CAR T-Cell Therapy for Relapsed/Refractory Non-Hodgkin's Lymphoma: A Comprehensive Review

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Abstract: Non-Hodgkin lymphoma (NHL) is the seventh most common type of malignancy worldwide, with approximately 544,000 cases diagnosed in 2020.[1-3] The vast majority of NHLs are derived from B cells. The more than 80 subtypes of B-cell NHL are categorized according to their typical clinical course: indolent or aggressive.[4] Aggressive B-cell NHLs that are refractory to first-line therapy or that relapse following initial treatment are historically associated with a poor prognosis, despite the use of salvage chemotherapy and autologous stem cell transplant.[5] The advent of chimeric antigen receptor (CAR) T-cell therapy has changed the treatment paradigm for patients who have relapsed/refractory aggressive B-cell NHL, with impressive response rates and the possibility for a durable remission in those whose disease has progressed despite multiple prior treatments.[6-8] This review outlines current indications for CAR T-cell therapy, major toxicities, novel CARs under investigation, and future directions.

Introduction

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of lymphoproliferative disorders that can originate from B cells, T cells, or natural killer cells.[2] An estimated 544,000 cases of NHL were diagnosed worldwide in 2020, the vast majority of which represented different subtypes of B-cell lymphoma.[1] B-cell NHL subtypes are categorized according to the indolent or aggressive nature of their clinical course.[4] Diffuse large B-cell lymphoma (DLBCL) is the prototype for aggressive NHL, accounting for 30% to 40% of all cases. Although most patients will have disease that is cured following first-line chemoimmunotherapy, the disease of approximately 25% or more, depending on its biological characteristics, will be refractory to therapy or will relapse within the first 2 years.[9] Patients with relapsed/refractory (R/R) aggressive B-cell NHLs have a poor prognosis despite second-line chemotherapy and autologous stem cell transplant (ASCT); their estimated 18-month progression-free

survival (PFS) rate is 45% to 50%,[5] and their 5-year overall survival (OS) rate is 53%.[10] The development of CD19-specific chimeric antigen receptor (CAR) T-cell therapy has revolutionized treatment for patients who have R/R aggressive B-cell NHL, with overall response rates (ORRs) ranging from 52% to 82%, 12-month PFS rates of 44% to 65%, 12-month OS rates of 49% to 59%, and overall tolerable toxicity.[6-8] CAR T-cell therapy is now also approved by the US Food and Drug Administration (FDA) for R/R mantle cell lymphoma (MCL), follicular lymphoma (FL), and B-cell acute lymphoblastic leukemia (ALL), and its use is being studied in other R/R indolent lymphomas and in chronic lymphocytic leukemia (CLL).[11-14] This review outlines the current uses of CAR T-cell therapy in R/R B-cell NHLs, common toxicities, and novel CARs/future directions.

CAR T-Cell Structure

CAR T cells are T lymphocytes that are genetically engineered to express an artificial receptor that directs them against a specific antigen.[15] The concept of the CAR T cell was first introduced in 1989 by Gross and colleagues,[16] who created chimeric T-cell receptor genes composed of a constant domain fused to a variable antibody domain. Genomic expression vectors were then constructed containing the rearranged gene segments coding for heavy and light chains of an anti-2,4,6-trinitrophenyl (TNP) antibody. When the researchers transfected the vectors into cytotoxic T cells, they found that the T cells specifically targeted TNP-bearing cells and were constitutively active, without requiring antigen presentation or interaction with the major histocompatibility complex.[16] Over the years, the technology was modified to allow transition from bench to bedside, and the first CAR T-cell therapy was approved by the FDA in 2017 for the treatment of B-cell leukemias and lymphomas.[15]

The current, most common CAR structure is that of a second-generation CAR and comprises an extracellular ligand-binding domain, a spacer domain, a transmembrane domain, and one or more intracellular (cytoplasmic) signaling domains (Figure).[15] The extracellular ligand-binding domain recognizes the tumor antigen. It most commonly consists of a single-chain variable fragment (scFv), although other types of domains, such as nanobodies and various small peptides, have been used.[17] The affinity, avidity, and aggregation of the scFv domain are modulated during the re-engineering process, with the goals of achieving CAR specificity for the target cell and avoiding the destruction of nontumor cells in an "on-target, off-tumor" fashion.[18] The spacer domain creates length between the CAR T cell and the site of ligand binding and allows modulation of the synaptic

cleft distance, or distance between the CAR T cell and the target cell. Modulation makes it possible to regulate signaling more precisely, optimize the signal strength and activation stimulus, and limit the surrounding nonspecific innate immune responses.[17] The transmembrane domain transmits ligand recognition signals to the intracellular domain(s). When a CAR T cell recognizes its target antigen, it is activated via the intracellular signaling domains and gains the ability to destroy targeted tumor cells.[19]

