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A Deep Insight Into CAR-T Cell Therapy in Non-Hodgkin Lymphoma: Application, Opportunities, and Future Directions

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Non-Hodgkin's lymphoma (NHL) is a cancer that starts in the lymphatic system. In NHL, the important part of the immune system, a type of white blood cells called lymphocytes become cancerous. NHL subtypes include marginal zone lymphoma, small lymphocytic lymphoma, follicular lymphoma (FL), and lymphoplasmacytic lymphoma. The disease can emerge in either aggressive or indolent form. 5-year survival duration after diagnosis is poor among patients with aggressive/relapsing form of NHL. Therefore, it is necessary to understand the molecular mechanisms of pathogenesis involved in NHL establishment and progression. In the next step, we can develop innovative therapies for NHL based on our knowledge in signaling pathways, surface antigens, and tumor milieu of NHL. In the recent few decades, several treatment solutions of NHL mainly based on targeted/directed therapies have been evaluated. These approaches include B-cell receptor (BCR) signaling inhibitors, immunomodulatory agents, monoclonal antibodies (mAbs), epigenetic modulators, Bcl-2 inhibitors, checkpoint inhibitors, and T-cell therapy. In recent years, methods based on T cell immunotherapy have been considered as a novel promising anti-cancer strategy in the treatment of various types of cancers, and particularly in blood cancers. These methods could significantly increase the capacity of the immune system to induce durable anti-cancer responses in patients with chemotherapy-resistant lymphoma. One of the promising therapy methods involved in

the triumph of immunotherapy is the chimeric antigen receptor (CAR) T cells with dramatically improved killing activity against tumor cells. The CAR-T cell-based anti-cancer therapy targeting a pan–B-cell marker, CD19 is recently approved by the US Food and Drug Administration (FDA) for the treatment of chemotherapy-resistant B-cell NHL. In this review, we will discuss the structure, molecular mechanisms, results of clinical trials, and the toxicity of CAR-T cell-based therapies. Also, we will criticize the clinical aspects, the treatment considerations, and the challenges and possible drawbacks of the application of CAR-T cells in the treatment of NHL.

Keywords: chimeric antigen receptor, non-Hodgkin's lymphoma, CD-19, target therapy, CAR T cells

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is the seventh common malignancy in the United States, mostly regarded as a malignancy with good prognoses and 5-year survival of approximately 70%. The most common types of NHL are diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL) (1). The typical therapeutic methods for lymphoma include radiation therapy, chemotherapy, immunotherapy, and so on. However, in approximately 20-30% of all patients with lymphoma, especially those with DLBCL (the most common invasive subtype), resistance to these treatment lines will develop (2, 3). The hematopoietic stem cell transplant (HSCT) is one of the standard care in patients with relapsed and refractory disease who have survived chemotherapy (4). However, due to underlying comorbidities and chemo-resistance disease, about 40% of patients may not be qualified for HSCT. Even about half of the patients treated with HSCT tend to relapse (5). In other words, the outcome of this treatment in patients with relapsed/refractory (R/R) disease, especially in DLBCL patients, is not entirely satisfactory. Accordingly, the presence of new therapies that improve therapeutic outcomes in patients with recurrent or refractory lymphoma is needed (6). Recently, T-cell immunotherapies with the CARs have been widely applied and have shown notable consequences in the treatment of B-cell malignancies (7). Unlike normal T cells, CAR-T cells detect unprocessed antigens. In other words, they recognize the tumor cells independently of the human leukocyte antigen (HLA) system and then eradicates them. This feature overcomes the main mechanisms of tumor escape such as defective antigen processing and decreased expression of class I HLA molecules, which prevents the recognition of HLA-restricted T cells (8, 9). The genetic sequence of the CAR molecule is transferred to T cells after loading into viral or non-viral vectors and then used to target tumor cells (10). The importance of this technology has recently been fully understood following the dramatic effect of CD19-specific CAR-T cells against the treatment-resistant B cell malignancies illustrated in primary-phase clinical trials. CD19-

specific CAR-T cells have been widely used to treat B-cell lymphoma since most B-cell NHLs also highly express the CD19 marker. However, the clinical effect of anti-CD19 CAR-T cells in patients with ALL seems more significant than in patients with lymphoma. In many patients with lymphoma in whom standard care approaches have been ineffective, utilization of CARs has yielded significant responses (6). In general, unlike B-cell lymphomas, peripheral T-cell lymphomas are composed of a heterogeneous set of diseases with a poor prognosis (11). At present, due to limited antigen availability, the treatment of T cell lymphomas is very challenging and there are few T cell therapies against the antigen of T cell lymphoma (12, 13). However, recurrent relapses and resistance to the therapeutic methods lead to failure to achieve treatment in all patients (13). This study aimed to evaluate CAR-T cell products in NHL patients and to describe the unique aspects of their use for the treatment of these patients.

CURRENT IMMUNOTHERAPEUTIC APPROACHES FOR NHL's

The identification of different oncogenic signaling pathways is considered an attractive therapeutic mark in B cell malignancies. Disorder of the BCR pathway is a common feature in the pathogenesis of B-NHL. Besides, targeting BCR pathway enzymes like phosphoinositol-3 kinase (PI3K), spleen tyrosine kinase (Syk) and Bruton's tyrosine kinase (Btk) has been largely successful in treating B-NHL subtypes. Also, inhibition of the microenvironment using immunomodulatory agents and checkpoint inhibitors, and targeting the anti-apoptotic protein of B-cell lymphoma 2 (Bcl-2), can be other attractive therapies (14) (**Table 1**).

Monoclonal Antibodies (mAbs)

One of the most prosperous therapeutic strategies for the treatment of NHL is utilization of mAbs. The emergence of Rituximab as an anti-CD20 antibody had a significant impact on the treatment of this group of diseases. Despite the successes, how to optimize the use, the optimal duration of treatment, and the best times to administer mAbs, especially Rituximab in the NHL have not yet been determined. It is also necessary to identify the mechanisms that develop resistance to Rituximab to increase the effectiveness of this and other similar drugs.

Abbreviations: CAR, chimeric antigen receptor; GvHD, graft-versus-host disease; NK cells, Natural killer cells; NHL, non-Hodgkin lymphomas; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; ALL, lymphoblastic leukemia; CRS, cytokine release syndrome; RCC, renal cell carcinoma.

TABLE 1 | Immunotherapeutic approaches for B-Cell Non-Hodgkin's lymphomas.

Class	Agent	Target	Histologic subtypes
Monoclonal antibodies	Rituximab	CD20	FL, DLBCL, and MCL
	Epratuzumab	CD22	FL, DLBCL, and
	Galiximab	CD80	B-cell lymphoma
	Tafasitamab	CD19	MCL, FL, and DLBCL
	Otlertuzumab	CD37	NHL and CLL
	MEDI-551	CD19	FL and DLBCL
Antibody drug conjugates	Polatuzumab Vedotin	CD79b	DLBCL
	Brentuximab Vedotin	CD30	DLBCL
	Pinatuzumab Vedotin	CD22	DLBCL and FL
	Vorsetuzumab Mafodotin	CD70	CD70-positive NHL, and metastatic renal cell carcinoma
	Inotuzumab Ozogamicin	CD22	NHL, HCL, CLL, and B-cell ALL
	Coltuximab Ravtansine	CD19	DLBCL
	IMGN529	CD37	B-NHL
Btk inhibitors	Ibrutinib	Btk	Marginal zone lymphoma, MCL, WM, and CLL
	Acalabrutinib	Btk	Mantle cell lymphoma and CLL
PI3K inhibitors	Copanlisib	PI3Kα/PI3Kδ	B-cell lymphomas, FL, and CLL
	Duvelisib	PI3K	FL and CLL/SLL
	Idelalisib	PI3Kδ	B-NHL, FL, and SLL
Syk inhibitors	Entospletinib	Syk	MCL, DLBCL, CLL, and AML
	Fostamatinib	Syk	Lymphoma, autoimmune thrombocytopenia, rheumatoid arthritis, IgA nephropathy, and autoimmune hemolytic anemia
Bcl-2 inhibitors	Navitoclax	Bcl-xL, Bcl-2, Bcl-w, and Mcl-1/A1	NHL, ALL, and CLL
	Venetoclax	Bcl-2	NHL (MCL, FL, and DLBCL)
Checkpoint inhibitors	Durvalumab	PD-L1	Lymphoma
	Nivolumab	PD-1	FL
	Pembrolizumab	PD-1-PD-L1/PD-L2	PMBCL
	Pidilizumab	PD-1	DLBCL

Btk, Bruton's tyrosine kinase; PI3K, phosphatidyl-inositol-3-kinase; Syk, spleen tyrosine kinase, Bcl-2, B-cell lymphoma; NHL, Non-Hodgkin's lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; PMBCL, mediastinal B cell lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; HCL, hairy cell leukemia; WM, Waldenstrom's macroglobulinemia; AML, acute myeloid leukemia.

Rituximab

Rituximab [Rituxan], a chimeric anti-CD20 mAb, was the early antibody approved by the FDA for the cure of R/R low-grade NHL or FL. Approval was based on an experiment in which 166 patients with indolent NHL received Rituximab and ultimately had a complete remission (CR) rate of 6% and an overall response rate (ORR) of 48% (15). Also, Rituximab activity was used as a second-line treatment in patients with invasive DLBCL or MCL but showed relatively lower therapeutic effect (16).

