeneic CAR T-cell therapy.[109,110] Autologous CAR-T cells are limited by the need for patients to undergo apheresis, have CAR T-cells generated and subsequently shipped, and then undergo infusion. This prevents dissemination of CAR T-cell treatments outside of academic centers with the logistic capacity to handle these complex pathways. The

promise of allogeneic CAR T-cell therapy is effective off-the-shelf agents without the need for patient-specific products. These products promise activity in any patient including those with T cells that may have reduced function after multiple lines of chemotherapy. Despite this promise these agents are limited by host versus graft responses that requires sometimes more intensive immune suppression to overcome as well as multiple infusions.

Bispecific T-cell antibodies

Bispecific T-cell antibodies, though not CAR T-cell therapies, represent a similar mechanism of engaging T cells against B-cell-specific surface antigens. Multiple CD3–CD20 bispecific antibodies have been tested with some success in LBCL.[35–40] The most clinically advanced of these agents in LBCL is glofitamab and epcoritamab which have completed phase 2 trials. In a recent phase 2 study, glofitamab had a 39% CR rate at a 12.6 month follow-up in 154 treated patients with at least 2 prior lines of therapy as a single agent.[36] These results were consistent in 52 patients who had received prior CAR T-cell therapy. Epcoritamab similarly had a high response rate of 63.1% with a 38.9% CR rate in 157 patients with pretreated LBCL.[40] Results again were not different in the 61 study patients who had prior CAR T-cell therapy. The success of bispecific antibodies in the setting of LBCL as well as other NHLs[111] represents a potential challenge to the dominance of CAR T-cell therapy as the preferred T-cell agent directed against cell-surface antigens. Reflecting the rapid pace of these agents entering clinical practice, epcoritamab was granted accelerated FDA approval on May 19, 2023 for relapsed and refractory LBCL after two or more lines of systemic therapy.

Benefits of bispecific antibodies include ease of construction and treatment relative to CAR-T cells. These therapies are off-the-shelf meaning that they have less requirement for treatment in large academic cell therapy centers. Bispecific therapy with glofitamab does require pretreatment depletion of CD19 with obinutuzumab, but bispecific antibody treatments do not require lymphodepletion leading to substantially lower rates of high grade cytopenia. Glofitamab and epcoritamab require hospitalization for the first cycle, but do not require hospitalization for subsequent infusions. CRS and ICANS are major adverse effects of bispecific antibodies similar to CAR19 therapy, but occur with less frequency and intensity.

Another potential benefit of bispecific therapy is certain breakdown of the monoclonal antibody over time. The typical half-life of a bispecific antibody containing an Fc domain is similar to that of other monoclonal antibody treatments (typically 6–11 days)[112] which would potentially counteract some of the longer term impacts of persistent CAR. This benefit is likely confounded by the possibility of persistent CAR-T cells to act in longer term tumor surveillance, though the importance of this potential feature and the necessary duration of effect remains unclear. Finally, bispecific antibody treatments require multiple infusions over time rather than a single infusion meaning the duration of therapy as well as frequency of clinic visits is substantially increased relative to a single CAR19 infusion. Both therapies are likely to suffer from geographic and racial disparities in access[113] which is an issue of major concern moving forward.

Sequencing of bispecific versus CAR T-cell therapy is undetermined. Theoretically similar mechanisms of anti-tumor function such as epitope spreading[114] should be shared, and thus mechanisms of resistance could overlap. Despite this theoretical limitation so far patients pre-treated with CAR T-cell therapies have not had reduced efficacy when subsequently treated with bispecific antibodies[36,40,111] though the total number of such treated patients is low.

Similar theoretical limitations in potential cross resistance apply when considering bispecific antibodies prior to CAR. An additional concern with CAR sequenced after bispecific antibodies is the potential of exhausting the T-cell population prior to creating the CAR T-cell product. Despite this potential limitation, data on the efficacy of CAR T-cell therapy after a bispecific antibody in LBCL in a preliminary registry study suggest the CAR may remain effective when sequenced after bispecific antibodies.[115] Additionally in B-ALL CD19-directed CAR T-cell therapy did remain effective after pretreatment with the CD19 bispecific T-cell engager (BITE) blinatumomab in patients who initially responded to the BITE.[116] Future research is necessary to assess for these potential interactions. Ultimately, the long-term outcome data will determine the relative place of each therapy in the sequencing of LBCL treatment and both types of therapies will have increasing use in the treatment of lymphoma for the foreseeable future.

Section V–Summary

CAR T-cell therapy targeting CD19 has revolutionized the treatment aggressive lymphomas. This treatment has provided durable responses and likely cures in over 40% of patients. In addition, CAR T-cell therapy use is now extended to adult ALL,[117] multiple myeloma,[119–122] mantle cell lymphoma,[45] follicular lymphoma,[46,118] and marginal zone lymphoma[46] providing broad utility across most B-cell malignancies. Use of axi-cel and liso-cel in the second-line treatment of LBCL is approved following the ZUMA-7 and TRANSFORM studies (**Fig. 4**). CAR-T cells are now actively studied in first-line clinical trials and may soon become front-line therapy in LBCL.

Despite immense clinical promise in treating relapsed and refractory aggressive lymphomas, CAR T-cell therapies have a number of well-documented toxicities. Early toxicities of CRS and ICANS are so-far manageable with algorithmic approaches that involve multi-modal immune suppression. As CAR T-cell therapy is a living therapy there is also a concern for persistent CAR T-cell toxicity resulting in long-term cytopenia and infection. These persistent toxicities will require close monitoring and follow-up of CAR T-cell patients and perhaps novel interventions yet to be determined.

Even with the success of CD19-directed CAR T-cell therapy in LBCL more than half of patients relapse and the complexity and logistics of autologous CAR T-cell therapy is largely restricted to major academic centers. New CAR T-cell therapies with strong efficacy profiles are in development to ensure multiple additional lines of curative therapy are available to patients well after initial CAR T-cell treatment. Continuous development of new constructs, off-the-shelf allogeneic products, and related bispecific immune therapies will extend the curative benefits of cell therapy to most patients with aggressive lymphoma.

CLINICS CARE POINTS

- CAR T-cell therapy with axi-cel and liso-cel is approved for second-line treatment of LBCL in patients who are refractory to front-line chemotherapy, and patients who relapse within 12 months of completing first-line therapy.
- CAR T-cell therapy with axi-cel, liso-cel, and tisa-cel is approved for the third-line treatment LBCL.
- Early CAR T-cell toxicity of CRS and ICANS should be treated promptly with steroids and tocilizumab.

- Prolonged CAR T-cell toxicity includes persistent cytopenia and infection that can last more than a year post-infusion. Long-term monitoring of CAR treated patients is warranted.

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