Physiologically, T-cell activation involves multiple costimulatory receptors. In first-generation CARs, a single CD3ζ intracellular signaling domain was employed; this relied mainly on the production of interleukin 2 (IL-2) for T-cell activation, so that the potential for CAR expansion was limited.[19] Second-generation CARs have added a second costimulatory domain to the original CD3ζ domain, typically either CD28 or 4-1BB, so that the T-cell activation process more closely resembles what occurs in vivo. Currently FDA-approved CAR constructs are second-generation CARs. Third-generation CARs contain multiple costimulatory domains, and both CD28 and 4-1BB are often combined with CD3ζ. Fourth-generation CARs contain an additional transduction domain, comprising the nuclear factor of activated T cells (NFAT) transcription factor, to promote the T cell–activating production of IL-12.[17-20] A recently constructed next-generation CAR will add a Janus-associated kinase (JAK)/signal transducer and activator of transcription (STAT) activation domain to stimulate cell proliferation and improve CAR T-cell durability.[21]

Antigen Selection

Selection of the antigen that will serve as a target for the CAR T cell is critical to the efficacy and specificity of CAR T-cell therapy. Ideally, the selected antigen would be continuously expressed on the targeted tumor cells and minimally expressed on normal cells. In the case of B-cell malignancies, the B-cell markers CD19, CD20, and CD22 are the most frequently used antigens. Because these markers are also expressed on normal B cells, CAR T-cell therapy directed to these antigens will also partially eliminate normal B cells. An alternative antigen with greater specificity is the B-cell maturation antigen (BCMA), which is classically expressed by malignant B cells and is not common to all normal B cells. BCMA is under investigation in multiple myeloma and is the target antigen of the recently FDA-approved CAR idecabtagene vicleucel (Abecma, Bristol Myers Squibb). However, this antigen is not entirely specific, as some BCMA is expressed in normal mature B-cell subsets.[20,22] Most commercially available CARs for B-cell malignancies target CD19.[19] In patients with R/R disease following CAR T-cell therapy,
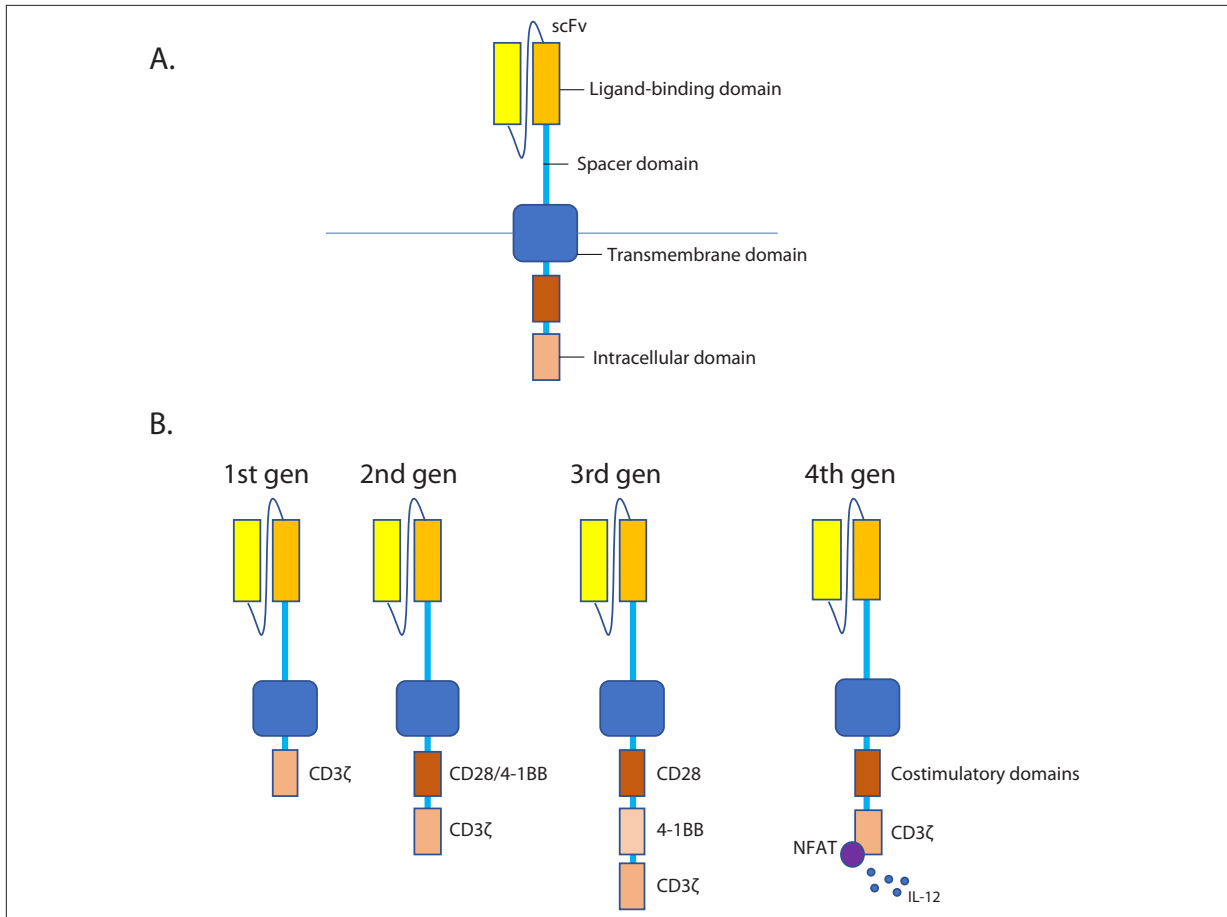
Figure. CAR T-cell structure, including **(A)** components of the basic CAR construct and **(B)** CAR generations.