Epratuzumab

Epratuzumab, the humanized IgG1 version of LL2 (anti-CD22 murine mAb), was designed to increase the half-life and effective performance, and reduce immunogenicity potential (17). The elementary clinical studies of this antibody labeled with ^{111}In/^{90}Y and ^{131}I have shown evidence of tumor localization, as well as the therapeutic activity for radioimmunoconjugate (18). The exact mechanism of action of Epratuzumab has not been elucidated, but binding of human CD22 to mAbs may induce tyrosine phosphorylation of the cytoplasmic tail of CD22, binding of tyrosine phosphatase SHP-1, and ultimately inhibiting B cell receptor signaling (19).

Galiximab

Galiximab is a cynomolgus macaque chimeric IgG1 mAb that is designed to target CD80 and the treatment of B-cell lymphoma. This antibody is not structurally distinct from human antibodies

and therefore cannot produce significant immunogenicity in humans. To date, several preclinical studies have demonstrated the antitumor activity of Galiximab alone or in combination with Rituximab against different B cell lymphoma cell lines *in-vitro/in-vivo* (20, 21). The mechanism of activity of Galiximab is not well understood but clinical studies with Galiximab have shown increased apoptosis and antibody-dependent cell-mediated cytotoxicity (ADCC), and decreased proliferation in various B cell lymphoma cells (22).

Tafasitamab

Tafasitamab (MOR208, XmAb5574) is a humanized Fc-engineered anti CD19 mAb that its preclinical activity has been shown in patients with R/R NHL including MCL, FL, and DLBCL (23). The Fc engineering, comprising the replacement of S239D and I332E amino acids is advantageous by reducing binding of FcγRIIa inhibitory receptor and increasing FcγRIIIa binding affinity on effector cells, leading to the enhancement of antigen-dependent cell-mediated phagocytosis and antigen-dependent cell-mediated cytotoxicity compared to using unmodified G1 CD19 antibodies. MOR208 potentially leads to disruption of B cell antigen receptor signaling resulting in cytotoxicity (24, 25).

Otlertuzumab

Otlertuzumab (TRU-016) is a protein therapeutic developed using the Modular Protein Technology (ADAPTIRTM

platform) that targets the CD37 molecule. Otlertuzumab, through binding to the CD37 receptor, leads to an increase in BIM proapoptotic protein expression and apoptosis induction (26). Preclinical studies show that Otlertuzumab mediates apoptosis and FcDCC (Fc-dependent cytotoxicity) against NHL cells and chronic lymphocytic leukemia (CLL) *in vitro* and *in-vivo* (27). Besides, Otlertuzumab activity was shown to be dependent on NK cell function in several B cell malignancy xenograft models (27). Other studies have shown that blocking CD20 on the surface of target B cells with Otlertuzumab may have therapeutic benefits, especially in CLL (28, 29), because the signal resulted from Otlertuzumab is provided by interacting with CD37 separately from CD20.

MEDI-551

MEDI-551 is a fucosylated anti-CD19 mAb which has antitumor activity against B cell malignancies alone or in combination with Rituximab (30). In phase 1 studies, unprotected safety characteristics and single-agent activity of MEDI-551 were observed in R/R FL and DLBCL with an overall response rate of 24% (31).

Antibody-Drug Conjugates (ADCs)

ADCs are a group of molecules made up of a mAb conjugated with a potent cytotoxic agent using a chemical linker. The linkers in these structures are cleaved by reduction, alterations in pH, or by proteases, and the drug is preferentially released at the tumor region (32). By choosing mAb against tumor-specific antigens, ADCs enable the targeted delivery of cytotoxic agents to cancer cells. In this section, the ADCs utilized to treat NHL will be discussed. ADCs change the treatment patterns of these diseases by increasing performance and improving tolerance to current chemotherapy-based regimens (33).

Polatuzumab Vedotin

Polatuzumab vedotin is an ADC comprised of an anti-CD79b mAb and an anti-mitotic agent called mono-methyl auristatin E (MMAE) (34). This therapeutic agent detects the CD79b protein from the B cell receptor complex and after binding to it, inhibits tubulin polymerization by entering the cytotoxic payload of MMAE drug into B-cell, leading to the death of the target cell. Targeting the CD79b pan-B marker is ideal in patients who may later need CD19-targeted CAR-T cell therapy because it will not develop resistance to CD19 regimens (35).

Brentuximab Vedotin

Brentoximab vedotin (BV) consists of an anti-CD30 mAb that binds to MMAE *via* a biodegradable ligand (36). After ADC binding, MMAE cleaves and undergoes endocytosis, then disrupts microtubules, arresting the cell cycle and inducing apoptosis (37). Recently, in a phase II study in DLBCL, the function of BV was investigated with an ORR of 44% (38).

Pinatuzumab Vedotin

Pinatuzumab Vedotin (DCDT2980S) is a humanized anti-CD22 IgG1 connected to the MMAE *via* the cathepsin-B-sensitive dipeptide (valine-citrulline, VC) linker. Binding of MMAE to

microtubules arrests cell cycle in the G2/M stage and induces apoptosis (33). This ADC has been studied alone and in combination with Rituximab in CLL and NHL in phase I and II clinical trials. The results showed that (DCDT2980S) can be used as a potential therapeutic option in patients with R/R DLBCL and FL.

Vorsetuzumab Mafodotin

Vorsetuzumab mafodotin (SGN-75) is composed of a humanized mAb targeting CD70 (h1F6) conjugated to the monomethyl auristatin F (MMAF) *via* the noncleavable maleimidocaproyl (MC) linker (39). MMAF is stronger than MMAE but less permeable to cells (40). The lysosomal degradation of this ADC causes the generation of cysteine-MC-MMAF in cancer cells (41). SGN-75 was investigated in a phase I clinical trial for CD70-positive R/R NHL and metastatic renal cell carcinoma (RCC).

Inotuzumab Ozogamicin

Inotuzumab is an anti-CD22 humanized IgG4 mAb, while ozogamicin is derived from calicheamicins, a group of potent anticancer antibiotics that cause strand cleavage in the DNA minor groove, cell cycle arrest, and eventually leading to leukemic cell apoptosis (42). The CD22 receptor is a very ideal therapeutic target because in most cases of B-cell hematologic malignancies such as NHL, hairy cell leukemia, CLL, and B-cell ALL, it is expressed in tumor tissues and not seen in normal tissues such as B lymphocyte precursors and hematopoietic stem cells (43).

Coltuximab Ravtansine (SAR3419)

SAR3419 (huB4/DM4) is a novel Ab–drug conjugate made from a humanized IgG1 anti-CD19 mAb (huB4) bound to a potent cytotoxic agent, a maytansine-derivative chemical agent (DM4). Phase I trials based on preclinical studies have illustrated optimistic antitumor activity of this drug with admissible safety results in human B-lymphoma models (44).

IMGN529 (CD37 ADC)

IMGN529 is a novel ADC for the treatment of CLL and B-NHL that consists of an anti-CD37 MAb bound to maytansinoid (DM1) toxin, a potent anti-tubulin. Previously, the therapeutic effects of ^{133}I-labeled CD37 MAb in the B-NHL have been investigated (45). The antitumor activity of IMGN529 has been assessed *in vitro* and xenograft models (46). Furthermore, its safety and tolerability in patients with R/R B-NHL in phase I, an open-label trial (NCT01534715) were evaluated.

Btk Inhibitors

Disruption of the B cell receptor pathway is closely related to the spread of B cell malignancies. This has made it possible to develop component inhibitors and various important steps along this pathway. Btk is a molecule present in the early BCR signaling pathway that plays an important role in regulating various cell functions including proliferation, differentiation, and survival in this type of malignancy and has been considered as a therapeutic target in this disease (47, 48).

Ibrutinib

Ibrutinib, the irreversible Btk inhibitor, has been approved for the treatment of a variety of B cell malignancies (49) including marginal zone lymphoma, MCL, Waldenström macroglobulinemia (WM), and CLL. It has also been shown that Ibrutinib also suppresses Th2 cells and enhances Th1-mediated immunity by inhibiting Interleukin-2 (IL-2) inducible T-cell kinase (ITK) (50).

Acalabrutinib

Acalabrutinib (ACP-196) is a second-generation inhibitor of Btk with a selective kinase activity pattern that covalently binds to the cysteine-481 residue at Btk and inhibits it more strongly than Ibrutinib (51). Furthermore, Acalabrotinib has shown an acceptable outcome in early clinical trials in patients with relapsed and refractory CLL (52).

PI3K Inhibitors

PI3K has three distinct classes (I, II, and III). The class I of PI3K pathway with 4 isoforms (α, β, γ, and δ) is most associated with the expansion and survival of malignancies and is one of the therapeutic targets of cancer (53). PI3K-α and-β are ubiquitously expressed, while the expression of PI3K-γ and -δ is more limited to leukocytes (54). Mutations and overexpression of PI3Kα are oncogenic and have been identified in various subtypes of cancer (55). Increased copy number and elevated PI3Kα protein expression have also been recognized in different lymphomas, indicating the basic role of PI3Kα in lymphomagenesis (56). Simultaneous silencing of PI3Kα and -δ is required for efficient blockage of PI3K signaling in clinical trials (57). Studies have shown that a combination of PI3Kα and δ-isoform inhibitors is required to suppress phospho-Akt and NFkB and PI3K pathways (56, 58). Therefore, molecular evaluation of PI3Kα/δ and the use of its inhibitors can be a promising therapeutic approach to eradicate lymphoma. Duvelisib, Copanlisib, and Idelalisib are three FDA-approved agents for the targeting of PI3Kδ in CLL/SLL and FL neoplastic B cells.

Copanlisib

Copanlisib is a PI3Kα/PI3Kδ inhibitor that has been approved as the third line of treatment for R/R FL. Besides, the antitumor activity of Copanlisib has been demonstrated in preclinical models of CLL and B-cell lymphomas (59) These researches eventually led to the first human study of Copanlisib in NHL patients.