CAR, chimeric antigen receptor; CD, cluster of differentiation; gen, generation; IL, interleukin; NFAT, nuclear factor of activated T cells; scFv, single-chain variable fragment.

the CD19 surface marker on the malignant cells may disappear, and its disappearance provides a rationale for targeting a different antigen in these situations.[22] Small, early-phase studies have studied CAR T cells that target CD20 or CD22 in the R/R setting, with some documented cases of durable remission.[23-27]

Manufacture and Delivery

The manufacture of CAR T cells may vary between commercially available and experimental settings, although the general steps remain constant; these include apheresis, T-cell selection, T-cell activation, gene transfer, CAR T-cell expansion, and finally, reinfusion into the patient. The process begins with the collection of a patient's peripheral blood mononuclear cells (PBMCs), or unstimulated leukocytes, via leukapheresis.[19,20,28] The PBMCs are transported to the manufacturing site at a regulated temperature (which varies but is generally between 1°C and 10°C).[20]

The T cells are isolated from the other circulating cells, and washing methods and/or density gradients are used to perform size-based cell fractionation; the T cells then are further separated into subsets (CD4, CD8, CD25, CD62L).[28,29] Anti-CD3 antibodies, anti-CD3/anti-CD28 immunomagnetic beads, or artificial antigen-presenting cells (AAPCs) are used to activate the T cells. Finally, CAR constructs are transfected into the activated T cells via viral transfer vectors (retrovirus or lentivirus) to produce genetically engineered T cells that are constitutively active against their target antigen. Various mechanisms are employed to expand the genetically engineered cells and generate therapeutic doses; many of these involve culture mediums or AAPCs, and this step may vary significantly for different CAR constructs.[29] Once manufacturing is complete, the CAR T cells are frozen and delivered to the treatment center for infusion into the patient. The time from apheresis to CAR T cell delivery differs among constructs because of variations in the manufacturing process.

Table 1. Summary of Characteristics of FDA-Approved CAR T-Cell Therapies for B-Cell NHL

CAR T-Cell Product	Clinical Trial	CAR Generation	Target Antigen	Costimulatory Domain	B-Cell NHL Subtypes	Vector
Axicabtagene ciloleucel	ZUMA-1[6]	2	CD19	CD28	DLBCL, HGBCL, PMBCL, tFL, R/R FL	Retrovirus
Tisagenlecleucel	JULIET[7]	2	CD19	4-1BB	DLBCL, tFL	Lentivirus
Lisocabtagene maraleucel	TRANSCEND[8]	2	CD19	4-1BB	DLBCL, FL3B, HGBCL, PMBCL, TL	Retrovirus
Brexucabtagene autoleucel	ZUMA-2[11]	2	CD19	CD28	MCL	Retrovirus

CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; FDA, US Food and Drug Administration; FL, follicular lymphoma; FL3B, follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; PMBCL, primary mediastinal B-cell lymphoma; R/R, relapsed/refractory; tFL, transformed follicular lymphoma; TL, transformed indolent lymphoma.

The manufacturing time is approximately 15 days for axi-cabtagene ciloleucel, also known as axi-cel (Yescarta, Kite), and brexucabtagene autoleucel (Tecartus, Kite), whereas the turnaround time for tisagenlecleucel, also known as tisa-cel (Kymriah, Novartis), and lisocabtagene maraleu-cel, also known as liso-cel (Breyanzi, Juno), is closer to 3 to 4 weeks.[20,28] Before the single infusion of CAR T cells, patients undergo lymphodepleting chemotherapy, typically with fludarabine and cyclophosphamide. This process increases CAR T-cell expansion in vivo through multiple mechanisms, one of which involves the elimination of immunosuppressive elements such as regulatory T cells and homeostatic cytokines.[30]

Importance of the CAR T-Cell Transcriptional Signature

The transcriptional signatures of the cells within CAR T-cell infusion products have been shown to be associated with clinical efficacy. In a study of 24 patients with R/R large B-cell lymphoma treated with CAR T-cell therapy, single-cell RNA sequencing with capture-based cell identification was performed on autologous axi-cel infusion products to identify transcriptomic features associated with efficacy and toxicity. A significant enrichment of memory CD8 T cells within the infusion products was found in the patients with a complete response (CR), whereas a pattern of exhausted CD8 and CD4 T cells was found in the patients with a partial response (PR). In addition, certain transcriptomic features appeared to predict CAR toxicities, such as cytokine release syndrome (CRS) and neurotoxicity.[31] The importance of CAR T-cell subsets was shown in the ZUMA-1 trial, in which a higher number of CCR7+/CD45RA+ CAR T cells was associated with a more durable response to therapy.[32] A separate study analyzed T-cell subsets in 71 patients before they underwent anti-CD19 CAR T-cell therapy and found patterns of signaling that were associated with CAR T-cell persistence.[33] These findings highlight the relevance of the CAR T-cell transcriptional signature to the efficacy and toxicity of the therapy and its likely contribution to the variations in clinical response seen among patients.

Commercially Available CARs

Currently, 5 CAR T-cell therapies are FDA-approved for the treatment of B-cell malignancies. Axi-cel, tisa-cel, and liso-cel are approved for aggressive R/R B-cell lymphomas on the basis of results from the ZUMA-1, JULIET, and TRANSCEND trials, respectively. Axi-cel is also approved for indolent R/R NHL on the basis of ZUMA-5, and tisa-cel is also approved for pediatric acute lymphoblastic leukemia (ALL).[6-8,34-36] Brexucabtagene autoleucel is specifically approved for MCL on the basis of the ZUMA-2 trial,[11] and for adult B-cell ALL on the basis of ZUMA-3.[37] Idecabtagene vicleucel was recently approved for the treatment of multiple myeloma on the basis of results from the KarMMa study.[38] All these agents employ CARs targeting CD19, with the exception of ide-cabtagene vicleucel, which uses a BCMA-directed CAR.[38] The characteristics of each commercially available CAR for B-cell NHL are outlined in Table 1.

CAR T-Cell Therapy in Large B-Cell Lymphoma

Approved Therapies

The ZUMA-1 multicenter phase 2 trial studied the safety and efficacy of axi-cel, the first FDA-approved CAR T-cell therapy for NHL. A total of 111 patients with DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma were included.[6] The JULIET multicenter phase 2 trial led to FDA approval of a second CAR T-cell therapy in R/R DLBCL, tisa-cel. A total of 93 patients with DLBCL or transformed follicular lymphoma were included.[7] Liso-cel became the

third FDA-approved CAR T-cell therapy on the basis of results from the multicenter phase 2 TRANSCEND trial. A total of 344 patients with DLBCL, high-grade B-cell lymphoma (HGBCL), transformed indolent lymphoma (TL), or follicular lymphoma grade 3B (FL3B) were included.[8]

In these phase 2 trials, patients were included only if they had prior immunochemotherapy with a monoclonal antibody to CD20 and an anthracycline-based regimen, and if their disease had progressed after ASCT or they were not candidates for ASCT. All patients received conditioning with a combination of fludarabine and cyclophosphamide, or in some cases bendamustine (JULIET trial). The ORRs were 82%, 52%, and 73% in the ZUMA-1, JULIET, and TRANSCEND trials, respectively. The CR rates were 54%, 40%, and 53%, respectively. Long-term outcomes for these trials reported a significant proportion of durable remissions lasting more than 1 year. In the ZUMA-1 trial, the median duration of response was 11.1 months, and 42% of patients had a continued response at 15 months.[6,35] In the JULIET trial, the 12-month PFS rate was 65% among the patients with a clinical response.[34] Data from the real-world US Lymphoma CAR T Consortium cohort of 298 patients confirmed the outcome results from ZUMA-1.[39] Although no randomized trials have compared CAR T-cell therapy with other salvage third-line therapies, an indirect, retrospective study comparing liso-cel and salvage chemotherapy (TRANSCEND vs SCHOLAR-1) found a significantly higher CR rate (odds ratio [OR], 12.9; 95% CI, 8.0-20.7) and ORR (OR, 7.0; 95% CI, 4.6-10.5) in the CAR T group, along with a significantly lower risk for mortality (hazard ratio [HR], 0.5; 95% CI, 0.4-0.6).[40] Table 2 summarizes the results of major trials.