Duvelisib

Duvelisib (IPI-145) is a second-generation inhibitor of PI3K that is used to treat relapsed FL and CLL/SLL after the failure of other treatments. Duvelisib also impedes the expression of PI3Kγ isoform in myeloid cells, T cells, and so on whereas Copanlisib, targets the PI3Kα isoform expressed in some types of NHL along with PI3Kδ (60). Treatment with Duvelisib by inhibiting PI3K/AKT/mTOR signaling pathway the homing and chemotaxis of CLL/SLL cells and leads to *in vitro* apoptosis (61). Thus, pharmacologic targeting of PI3Kγ reduces the migration rate of CLL/SLL cells, but the effect of Duvelisib on migration inhibition is greater than selective single isoform inhibitors (62).

Idelalisib

Idelalisib (CAL-101, GS-1101) is a potent inhibitor of PI3Kδ isoform and significantly suppresses B-NHL progression. The use of Idelalisib alone in patients with small lymphocytic lymphoma and FL and combination with Rituximab in patients with CLL has been approved (63).

Syk Inhibitors

Syk is a non-receptor cytoplasmic kinase that is primarily expressed in hematopoietic cells and is one of the essential components in BCR signaling (64). Syk activation leads to BCR signal initiation through binding to adapter proteins and phosphorylation signaling mediators including Btk, B-cell linker protein (BLNK), and phospholipase Cγ2 (PLC-γ2), leading to differentiation, cell proliferation, and survival (65). Aberrant Syk signaling is involved in the pathogenesis of multiple B-cell malignancies, such as constitutive Syk activation (66) and overexpression of the protein and mRNA levels of Syk (67). As a result, Syk is an attractive target for the treatment of B-cell malignancies.

Entospletinib

Entospletinib (GS-9973) is a selective Syk inhibitor and its impacts were evaluated in phase 2 of the study in patients with MCL and R/R NHL (68). As a result, Entospletinib showed a toxic profile and intermediate single-agent activity in NHL, although its toxicity was controllable compared to other BCR pathway inhibitors such as Ibrutinib and Idelalisib.

Fostamatinib

Fostamatinib is a prodrug of the active compound R406 and a potent inhibitor of the enzyme Syk, which is administered in an oral formulation (69). So far, the clinical trials of Fostamatinib have been accomplished on autoimmune thrombocytopenia, rheumatoid arthritis, IgA nephropathy, autoimmune hemolytic anemia, and lymphoma (70, 71). The evidence from several human clinical trials has revealed that daily administration of this drug significantly reduces Syk activity without any adverse effects on hemostasis or innate immunity (69).

Bcl-2 Inhibitors

BCL2 is a gene with unknown function that was discovered as the anonymous partner of the heavy chain locus of immunoglobulin in the typical translocation occurred in FL: t (14, 18, 72). In 60-90% of NHL cases, mentioned translocation and the placement of the Bcl-2 gene under the control of the enhancer region of IgH is observed (73, 74), whereas upregulation of Bcl-2 in the NHL without this translocation also with increasing relapse of the disease and mortality rate are associated (75).

Navitoclax

Navitoclax (ABT-263) is used as an inhibitor of the anti-apoptotic proteins of Bcl-xL, Bcl-2, Bcl-w, and Mcl-1/A1 in hematological malignancies, alone or combination with other apoptotic inhibitors. Navitoclax competitively averts Bcl-2 pro-apoptotic family members from being interrupted by Bcl-xL or Bcl-2 and thereby activating the intrinsic apoptotic pathway (76).

In general, pre-clinical and clinical results have displayed strong Navitoclax activity in acute and chronic lymphocytic leukemia (77–79).

Venetoclax

Venetoclax (ABT-199, GDC-0199) is another selective Bcl-2 inhibitor that has safety and noteworthy activity in patients with different subtypes of NHL (80). In previous studies, Venetoclax showed notable activity in multiple subtypes of NHL, such as MCL, FL, and DLBCL.

Checkpoint Inhibitors

Programmed death-1 (PD-1) is an inhibitory receptor expressed by active T cells that upon binding to its corresponding ligands, PD-L1/PD-L2 leads to suppression of T cell-induced immune responses and restriction of autoimmunity (81). Tumors often elude immune monitoring by up-regulating the PD-1 and/or PD-L1 level on tumor cells and tumor-associated immune cells (82). Recent studies have shown that PD-1 signaling, which is currently considered as one of the prominent mechanisms of immune escape, preferentially dephosphorylates and inhibits the co-stimulatory molecule CD28 (83). Many tumors, through overexpression of PDL-1, reduce the cytotoxic function of tumor-infiltrating T lymphocytes and thus escape immune surveillance. In some subset of patients with DLBCL, the PD-1 ligand gene amplification and PD-L1 overexpression have been observed in tumor cells and tumor-associated macrophages (84) so that after standard treatment, survival is attenuated significantly (85). In addition, overexpression of PD-1 has been observed in CD4^{+} tumor-infiltrating lymphocytes (TIL) in FL (86). Therefore, PD-1 inhibitors have been developed to disrupt this pathway and increase immune activity for the clinical advantage (87).

Durvalumab

Durvalumab is an anti-PD-L1 mAb that enhances anti-tumor immune responses by suppressing the interaction of PD-1 with PD-L1 (88). Data from previous studies in murine lymphoma models showed significant antitumor activity of Ibrutinib with the anti-PD-L1 Ab (89).

Nivolumab

Nivolumab is an anti-PD-1 Ab (a fully human IgG4 mAb) which activates T cell signaling through the PD-1 blockade, and thus enhances the anti-tumor response. Some studies propose that this drug may be beneficial for patients with relapsed FL after discontinuation of previous treatments (90).

Pembrolizumab

Pembrolizumab (formerly lambrolizumab) is a humanized mAb that targets the interaction between PD-1 and PD-L1/PD-L2 (91). The clinical effects of Pembrolizumab on Hodgkin's lymphoma (HL) are significant, whereas the results are different in NHL. Subtypes of the NHL such as Primary mediastinal B cell lymphoma (PMBCL), that share genetic characteristics with HL, like chromosome 9p24.1 alterations and increased expression of PD-L1, have shown favorable responses in early-phase experiments (92). Pembrolizumab has been shown to potentiate the T lymphocytes' immune responses in cultured blood cells from cancer patients and healthy human donors. Besides, it greatly modulates the levels of cytokines such as TNF-α, IFN-γ, and IL-2. Pembrolizumab does not induce cell-dependent cytotoxicity (CDC) or ADCC, and nonspecific T cell activation (93, 94).

Pidilizumab

Pidilizumab (CT-011) is a recombinant human IgG1 Kappa mAb binding to PD-1. Pidilizumab treatment is safe and tolerable, and its clinical activity has been recently demonstrated in DLBCL. PD-1 is an inhibitory receptor belonging to the B7 receptor family that is expressed on the myeloid cells and lymphocytes (95, 96) and by binding to the corresponding ligands (PD-L1 and PD-L2) adjust the immune response (97). In inflammatory conditions such as malignancy, continuous expression of PD-1 and its ligands by tumors leads to inhibition of the antitumor activity of tumor-infiltrating lymphocytes, T cell exhaustion, and immune escape (98). The binding of Pidilizumab to PD-1 attenuates the apoptotic process in this effector memory T cells. Pidilizumab upregulates the expression level of Bcl-xL protein by inducing the P13K signaling pathway, thus protecting effector/memory (CD45RO^{+}) lymphocytes from apoptosis (99). Also, Pidilizumab may increase the antitumor activity of NK cells through the P13K signaling pathway.

COMBINATION STUDIES

The therapeutic effect of Rituximab in combination with Bendamustine was tested *in vitro* in primary CLL and CD20-positive DLBCL (100) and *in vivo* in a model of Burkitt's lymphoma (BL) (101). Bendamustine is currently used to treat some hematological tumors, including the Rituximab-resistant and indolent NHL (102).

The Epratuzumab plus Rituximab can exert greater therapeutic impacts than any of the drugs alone in low-grade FL and DLBCL, which is characterized by a significant improvement in CR rate (103).

In a phase II study, MOR208 with Lenalidomide was evaluated in patients with R/R DLBCL (L-MIND study) (104).

Otlertuzumab in combination with Rituximab as well as chemotherapeutic drugs increased apoptosis in human B cell tumors. The use of TRU-016 and bendamustine also significantly delayed tumor growth *in vivo* and improved survival in xenograft lymphoma models compared with single agent therapy (105).

Inotuzumab ozogamicin (IO) has been tested in clinical trials along with Rituximab (106, 107), as well as in combination with Rituximab plus chemotherapy to treat NHL (108). The combination therapy with IO and Rituximab provides non-overlapping and distinct antitumor mechanisms including Ab-dependent cytotoxicity, cytotoxic agent delivery by IO, complement-dependent cytotoxicity, and induction of apitosis by Rituximab.

It has been shown that Ibrutinib together with ACY1215, a selective histone deacetylase-6 inhibitor, synergistically resulted in increased apoptosis in MCL cell lines compared to the monotherapy (109). Moreover, Ibrutinib in combination with Bortezomib raised cytotoxicity in DLBCL and MCL cells through mitochondrial damage and apoptosis (110). Also, the combination treatment of Ibrutinib and lenalidomide synergistically resulted in the eradication of ABC-type DLBCL cells (111). Ibrutinib along with Idelalisib synergistically disrupt BCR-stimulated integrin-mediated adhesion and inhibit the migration of CLL and MCL cells, supporting the justification for combination therapy (112).