CAR T-Cell Therapy in the Second-Line Setting

Recently, 3 phase 3 trials were completed that compared CAR T-cell therapy with ASCT in R/R aggressive B-cell NHL: the BELINDA trial with tisa-cel, the TRANSFORM trial with liso-cel, and the ZUMA-7 trial with axi-cel. An event-free survival (EFS) benefit was observed in the CAR T-cell group in both ZUMA-7 and TRANSFORM, whereas the primary endpoint was not met in the BELINDA trial.[41-43] In ZUMA-7, EFS was 8.3 vs 2 months, favoring the group that received second-line CAR T-cell therapy with axi-cel. The CR rate also was higher in the axi-cel group than in the ASCT group (65% vs 32%).[41] In BELINDA, the 2 groups had similar response rates and an EFS of 3 months.[42] Results from TRANSFORM remain preliminary. Differences in trial design may account for some of the variability between BELINDA and the other 2 trials. Importantly, in ZUMA-7, bridging with chemotherapy was not allowed, and

patients with impending organ-compromising disease were ineligible. In BELINDA, bridging chemotherapy was allowed, and impending organ-compromising disease was not an exclusion criterion. The differing results between these trials suggest that the presence of bulky or rapidly progressing disease may be a barrier to successful outcomes of CAR T-cell therapy. The longer manufacturing time for tisa-cel than for axi-cel should also be noted, as it may have resulted in fewer patients receiving their CAR T-cell infusion in BELINDA. ZUMA-7 provides good evidence to suggest that for patients with nonbulky disease who can do well without bridging chemotherapy, second-line CAR T-cell therapy with axi-cel is superior to the standard of care with ASCT. It remains uncertain whether the same holds true for patients with bulky disease and impending organ damage. FDA approval has not yet been granted for CAR T-cell therapy in the second-line setting.[44]

Novel CARs

Several early-phase trials are investigating novel CARs for the treatment of aggressive B-cell NHL. Phase 1 trials for third- and fourth-generation CD19-directed CARs have shown an adequate safety profile.[45-47] The fourth-generation CARs, also called "armored CAR T cells," encode an additional NFAT transcription factor, which increases the production of cytokines exhibiting an antitumor effect.[20] Alternate antigen targets are also under investigation. For example, a CD20-directed CAR has been studied in a phase 1 trial of patients with R/R B-cell NHL whose disease failed to respond to CD19-directed CAR T-cell therapy (N=7). Results showed an ORR of 100% at 7.8 months, with a CR achieved in 71% of patients. The risk for CRS was higher than that reported with CD19-directed CAR therapy; all patients experienced some degree of CRS (85% grade 1-2).[48] Recent data for a CD22-directed CAR also show promising results, with an ORR of 86%, a CR rate of 67%, and median PFS and OS not yet reached at a median follow-up of 7.3 months. Again, the reported rate of CRS was higher than that with CD19-directed CAR; 100% of patients experienced some degree of CRS (95% grade 1-2). Macrophage-activating syndrome, characterized by pancytopenia and diffuse intravascular coagulation, was described in 24% of patients.[27]

Great interest is being shown in the development of dual-target CAR T cells. Preliminary results from the phase 1 AUTO3 trial, which is evaluating CD19/CD22 CAR T-cell therapy followed by programmed death 1 (PD-1) blockade with pembrolizumab (Keytruda, Merck) in 33 patients who have R/R DLBCL or TL, show an ORR of 69% and a CR rate of 52% without severe neurotoxicity or CRS.[49,50] Bispecific CARs targeting both CD19 and CD20 have shown promise in mouse models, and a

phase 2 trial of co-administration of a CD19 and a CD20 CAR in 21 patients with DLBCL resulted in an ORR of 81%, a CR rate of 52%, and a rate of grade 3 or 4 CRS of approximately 37%.[51,52] A tri-specific CAR directed to CD19, CD20, and CD22 is also under investigation in preclinical models.[53]

Monospecific CARs evaluated in preclinical models have targeted CD79b,[54] CXCR5,[55] CD37,[56] or CD38,[57] among others. Allogeneic CARs are also under investigation in phase 1 trials, with the aim of reducing the time required to produce CAR T cells by deriving them from healthy donor T cells, so that they can be immediately available "off the shelf."[58-60] Gene-editing technologies have made it possible to block endogenous T-cell receptor expression on allogeneic CARs to limit the incidence of graft-versus-host disease (GVHD), and CD52 suppression has been used to reduce the likelihood of rejection.[20]

CAR T-Cell Therapy in Mantle Cell Lymphoma

Patients with R/R MCL are recognized as having high-risk disease, with a historically poor prognosis. The ZUMA-2 multicenter phase 2 trial evaluated the safety and efficacy of brexucabtagene autoleucel in 74 patients with MCL who had failed prior treatment with anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and a Bruton tyrosine kinase (BTK) inhibitor. In the primary efficacy analysis, which included 60 of the initial 74 patients, the primary endpoint of ORR was 93%, and a CR was achieved in 67% of the patients. At 12 months, the PFS and OS rates were 61% and 83%, respectively. Grade 3/4 CRS and neurotoxicity occurred in 15% and 31% of patients, respectively, with no fatal adverse events (AEs).[11] These results led to the FDA approval of brexucabtagene autoleucel for R/R MCL, which provides an opportunity for durable remission in patients with an otherwise poor prognosis.

CAR T-Cell Therapy in Indolent Forms of B-Cell Lymphoma

Chronic Lymphocytic Leukemia

Several clinical trials are evaluating the safety and efficacy of CAR T-cell therapy in R/R CLL. These are all small trials, with cohort sizes ranging between 3 and 32 patients.[14,61,62] Most of the trials have studied CD19-directed CARs, and one trial is using a bispecific CD19/CD20-directed CAR.[63] The trials are employing autologous second-generation CARs except for 2 small studies (4 and 5 patients) using allogeneic CARs, one of which is a fourth-generation allogeneic CAR natural killer cell. Among the studies using CD19-directed autologous CAR T-cell therapy, the ORRs range from 44% to 100%. It should be noted that

studies with lower ORRs often did not administer lymphodepleting chemotherapy before CAR T-cell infusion.[14] The phase 1/2 TRANSCEND CLL 004 trial is a major 4-arm study currently evaluating the safety and efficacy of liso-cel in R/R CLL. The trial includes a phase 1 arm of liso-cel monotherapy, a phase 1 arm of liso-cel combined with ibrutinib (Imbruvica, Pharmacyclics), a phase 1 arm of liso-cel combined with venetoclax (Venclexta, AbbVie), and a phase 2 arm of liso-cel monotherapy in patients with R/R CLL. In preliminary results from the phase 1 arm of liso-cel monotherapy, in 23 patients who received the therapy, the ORR was 82% and the CR rate was 45%. In 20 patients evaluable for minimal residual disease, the rates of undetectable minimal residual disease in blood and marrow were 75% and 65%, respectively. A total of 74% of patients experienced CRS (9% grade 3), and 39% experienced neurotoxicity (22% grade 3/4).[64] The phase 2 portion of this trial is ongoing.

It is thought that BTK inhibitors may interact synergistically with CAR T-cell therapy. Ibrutinib is an irreversible inhibitor of BTK but also inhibits inducible T-cell kinase (ITK), thereby enhancing Th1-type immunity and shifting the tumor microenvironment (TME) to a pro-inflammatory environment that favors tumor regression.[65] A phase 1 trial of 16 patients who had R/R CLL evaluated treatment with CD19-directed CAR T-cell therapy in combination with ibrutinib. At the time of T-cell collection and/or CAR T-cell administration, 5 patients were receiving ibrutinib, and it was found that the ex vivo expansion of T cells was significantly greater in the patients on ibrutinib at the time of leukapheresis.[66] Preliminary results from the arm of the TRANSCEND CLL trial receiving CAR T cells plus ibrutinib (n=19) show a 95% ORR and a 47% CR rate in this group. CAR toxicity was similar to that seen in the phase 1 monotherapy arm.[67] In addition, recent evidence suggests that the BCL-2 inhibitor venetoclax enhances the cytotoxic effect of CAR T cells through the upregulation of pro-apoptotic proteins in the TME.[68,69] As mentioned previously, an arm of the phase 1/2 TRANSCEND CLL trial is currently evaluating the safety and efficacy of liso-cel in combination with venetoclax in patients with R/R CLL.