The evaluation of Navitoclax in combination with Rituximab in patients with R/R CD20$^+$ lymphoid malignancies and patients with previously untreated B-cell CLL exhibited synergistic antitumor activity and good tolerability (113, 114). In another study, the effects of combining Bendamustine or Rituximab with Navitoclax in the treatment of several NHL tumors were investigated. The results showed that Navitoclax enhanced the response of NHL tumors to Bendamustine in mouse xenografts and the addition of Rituximab increased the effectiveness of Bendamustine. In fact, treatment with Bendamustine increased p53 levels in Granta-519 tumors, thereby increasing the cleavage of caspase-3 and inducing apoptosis (115).

Previous studies have shown that Syk inhibitors (R406), Btk inhibitors (Ibrutinib), PI3K inhibitors (Idelalisib, Copanlisib, ACP-319, and KA2237), and other kinase inhibitors alone or in combination with Venetoclax significantly reduce the expression of BCL2 proteins in vitro and exerted synergistic killing impacts on lymphoma cells (116, 117). Clinical studies have confirmed that the combination of Ventoclax with Rituximab and Bendamustine can illustrate synergistic effects and significantly increase ORR and complete response (CR) rate in patients with DLBCL, FL, and MZL. Preclinical studies have also shown that Venetoclax along with Rituximab leads to complete tumor regression (100%) in R/R FL xenograft models (118). A phase II clinical trial investigated the combined influence of Venetoclax and Ibrutinib in patients with previously untreated or RR MCL. After completing the treatment, approximately 70% of the patients were negative for MRD (minimal residual disease) and indicated a CR of 67% (119).

MANUFACTURING AND DELIVERY OF CAR-T CELLS

The production processes of different CAR-T cell lines are similar for the treatment of lymphoma. Peripheral blood mononuclear cells (PBMCs) are collected from blood, through the central or peripheral venous during outpatient leukapheresis. In the next step, PMBCs are transported to the production site at a temperature of 1-10°C and after being selected using density gradient T- lymphocytes or magnetic beads, they are activated by provoking their T cell receptor (TCR) (120). A viral transfer vector (retrovirus or lentivirus) then transfects the CAR gene to

the activated T cell genome, causing the modified T cell to express the CAR molecule forever (121). Finally, after the T cells have spread in the flask, culture bags, or bioreactor systems, the CAR-T cell product is frozen and sent to the treatment site. The manufacturing process of a CAR-T cell product takes an average of 10-21 days, depending on the sort of CAR-T product. Before injection, lymphodepleting chemotherapy such as cyclophosphamide and fludarabine by depletion of regulatory T cells allow incoming T cells to proliferate and expand (**Figure 1**) (122).

CAR STRUCTURE

A CAR molecule consists of three major domains: antigen recognition, transmembrane, and intracellular domain. The antigen detection domain consists of a single-chain variable fragment (scFv) containing the variable regions of the light and heavy chains of a monoclonal antibody against a certain antigen (eg CD19) (123). scFv, which partially modulates the function and safety of CAR-T cells, is attached to the membrane domain by a spaced region derived from IgG4 or CD8 molecules (124). Signal transduction due to antigen binding occurs via scFv to the intracellular domain (s). Ultimately, the intracellular domain, which usually includes the CD3ζ chain, acts as a signaling domain. The existence of additional costimulatory domains in CARs preserves T cell proliferation, activation, and survival (125). The CARs design has developed dramatically over the years.

The first-generation CAR-T is made of a CD3ζ chain as a crucial transmitter of endogenous TCR signals. After successful results in preclinical trials, the drug entered into phase 1 clinical trials for lymphoma, leukemia, neuroblastoma, ovarian cancer, etc (126). The variable regions of light and heavy chains of the B-cell receptor are called scFv, which, after fusion with ζ chain of the TCR or CD3 domain, form the activating receptor molecules that are non-HLA-restricted. By specifically targeting tumor cells, these molecules accelerate the detection of antigen by T cells and increase cytotoxicity (127). The artificial signaling receptors, CAR or chimeric receptors, and their synthesis method are called the T body approach (128).

The second-generation CAR-T cell therapy was established after the success of first-generation CARs in phase 1 clinical trials. Initially, these CAR-T cells were utilized in patients with recurrent B−cell ALL, and they created a more significant anti-leukemic response with a full recovery rate of up to 90%. The second-generation CARs contain a CD3ζ chain and an intracellular signaling domain of various co-stimulatory molecules, such as 4-1BB (CD137), CD28, OX40 (CD134), and induction T cell stimulator (ICOS or CD278) (129). For example, second-generation anti-CD19 CAR-T cells were constructed from a 4−1BB or CD28 costimulatory domain bound to the CD3 domain (130) which in patients with R/R B-cell malignancies produces remarkable complete response (CR) rates (131). While 4-1BB-based CARs accelerate the accumulation of T cells, CD28-specific CAR-T cells significantly increase effector T cells' activity (132).
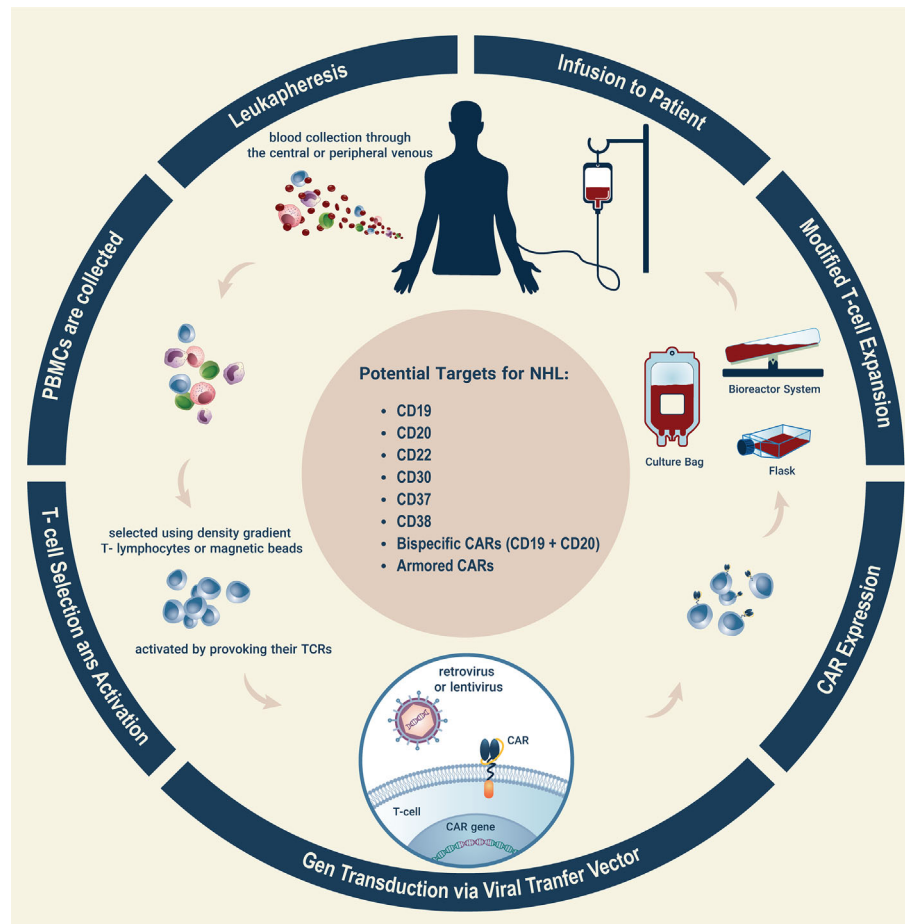
FIGURE 1 | Characteristic of CAR-T cells and their isolation, engineering, transfection, and expansion in patients with NHL. The first stage of CAR-T cell engineering is leukapheresis in which leukocytes are collected through central or peripheral venous (Stage 1). Then, PBMCs are purified among collected leukocytes (Stage 2). Next, density gradient or magnetic beads are used to purify T cells among collected PBMCs. Also, T cells get activated by provoking their TCRs (Stage 3). Viral transfection methods using viral vectors such as retrovirus or lentivirus are the next steps (Stage 4). The next step is done ex-vivo in which the cells are directed to be expanded (stage 5). In the last stage, modified CAR-T cells are expanded by culturing or bioreactor system and were injected into the same patients (step 6). Various antigens used as CAR-T cells' targets in NHL have been shown. CAR, chimeric antigen receptor; PBMC, peripheral blood mononuclear cell; TCR, T-cell receptor.

Third-generation CARs consist of two signaling domains and a CD3ζ chain such as the CD3ζ-CD28-OX40, which, compared to second-generation CARs, have increased activation signals, the length of the proliferation period, cytokine production, and effective anti-tumor activity in these cells (133). For example, a third-generation CAR consisting of α-CD19/CD3ζ/CD28/4–1BB segments dramatically increased the rate of complete recovery in patients with CLL by penetrating and lysing tumor cells (134).

Although all previous CARs have effectively contributed to T cell anti-cancer responses, they also have limitations, including degradation caused by antigen-negative cancer cells and the absence of antitumor action against solid tumors due to the broad phenotypic heterogeneity. These restrictions paved the way for the emergence and development of a new generation of CARs (135). Fourth-generation CARs, through the triggered expression of transgenic immunomodulators, such as IL–12,

activates innate immune cells and thus increases T cell function, to lessen antigen-negative tumor cells in the designated lesion (134).