Follicular Lymphoma and Marginal Zone Lymphoma

The largest phase 2 trial evaluating the use of CAR T-cell therapy in R/R indolent FL is the multicenter ZUMA-5 trial, which led to the FDA approval of CAR T-cell therapy with axi-cel in patients with R/R FL.[70] In ZUMA-5, 146 patients with R/R FL or marginal zone lymphoma whose disease had failed to respond to at least 2 prior therapies were enrolled and received axi-cel. With a median follow-up time of 17.5 months, the ORR was 92%, and 76% of patients achieved a CR. The CR rate appeared

Table 2. Summary of Major Trials Evaluating Efficacy of CAR T-Cell Therapy in Lymphoma

Study	N	Agent(s)	CAR Target	Histology	Phase	Median No. of Prior Therapies	Median Follow-up, mo	ORR, %	CR Rate, %	Median PFS, mo	Median OS, mo
ZUMA-1[6]	111	Axi-cel	CD19	DLBCL, PMBCL, tFL	2	3	15.4	82	54	5.8	NR
JULIET[34,90]	93	Tisa-cel	CD19	DLBCL, tFL	2	3	28.6	52	40	2.9[a]	12
TRANSCEND[8]	344	Liso-cel	CD19	DLBCL, HGBCL, TL, FL3B	2	3	18.8	73	53	6.8	21.1
AUTO3[50]	29	CAR + pembro	CD19/CD22	DLBCL, TL	1	3	3	69	52	Not reported	Not reported
ZUMA-2[11]	74	KTE-X19	CD19	MCL	2	3	12.3	93	67	NR	NR
TRANSCEND CLL[64]	23	Liso-cel	CD19	CLL	1/2	4	Not reported	82	45	Not reported	Not reported
TRANSCEND CLL[67]	19	Liso-cel + ibrutinib	CD19	CLL	1	4	Not reported	95	47	Not reported	Not reported
ZUMA-5[71]	146	Axi-cel	CD19	FL, MZL	2	3	17.5	92	76	NR	NR
ELARA[73]	98	Tisa-cel	CD19	FL	2	4	10.6	86	66	NR	NR

[a]In reported long-term clinical outcomes, median follow-up was 40.3 months.

Axi-cel, axicabtagene ciloleucel; CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; FL3B, follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; KTE-X19, brexucabtagene autoleucel; liso-cel, lisocabtagene maraleucel; MCL, mantle cell lymphoma; mo, months; MZL, marginal zone lymphoma; N, number of patients included in the analysis; NR, not reached; ORR, overall response rate; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphoma; tFL, transformed follicular lymphoma; tisa-cel, tisagenlecleucel; TL, transformed indolent lymphoma.

higher in the patients with FL (80%) than in those with marginal zone lymphoma (60%). At the time of data cutoff, 62% of all patients had an ongoing response, and the median duration of response, PFS, and OS were not reached. A total of 7% and 19% of patients experienced grade 3 or higher CRS and neurotoxicity, respectively.[71,72]

The second largest trial to date of CAR T-cell therapy in R/R indolent NHL is the phase 2 ELARA trial, which evaluated the safety and efficacy of tisa-cel in 98 patients with R/R FL (grades 1-3A) after 2 or more lines of therapy or failure of ASCT. A total of 86% of patients achieved an objective response, and 66% achieved a CR. The PFS rate at 6 months was 76%, and of the patients who had achieved a CR, 90% were still in clinical remission at 6 months. Any-grade CRS occurred in 49% of patients, and no cases were grade 3 or higher. In addition, 9% of patients experienced any-grade neurotoxicity, which was grade 4 in 1 patient. A total of 15% of patients required tocilizumab (Actemra, Genentech) for CRS, and 3% required corticosteroids.[73,74] We await the final results from these 2 trials upon study completion.

Overcoming Resistance to CAR T-Cell Therapy

Although the exact mechanisms of tumor escape from CAR T-cell therapy remain unknown, several are hypothesized to be implicated in the acquisition of therapy resistance. Loss of CD19 has been well described and is the rationale for the development of novel bispecific CARs.[75-77] Various other T cell–specific factors, including CAR T cells with inadequate central memory, pre-manufacture T-cell dysfunction owing to disease or prior therapy, inadequate cytokine profile, paucity of CD4+ CAR T cells, and insufficient CAR T-cell expansion, have also been hypothesized as potential mechanisms of resistance. These hypothetical mechanisms have inspired a search for "off-the-shelf" allogeneic or "universal" CARs and are the rationale for immunomodulation strategies such as the use of ibrutinib for ITK inhibition at the time of T-cell collection.[76] An additional proposed mechanism of CAR T-cell failure involves cellular epigenetic modifications within the TME that result in decreased immune

surveillance and so promote tumor growth.[78,79] Genetic analysis has indicated that the TME following axi-cel therapy is characterized by the upregulation of immune checkpoints (programmed death ligand 1 [PD-L1], lymphocyte activation gene 3 [LAG3], and cytotoxic T lymphocyte–associated antigen 4 [CTLA-4]), suggesting that these could be contributing to the downregulation of immune surveillance and that checkpoint blockade could augment immune function following CAR T-cell therapy.[80] There is evidence that immune checkpoint blockade following ASCT improves PFS.[81] In interim data from the ZUMA-6 phase 1 trial, the PD-L1 monoclonal antibody atezolizumab (Tecentriq, Genentech), in combination with CAR T-cell therapy, resulted in an ORR of 92% among patients with R/R DLBCL.[82,83] Results from the phase 1 AUTO3 trial of CAR T-cell therapy in combination with pembrolizumab in patients with R/R DLBCL showed a CR rate of 52%, with only one relapse among the 15 patients in CR at median follow up of 3 months (1-24 months).[49,50] Determining the optimal way to conserve immune surveillance function following CAR T-cell therapy will be important in ensuring effective and durable results.

Toxic Effects of CAR T-Cell Therapy

CAR T-cell toxicity depends on various factors, including CAR manufacturing (vector, costimulatory domain), dosing, disease type/severity, and preconditioning regimen.[22] For example, the incidence of toxicity appears to be higher with CARs utilizing a CD28 costimulation domain than in those containing a 4-1BB domain, possibly because CD28 results in a faster expansion of CAR T cells.[20,84] In pivotal phase 2 studies of CD19-directed CAR T-cell therapy, the rate of grade 3 or higher AEs is typically higher than 90%, although the vast majority of high-grade toxicities are reversible hematologic side effects such as neutropenia. CRS, neurotoxicity, hypotension, acute renal failure, and hypoxia are other commonly reported AEs.[6-8] A meta-analysis conducted by the World Health Organization that included 19 trials and 890 patients treated with axi-cel or tisa-cel found a low rate of fatal toxic events; treatment-related death occurred in 5.4% of patients. Infection was the most common cause of death. The rates of neurotoxicity and CRS were higher with axi-cel than with tisa-cel (60% vs 31% and 61% vs 47%, respectively; $P<.05$).[85] CRS is characterized by fever, which can be high-grade, can persist for several days, and in severe cases can be associated with other features of a systemic inflammatory response, including hypotension, hypoxia, and organ dysfunction.[86] It is imperative that CRS be detected early and treated as appropriate with tocilizumab, an anti–IL-6 receptor, with or without the addition of systemic corticosteroids.[87] Neurotoxicity, also referred to as immune effector cell–associated neurotoxicity syndrome (ICANS), is another AE frequently seen in CAR T-cell therapy. Classic initial findings in ICANS include aphasia and tremor, and symptoms may progress to global aphasia, seizures, obtundation, and in the most severe form, coma. ICANS typically resolves within 1 week of treatment with systemic corticosteroids, although in some cases, it may be fatal.

Treating the Older Patient

Results from the ZUMA-1 trial outlined outcomes in 27 patients who were 65 years old and older (range, 65-76 years). CAR T-cell expansion in vivo in the older patients was found to be similar to that in patients younger than 65 years. Efficacy outcomes were also found to be similar in the 2 age groups; the ORR was 92% for patients 65 years and older and 81% for patients younger than 65 years, with a higher CR rate in the older population (75% vs 53%). The median duration of response (12 vs 8.1 months) also favored the older cohort. Approximately 50% of patients in both age groups were alive at 24 months.[88] In the pre-CAR T era, patients older than 65 years typically had an ORR of only 19% and a 2-year OS rate of 19%, according to reported results from the SCHOLAR-1 study.[88,89] Importantly, rates of AEs were similar in the 2 age cohorts. Patients aged 65 years and older had a slightly higher rate of encephalopathy (30% vs 21%), lymphopenia (30% vs 17%), agitation (11%), and delirium (11%), but the rates of other cytopenias, grade 3 or higher CRS, and infection were similar. The rates of grade 5 AEs did not differ (4% in each group).[88] CAR T-cell therapy can be considered and appears to be safe in older patients, although improved methods to stratify risk in the elderly are needed.

Conclusion

CAR T-cell therapy has provided a new opportunity to achieve durable remission in patients with highly refractory B-cell NHL and a poor prognosis. It may offer durable remission for patients with R/R indolent NHLs that are otherwise considered "incurable." The future for CAR therapy is bright and likely will involve the development of "off-the-shelf" allogeneic CARs that will be more readily available for sick patients, CAR-modified natural killer cells, and CARs directed at novel antigens and bispecific antigens with increased specificity for malignant cells and decreased off-target effects, in addition to modulation of the TME in conjunction with CAR T-cell therapy to overcome resistance.

Disclosures

Drs St-Pierre and Gordon have no disclosures.

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