ANTIGEN SELECTION

The constant expression of B cell markers CD19, CD20, and CD22 in many B cell malignancies and previous reports of safety and efficacy of mAb against a mentioned surface antigen in these diseases have made them ideal targets for CAR-T cell therapy (25, 136). CAR therapy partially eliminates normal B cells because they also express most of the CAR-targeted lymphoma antigens, although this state can be compensated by intravenous immunoglobulin administration. Thus the use of more specific

antigens that are limited to B cell malignancies as a target, compared with ordinary antigens, CD19/CD20/CD22, has fewer side effects. One of these alternative antigens is BCMA (B cell maturation antigen), which is expressed by the mature B cell subsets, plasma cells, and the light chain κ/λ of malignant B cells. In T cell lymphoma, the expression of many target antigens is common between malignant and normal T cells, so finding the ideal target antigen is more challenging. This joint expression of antigen can disrupt CAR-Ts function, prevent them from proliferating and surviving, and lead to the extinction of normal peripheral T cells (**Figure 1**) (137).

CAR-T CELLS FOR NHL

Most CAR-T clinical trials for the treatment of B-cell lymphoma target the CD19 marker. Because the expression of this antigen is seen in all stages of B cell differentiation and most B cell lymphomas (138). Different types of scFv can be applied to target the CD19 antigen. SJ25c or FMC63 are two of the most widely used scFvs in clinical trials (139). In the primary clinical trials for lymphoma therapy, a first-generation CAR-T (FMC63 19z CAR-T) without the costimulatory domain was used with the targeting CD19 (140). In this trial, patients with R/R FL after lymphodepletion with fludarabine and injection of IL-2 subcutaneously were treated using the first-generation anti-CD19 CAR-Ts. Despite proving the safety and feasibility of this new method, the first generation of anti-CD19 CAR-T cells did not show significant antitumor effects (140). However, the use of the second generation anti-CD19 CAR-T-cells with a costimulatory domain (4-1BB, CD28, and ICOS) in preclinical studies have shown considerable anti-tumor impacts *in-vitro/in-vivo* (141). Recently, the use of second-generation CAR-Ts targeting CD19 with stimulatory domains of CD28/4-1BB has reported considerable outcomes in the treatment of B-cell lymphomas, particularly PMBCL, DLBCL, splenic marginal zone lymphoma (SMZL), FL, and MCL (142).

One of the most common forms of aggressive NHL is DLBCL, which accounts for approximately 40% of cases (143). The standard initial treatment is combination of a chemotherapy regimen, usually R-CHOP (Rituximab, Cyclophosphamide, Adriamycin, and prednisone) and immunotherapy for 6-8 courses (144). Treatment is usually poor in people with high-risk characteristics such as early relapse in less than a year, preliminary refractory disease, and single/double-hit lymphoma (145). The preparatory examination of anti-CD19 CAR-T cells provided promising therapeutic effects (146). Jensen et al. used CD20-targeted CAR-T cells to treat two patients with recurrent DLBCL who had previously undergone autologous hematopoietic stem cell transplantation. They did not observe any obvious toxicity or clinical complication in these patients after treatment (140). In another experiment, anti-CD19 CAR-T cells were used on several patients with advanced B cell malignancies. After treatment, complete remission (CR) was observed in 4 patients out of the total number of

chemotherapy-refractory DLBCL patients (147). Besides, Stirrups et al. injected anti-CD19 CAR-T cells into several patients with large B cell lymphoma, including PMBCL and DLBCL. After treatment, the analysis of patients showed that 28% of them had PR and 54% had CR (148).

Follicular lymphoma is the most common indolent lymphoma that accounts for 10-20% of NHL. The genetic characteristic of FL is the translocation of t (14; 18) (q32; q21), which leads to overexpression of BCL-2 protein and disruption of the apoptotic program of the germination center (149). Besides, FLs show additional genetic changes such as mutations, losses, or gains in genes such as EPHA7, MLL2, CREBBP, CREBBP, TNFRSF14, EZH2, BCL6, and so on (150). Many patients with FL remain asymptomatic despite the widespread disease. About 10-15% of FLs are diagnosed in the primary stages and the rest in advanced stages III and IV (150). Advanced-stage III/IV follicular lymphoma becomes resistant to chemotherapy and may convert into a more aggressive subtype of the NHL, such as DLBCL (151). The biological nature of this malignancy is such that eventually, most patients experience relapsing stages of the disease or resistance to treatment. Therefore, CAR-T cell therapy can be considered an attractive treatment approach. Schuster et al. used CTL019 in a phase IIa study in patients with FL and showed that disease progression in these patients occurred 2 years after remedy with two or more treatment lines (152). Furthermore, In another study, a patient with R/R acute B cell lymphoblastic lymphoma and Li-Fraumeni syndrome (LFS) received dual specific CD19/CD22-targeted CAR-T cells. After that, several parameters showed complete relief of the tumor and negative MRD (153). Also, a group of researchers used KTEC19 consisting of FMC-63 (a single-chain Ab in the extracellular region) that detect CD19 at the tumor cell surface to treat aggressive and refractory B-NHL patients (154).

Mantle cell lymphoma is an uncommon form of NHL with unique immunophenotypic and clinical features that accounts for about 6% of NHL cases. In MCL cells, due to chromosomal translocation t (11:14), the expression of cyclin D1 is greatly increased (155). The standard therapy is induction chemotherapy with or without autologous grafting to integrate into responsive patients followed by maintenance therapy with anti-CD20 mAb therapy. This method can lead to lasting improvement but does not seem to be the mainstay of treatment, and the prognosis for patients with early recurrence can be poor (156). One way to diagnose this malignancy, like other forms of NHL, is to examine the CD19 expression. CAR-T cell therapy is an effective way to treat MCL and to some extent makes the disease a treatable condition. In a clinical trial, the effect of third-generation CD20-directed CAR-T cells on several patients with MCL and relapsed indolent B cells was evaluated. The results showed that this treatment was well tolerated, although disease relapsed in one of the patients one year after injection (129).

Burkitt's lymphoma is one of the most common forms of NHL in children, and about 10% of patients with a poor prognosis, relapse even after vigorous chemotherapy. In a recent study, an eight-year-old child was initially treated with

CD19-specific CAR-T cell but showed progressive disease (PD) and illustrated no clear response to cell therapy. CD22-specific CAR-T cells were then injected into the child, but recurrence of the disease was observed. Finally, CD20 CAR-T cell treatment resulted in the achievement of CR (157). Besides, CAR-T cell therapy targeting tyrosine kinase-like orphan receptor (ROR1) and CD23 has yielded promising results in advancing R/R NHL therapy (**Figure 2**) (158).

CURRENT CAR T-CELL PRODUCTS

Anti-CD19 CAR-T Cell Therapy for B-Cell NHL

Numerous studies have been actively conducted since 2010 when the first case of anti-CD19 CAR-T cell treatment was reported, until 2017 when the first approval for this product was received by the US FDA (142, 152, 159). To date, several CD19-specific
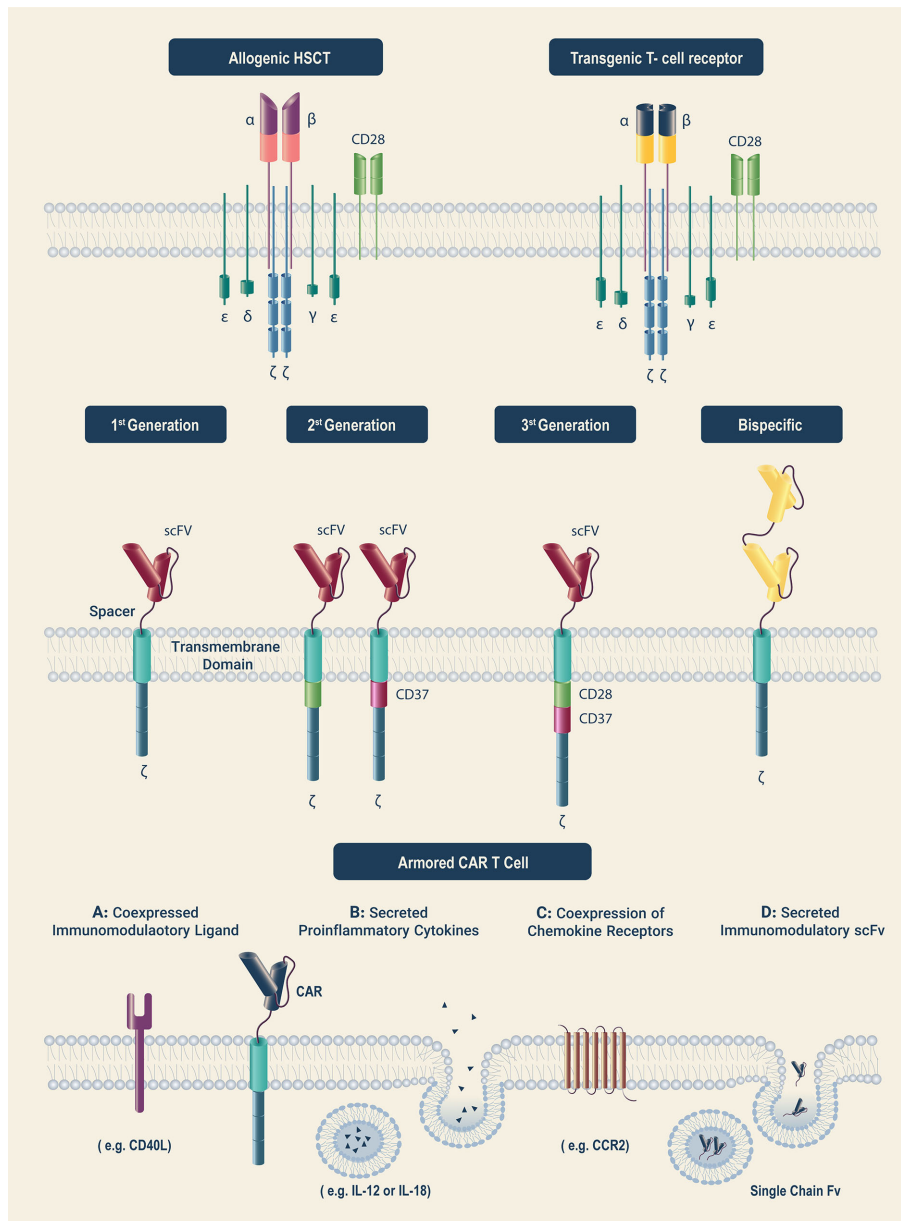

FIGURE 2 | Generations of CAR-T cells along with allogenic, transgenic, bispecific, and armored CAR-T cells. In the upper quadrant, allogeneic and transgenic CAR-T cells are seen. Allogeneic CAR-T cells are seen in patients that have allogeneic HSCT and can be either donor- or recipient-derived. On the other hand, transgenic CAR-T cells are engineered CAR-T cells that have been made by transfection of a special gene to encode the surface receptor of CAR-T cells. In the middle quadrant, three generations of CAR-T cells are shown. Besides, bispecific CAR-T cells are engineered to target two different targets simultaneously. In the lower quadrant, armored CAR-T cells which have been potentiated by secreting cytokines and chemokines are seen. HSCT, hematopoietic stem-cell transplantation; CCR2, chemokine receptor 2.

CAR-T cell therapies have been tested in B cell malignancies. Among these CAR-T products, tisagenlecleucel (tisa-cel), axicabtagene-ciloleucel (axi-cel), and lisocabtagene-maraleucel (liso-cel) in a relatively wide range on patients with aggressive B cell lymphomas especially DLBCL are being tested (160). To produce Axi-cel, a retroviral vector, and the co-stimulatory/transmembrane domains of CD28 are used (161). Tisa-cel is generated using a lentiviral vector, a CD8-α transmembrane domain, and a 4-1BB co-stimulatory domain (162). Liso-cel is made with a lentiviral vector, a CD28 transmembrane domain, and a co-stimulatory domain of 4-1BB. The manufacturing and time required to produce distinct products are different. For example, liso-cel is made up of equal proportions of CD4$^+$ and CD8$^+$ CAR-T cells, while both tisa-cel and axi-cel are produced from bulk T cells in which the cell dose varies from patient to patient. The turnaround time (from leukapheresis to product accessibility) of both tisa-cel and Liso-cel is approximately 24 days, while in Axi-cel it is approximately 17 days (162, 163).

Axicabtagene-Ciloleucel (KTE-CD19, Axi-cel)

Axi-cel is a second-generation CAR-T with a CD28 domain embedded in its structure and was first developed by the National Cancer Institute (NCI) researchers. Kite Pharma, Daiichi Sankyo, and Gilead Sciences conducted a fundamental phase I/II study of axi-cel in patients with PMBCL, transformed FL, and high grade and R/R DLBCL called the ZUMA-1 test (NCT02348216) (164, 165).

Tisagenlecleucel (CTL019)

Tisa-cel was the second CAR-T cell product for invasive B cell lymphoma that received FDA approval based on the JULIET trial. In an international phase 2 JULIET study, patients with DLBCL, HGBCL (double-hit lymphoma), and transformed FL had received two or more treatment lines and were chemotherapy or multiply refractory/relapsed or unqualified for autologous stem cell transplantation (166). This product is the first CAR-T cell to be approved by the FDA in 2017 for the treatment of pediatric B-cell acute lymphoblastic leukemia (B-ALL) (167). It should be noted that this research was first conducted by researchers at the University of Pennsylvania (UPenn) in assistance with Novartis.

Lisocabtagene Maraleucel (JCAR017, Liso-cel)

Liso-cel is the third major CD19-specific CAR-T cell product and is awaiting FDA approval based on TRANSCEND-NHL-001 data, a monolithic pivotal project that studied patients with DLBCL NOS, HGBCL (double-hit lymphoma), transformed indolent B-cell lymphomas, follicular lymphoma grade 3B, and PMBCL (163). The researchers at the Memorial Sloan Kettering Cancer Center, Fred Hutchinson Cancer Research Center (FHCRC), and Seattle Children's Research Institute founded a venture, Juno Therapeutics, performed several clinical trials on anti-CD19 CAR-T cell products including JCAR014/015/017/

021, and so on. In the next phase clinical trial, JCAR017 (lisocabtagene-maraleucel, liso-cel) was evaluated in patients with B-NHL. Liso-cel is a second-generation anti-CD19 CAR-T cell with a costimulatory domain of 4-1BB and is made from an isolated subset of CD4$^+$ and CD8$^+$ cells with a 1:1 CD4/8 ratio. The results of researchers' preclinical studies at the FHCRC reported that CAR-T produced from different T cell subsets showed distinct activity *in-vivo* (168). For example, the direct anti-tumor activity of CD8$^+$ central memory (CD8$^+$ CM)-CAR-T is much stronger than that of CD4$^+$ CAR-T. CD4$^+$ CAR-T cells lead to a synergistic increase of proliferation after CD8$^+$ CM-CAR-T injection by producing several inflammatory cytokines (**Table 2**) (160).

Novel CAR-T Cells in NHL

Although the excitement of using CD19 CAR-T cells was initially significant in patients with R/R NHL, the (progression-free survival) PFS rate ranges between 30- 50%, and for those who do not receive CAR-T treatment, the results were unpleasant. According to studies, mechanisms such as lack of CAR-T durability, loss of CD19 antigen, and the presence of immune checkpoint molecules in tumor cells can cause recurrence of malignancies (184, 185). Several new clinical structures are currently being developed to remove these restrictions.

Bispecific CARs or Dual Targeted CAR-T Cells

A bispecific receptor consists of two distinguished antigen recognition domains that bind to two separate intracellular domains and are expressed as tandem scFvs in one CAR, or as two different CARs on T cell surface. At current, CD19/CD20-bispecific CAR-T cells have been presented as a new synthetic molecule that, after recognition and binding to target tumor antigens on the surface of malignant cells, can establish a synergistic cascade of executive molecules (186). If one of the target molecules is not available to CAR T cells for reasons such as removal or mutation of the target antigen on malignant cells, a dual-function machine can largely prevent tumor escape. Thus, the bispecific CAR retains the cytolytic property of T cells (184). In addition to the mentioned CARs molecule, several other bispecific CARs including CD20/CD19 and CD20/CD3 have also been preclinically studied (187, 188).

Inhibitory CARs (I–CARs)

The interaction of PD-1 receptors with PD-L1 inhibits the activity of T cells and is one of the mechanisms of escape from the immune system that promotes the survival of malignant diseases. This pathway is thought to play a key role in tumor escape from CAR-T cells, so treatments combining PD-1 inhibition with CAR-T cell therapy are being studied. In a recent study, Pembrolizumab was used as an immune checkpoint inhibitor (anti-PD1) at various intervals after CART19 treatment, including during early progressed or late relapsed of NHL to inhibit T cell exhaustion (189). Besides, Jacobson et al. showed that blockade of PD-L1 with the

TABLE 2 | The clinical trials of CD19-targeted CAR T cells.

No. of patients/age (years)	Disease/No. of patients	CAR generation	Co-stimulatory domain	Injected CAR T cell dose	Result	Ref
4 (n/a)	FL:2	I	None	$1–2×10^9/m^2$	2 PD	(140)
1 (n/a)	FL	II	CD28	$1–3×10^8$	1 PR	(142)
6 (46–59)	NHL	I+II	None/ CD28	$2–20×10^7/m^2$	2 SD, 4 NR	(169)
3 (64–77)	CLL	II	4-1BB	$1.4×10^5/kg –1.6×10^7/kg$	2 CR, 1 PR	(170, 171)
8 (47–63)	CLL: 4, FL: 3 SMZL:1	II	CD28	$0.3–2.8×10^7/kg$	CLL: 1 CR, 2 PR, 1 SD FL: 2 PR, 1 NE SMZ: 1 PR	(172)
10 (44–66)	CLL: 4 DLBCL: 2 MCL: 4	II	CD28	$0.4–7.8×10^6/kg$	CLL: 1 CR, 1 SD, 2 PD; DLBCL: 2 SD; MCL: 3 SD, 1 PR	(173)
8 (9–59)	ALL: 4 CLL: 4	II	CD28	$1.5–12×10^7/m^2$	3 CR, 1 PD 1 PR, 1 SD, 2 PD	(174)
14 (51–78)	CLL	II	4-1BB	$0.14–11×10^8$	4 CR, 4 PR, 6 NR	(175)
21 (1–30)	ALL: 20 DLBCL: 1	II	CD28	$1–3×10^6/kg$	ALL: 14 CR, 3 SD, 3 PD DLBCL: 1 PD	(176)
15 (30–68)	CLL: 4 DLBCL: 5 SMZL: 1 PMBCL: 4 LG-NHL: 1	II	CD28	$1–5×10^6/kg$	CLL: 3 CR, 1 PR; DLBCL: 2 CR, 2 PR, 1 NE; SMZL: 1 PR; PMBCL; 2 CR, 1 SD, 1 NE; LG-NHL: 1 CR	(147)
20 (25–68)	CLL: 5 DLBCL: 5 MCL: 5 ALL: 5	II	CD28	$0.4–8.2×10^6/kg$	CLL: 1 CR, 1 PR, 1 SD, 2 PD; DLBCL: 1 CR, 3 SD, 1 PD; MCL: 1 PR, 4 SD ALL: 4 CR, 1 PD	(177)
32 (36–70)	NHL	II	4-1BB	$0.2–20×10^6/kg$	11 CR, 9 PR, 10 NR, 2 NE	(178)
16 (23–75)	DLBCL: 11 MCL: 5	I+II	None/ CD28	$2.5–20×10^7$	DLBCL: 8 CR, 2 PR, 1 PD; MCL: 5 CR	(179)
26 (23–61)	ALL: 17 FL: 3 DLBCL: 4 MCL: 1 HL: 1	II	CD28	Varying doses	9 CR, 2 SD, 6 PD FL: 3, DLBCL: 4, MCL: 1, HL: 1 DLBCL: 2 CR, 1 SD, 1 PD; FL: 3 CR; MCL: 1 CR; HL: 1 CR	(180)
7 (29–69)	DLBCL	II	CD28	$2×10^6/kg$	4CR, 1 PR, 1 SD, 1n/A	(165)
24 (40–73)	CLL	II	4-1BB	$0.2–20×10^6/kg$	CR+PR: 17, 7 NR	(181)
101 (23–76)	DLBCL: 77 PBMCL or FL: 24		CD28	$2×10^6/kg$	38 CR, 25 PR, SD 9, PD 4; NE: 1 17 CR, 3 PR, 2 SD, 1 PD, 1 NE	(178)
14 (25–77)	DLBCL	II	4-1BB	$1–5×10^6$	6 CR, 1 PR, 7 NR	(152)
14 (43–72)	FL				10 CR, 1 PR, 3 NR	
15 (24–71)	ALL: 4 CLL: 2 DLBCL: 6 MCL: 2 FL-Burkitt: 1	III	CD28+4–1BB	$2–20×10^7/m2$	ALL: 2 CR, 2 PD; CLL: 1 CR, 1 SD; DLBCL: 3 CR, 3 PD; MCL: 1 SD, 1 PD; FL-Burkitt: 1 PD	(182)
16 (16–75)	DLBCL: 11 ALL:2 BCLU: 1 LBL: 1 CLL: 1	II+III	CD28/ CD28+4–1BB	$2–40×10^6/m2, 0.05–1.25×10^6/kg$	DLBCL: 6 CR, 2 PR, 2 SD, 1 NR; ALL: 1 PR, 1 NR; CLL: 1 NR; BCLU: 1 CR; LBL: 1 CR	(183)

ALL, acute lymphoblastic leukaemia; lymphoma unclassified; CLL, chronic lymphocytic leukaemia; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; EP, electroporation; FL, follicular lymphoma; Gen, CAR generation; HL, Hodgkin's lymphoma; LBL, lymphoblastic lymphoma; LG, low grade; MCL, mantle cell lymphoma; n/a, not assessed; NE, not evaluable; NHL, non-Hodgkin's lymphoma; NR, no response; PD, progressive disease; PMBCL, primary mediastinal B cell lymphoma; PR, partial response; SD, stable disease; SB, Sleeping Beauty; SMLZ, splenic marginal zone lymphoma.

anti-PD-L1 antibody atezolizumab (atezo) significantly increased the efficacy and safety of ZUMA-6 in refractory DLBCL patients (190). It has already been shown that CTLA-4-/PD-1- based I-CARs can significantly control cytokine secretion, cytotoxicity, and proliferation induced by activating chimeric receptor or endogenous TCR (191). I-CARs control CAR T cell function by inhibitory receptors. I-CARs differentiate between normal and cancer cells by inhibiting the activator CAR response to antigens

expressed only by normal cells (192). Therefore, the design of I-CAR using PD-1 and CTLA-4 surface antigen detection domains to regulate T cell response and prevent T cell inhibition physiology in mouse models has been confirmed. However, the use of this technique in mice lacking CTLA-4 and PD-1 receptors leads to severe systemic autoimmune diseases such as glomerulonephritis and arthritis (193, 194).

Armored CAR-T Cells

Inducing the expression of an extra transgene - along with CAR – by effective T cells is one of the recent strategies to enhance CAR-T cells effector functions and control the immunosuppression caused by the tumor microenvironment. TRUCKs (T cells redirected for universal cytokine killing) are examples of armored CAR-T cells that transgenic cytokines (IL-12/-15/-18) produced by them accumulate in malignant tissue and show beneficial effects (195–197). Besides, some modifications allow armored CAR-T cells to express a ligand for costimulation molecules. Batlevi and colleagues used different doses of 19-28z/4-1BB-L CAR-T cells in phase I clinical trial to treat patients with CLL or NHL (198). Furthermore, in other studies, CAR-T cells were modified to deal with immunosuppressive signals. For example, CD19-targeted CAR-T cells with co-expressing of the chimeric switch receptor of PD-1/CD28 were examined for the treatment of patients with R/R DLBCL in phase I clinical trial (199). Also, the direct embedding of anti-PD-1 or anti-PD-L1 blockers in CAR-T cells can clearly illustrate the combined anti-tumor effects of CAR-T cells with checkpoint inhibitory antibodies (200).

Allogeneic CAR-T Cells

To prevent the use of patient-derived inefficient T cells and reduce the cost/time of producing products, healthy donors-derived allogeneic CAR-T cells can be used. Because allogeneic products can cause graft versus host disease (GVHD) as well as CAR T cell rejection, strategies should be used to minimize donor-derived T cells alloreactivity before using off-shelf products. Recently, gene-editing technologies have been utilized to forbid the endogenous TCR expression on modified T cells. Several methods can be used to disrupt the TCR alpha constant (TRAC) gene, such as the CRISPR/Cas9 system, transcription activator-like effector nucleases (TALEN), and zinc finger nucleases (ZFN) (201). The universal CD19-targeted CAR-T cell product (UCART19) was produced following the simultaneous introduction of CAR and TCR knockout to prevent GVHD and CD52 suppression to induce resistance to anti-CD52 Ab to reduce the likelihood of UCART19 rejection in allogeneic T cells (202). ALLO-501 is an anti-CD19 allogeneic CAR-T (AlloCAR T^{TM}) with the same structure as UCART19, which has recently undergone clinical trials in the ALPHA study for the treatment of FL and R/R DLBCL. PBCAR0191 is another allogeneic CD19-directed CAR-T cells produced by using a single-stage TCR knock-out and CAR knock-in, and its antitumor effects have been demonstrated in a phase 1 trial in patients with NHL (203).

OTHER TARGETS AGAINST NHL

Sometimes mutations in the CD19 antigen or the downregulation/disappearance of this antigen from the surface of malignant lymphocytes lead to tumor escape and resistance/refractory to CD19-targeted CAR-T treatment in patients (204). According to recent studies, 40% of reported recurrences are due to epitope loss (205, 206). Therefore, alternative markers such as CD20, CD22, etc. with higher expression in B-NHL and B-ALL, respectively, can be used as a target for T cell therapies (207, 208). In the FHCRC phase-I experiment, third-generation anti-CD20 CAR-T cells containing CD28 and 4-1BB domains were used to treat MCLs and intolerant B-cell lymphomas. In this section, new studies of CAR-T cell therapy, which recognize different CAR-T cells and intensifies tumor cell death, are reviewed.

CD20 CAR-T Cell Therapy

CD20 is a non-glycosylated membrane phosphoprotein that is highly expressed not only in normal B cells but also on the surface of malignant B cells (209). CD20 is expressed by CLL, all NHL cases, and about 40% of precursor B-ALL (210). Recently, Xu et al. evaluated the cytotoxicity effect of CD20-specific CAR-T cells on B cell malignancy using in vitro/in vivo true lytic ability, CD107a degranulation, and production of proinflammatory cytokines. They also used histone deacetylase inhibitors (HDACi) to increase CD20 marker expression on the surface of B- malignant cells by inducing H3K9 acetylation at the CD20 promoter region. The final results showed that the cytotoxicity of CD20-specific CAR-T cells in malignant B cells treated with HDACi was significantly increased compared to the untreated state (211).

CD30 CAR-T Cell Therapy

CD30 (TNFRSF8), a cell membrane protein and tumor marker belonging to the TNF receptor family, is found on the surface of NHL cells including DLBCL, anaplastic large cell lymphoma (ALCL), PMBCL (212), adult T-cell leukemia/lymphoma (213), and peripheral T cell lymphoma (PTCL) (214), as well as in HL, and rare solid tumors (215). So far, this antigen has been widely used as a potential target for antibody-based therapy. One of the most notable results was obtained after treatment of ALCL and HL with an ADC-targeted CD30 (Brentuximab-vedotin/BV) (216). Afterward, CAR-T cells were explored to overcome the challenges posed by antibody-based therapy, such as low tumor penetration and inadequate response durability (217). Recently, the effect of immunotherapy with second CD30-targeted CAR-T cells has been demonstrated in preclinical models and clinical trials. However, after this treatment, no optimal response was observed in the patients, as most of them showed stable disease after multiple CAR-T cell injections. Besides, extra-nodal lesions showed a weaker response than lymph nodes, and T cells lasted only about two months after infusion (218–221). Thus, Guercio et al. demonstrated that using a new third-generation structure designed with the novel scFv, a combination of OX40 and CD28 costimulatory molecules, as

well as the addition of the production process of IL-7 and -15, resulted in prolonged persistence and high proliferation of T cells, and immunological memory to prevent lymphoma recurrence (222).

CD37 CAR-T Cell Therapy

CD37 is a tetraspanin protein that is widely expressed in all types of B-NHL (223). Its biological function is not completely understood, but it may be associated with apoptotic signals and survival as well as tumor suppression (224). Accordingly, CD37 is a potential target for B cell malignancies immunotherapy. So far, several anti-CD37 therapeutic agents have been investigated in phase 1 and 2 trials including a targeting peptide (Otlertuzumab), a mAb (BI836826), a radioimmunoconjugate (Betalutin; ^{177}Lu-lilotomab-satetraxetan), and antibodies-drug conjugate (AGS67E and IMGN529) (225, 226). The preclinical development and efficacy of anti-CD37 CAR-T cells have been recently demonstrated in T- and B cell malignancies (227). The effect and specificity of CD37 CAR-T cells against B-cell lymphoma have already been demonstrated in the mouse lymphoma xenograft models and *in vitro*. It has also been observed that CD37-expressing tumor cells, do not resist CD37 CAR-T cells (228). Koksal et al. developed a second-generation CD37-targeted CAR structure and compared its performance on T cell function in different B lymphoma cell lines with anti-CD19 CAR-T cells. They showed that in one xenograft model of aggressive B-cell lymphoma, both CAR-T cells were equally capable of controlling tumor growth, but in the second xenograft model, using the U2932, a CD19- subpopulation of lymphoma cells, CD37 CAR-T cells dramatically controlled the survival and tumor growth, while CD19 CAR-T cells were much less effective. Overall, the results of their studies showed that CD37 CAR-T cells could be used to eradicate those B-cell lymphoma tumors in which CD19 antigen expression has been lost, and after further investigation for patients with R/R B-NHL (229).

CD38 CAR-T Cell Therapy

CD38, like CD19 due to its wide distribution on B-NHL cells, is an ideal molecular target for the treatment of this malignancy and, as previously reported, so far, no side effects following treatment with anti-CD38 Ab in B cell lymphoma patients has been reported (230). Furthermore, several types of Ab or Anti-CD38 Ab have been used in the treatment of CD38^{+} malignancies (209, 231–233). Recently, Mihara et al. demonstrated that anti-CD38-CAR-T cells have potent cytotoxicity and eradicate B-NHL *in vitro* and *in vivo* (**Table 3**) (234).

CAR-T CELLS TOXICITIES & MANAGEMENT

The observation of some life-menacing toxicities following the activation of the immune system with CAR-T cell therapy limits the widespread use of this therapeutic approach (235). It seems that the degree of toxicity created depends on various factors such as the type of vector, scFv, co-stimulatory domain, CAR-T cells' dose, disease burden, and preconditioning regimen (7). Studies show that in practice, the incidence and severity of toxicity in CAR-T cell products with a CD28 costimulation domain are higher than products containing a 4-1BB domain. Because the CD28 domain leads to the fast and high expansion of CAR-T cells, while the 4-1BB domain leads to gradual expansion and long continuance (236). Cytokine release syndrome (CRS) and neurotoxicity are among the most common toxicities caused by CAR-T cell therapy (237). CRS is a systemic inflammatory response that happens after the secretion of inflammatory cytokines such as IL -1, 2, 6, 10, TNF-α, and IFN-γ from the immune cells and CAR-T cells (238). This toxicity can occur from a few hours to several days after the CAR-T cell inoculation. CRS is characterized by symptoms such as hypotension, high fever, hypoxia, sinus tachycardia, and organ dysfunction (239) and altered laboratory values include significant increases in ferritin, increased CRP, and low fibrinogen (240). Early detection and management are important because some reports indicate death from severe CRS (239). CRS is graded based on the degree of hypoxemia, hemodynamic instability, and organ injury (241, 242). Treatment of CRS depends on the intensity of the signs as well as the patient underlying diseases. Specialists recommend supportive and precise surveillance with fluids for grade 1 CRS. However, for higher-grade CRS, immunosuppressive agents are commonly employed (243). Because IL-6 plays a crucial role in the development of CRS, one of the IL-6 receptor blockers, tocilizumab, is used in patients with higher CRS (244). Corticosteroids are also applied in cases where tocilizumab is incapable to control the symptoms of severe CRS (242). Furthermore, CAR-T cells cause neurologic toxicity, which is called CAR-T cell-related encephalopathy syndrome or CRES and recently this term was replaced by "Immune effector cell-associated neurotoxicity syndrome (ICANS)" (245, 246). Neurotoxicity probably indicates the capability of CAR-T cells to infiltrate into the blood-brain barrier (242). This toxicity can lead to ataxia, mild cognitive defects, tremor, somnolence, dysphagia, obtundation, snoring, and seizures, as well as death in severe cases. The occurrence of neurotoxicity may be simultaneous or independent of CRS (247). Dexamethasone appears to penetrate the blood-brain barrier to some extent reversing neurological symptoms. However, it is unlikely that the monoclonal antibody tocilizumab will penetrate the blood-brain barrier (248). There have been no reports of tocilizumab being effective in this type of toxicity. According to previous studies, steroids are the mainstay of CRS treatment. Other complications of CAR-T cell therapy include infection and cytopenias. In addition, B cell aplasia leads to hypogammaglobulinemia and subsequent recurrent infections due to targeting CD19 present on B lymphocytes. Intravenous immunoglobulin administration in these patients largely helps to control the mentioned symptoms. Due to chemotherapy and malignancy, patients' immune systems are significantly suppressed and they are prone to fungal, bacterial, and viral infections. Prophylactic antibiotics, antiviral and antifungal drugs are used to prevent the spread of infection in these patients (248).

TABLE 3 | The clinical trials of CAR-T cell therapies in T-NHL.

NCT	Study phase	Type	Disease
NCT03081910	1	CD5 CAR-T	R/R lymphoma or leukemia
NCT02963038	I+II	CD19 CAR T	B-NHL+ B-ALL
NCT03068416	II	CD19 CAR T	B-NHL + B-ALL
NCT03146533	I+II	CD19 CAR T	B-NHL
NCT02132624	I	CD19 CAR T	B-NHL
NCT03105336	II	CD19 CAR T	R/R Indolent B-NHL
NCT03676504	I+II	CD19 CAR T	B-NHL + B-ALL
NCT01853631	I	CD19 CAR T	B-NHL + B-ALL
NCT03277729	I+II	CD20 CAR T	R/R B-NHL
NCT03019055	I	CD19/20 CAR T	R/R B-NHL
NCT03448393	I	CD19/22 CAR T	R/R B-NHL or ALL
NCT03233854	I	CD19/22 CAR T	R/R B-NHL or ALL
NCT03330691	I+II	CD19/22 CAR T	R/R lymphoma
NCT02153580	I	CD19/EGFR CAR T	R/R B-NHL
NCT03244306	I	CD22/EGFR CAR T	R/R lymphoma or leukemia
NCT02601313 (ZUMA-2)	II	Axi-cel	MCL
NCT03105336 (ZUMA-5)	II	Axi-cel	MZL, FL
NCT03624036 (ZUMA-8)	I+II	Axi-cel	CLL
NCT04162756 (ZUMA-18)	EA	Axi-cel	MCL
NCT02631044 (TRANSCEND-NHL-001)	I	Liso -cel	FL G3b, MCL
NCT03483103 (PILOT)	II	Liso -cel	FL G3b
NCT03744676 (OUTREACH)	II	Liso -cel	FL G3b
NCT03568461 (ELARA)	II	Tisa-cel	FL
NCT03331198 (TRANSCEND-CLL-004)	I+II	Liso-cel +/- ibrutinib	CLL
NCT03575351 (TRANSFORM)	III	Liso-cel *vs* ASCT	FL G3b
NCT03310619 (PLATFORM)	I+II	Liso-cel + CC-122	FL G3b
		Liso-cel + durvalumab	
NCT03049449	I	CD30 CAR T	R/R lymphoma
NCT02663297	I	CD30 CAR T	Lymphoma s/p auto SCT
NCT02917083	I	CD30 CAR T	R/R lymphoma
NCT02690545	I+II	CD30 CAR T	R/R lymphoma
NCT03602157	I	CD30/CCR4 CAR T	R/R lymphoma
NCT02917083	I	CD30 CAR T	R/R CD30+ HL and NHL
NCT03049449	I	CD30 CAR T	R/R CD30+ HL and NHL
NCT03383965	I	CD30 CAR T	R/R CD30+ HL and NHL
NCT02663297	I	CD30 CAR T	R/R CD30+ HL and NHL
NCT02690545	I+II	CD30 CAR T	R/R CD30+ HL and NHL
NCT02259556	I+II	CD30 CAR T	R/R CD30+ HL and NHL
NCT02958410	I+II	CD30 CAR T	R/R CD30+ HL and NHL

ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; CAR, chimeric antigen receptor; HL, Hodgkin lymphoma; R/R, relapsed/refractory; EA, expanded access; G3b, grade 3b.

Anaphylaxis, tumor lysis syndrome, and hemophagocytic lymphohistiocytosis are among the less common complications after treatment with CAR-T cells (238).

FUTURE DIRECTIONS

At present, anti-CD19 CAR-T cells created a sustainable recovery in 40% of chemotherapy-resistant DLBCL, HGBCL, and PMBCL patients who have not previously received any treatment options. Also, these products are currently used in patients with aggressive lymphoma who have relapsed after at least 2 previous treatment lines. Besides, clinical trials of anti-CD19 CAR-T cells in patients with DLBCL are being considered as a treatment option in the first recurrence. Currently, high-dose chemotherapy with ASCT has been considered as the second line of treatment for DLBCL, and about 20% of patients are treated with this method (249, 250). However, in

many patients, due to resistance to chemotherapy, old age, and the presence of comorbidities diseases, there will be no necessary conditions for such treatment. Additional strategies are needed to overcome mechanisms of resistance to CD19 CAR-T cells, including T cell depletion, loss of target antigen, loss of continuance, and immune escape. Approaches such as combining CAR T cell products with immunomodulating drugs (251), tyrosine kinase inhibitors (252, 253), and immune checkpoint inhibitors (254) have shown promising results *in vitro*. Besides, the novel CAR structures, known as third-generation CARs, greatly enhance the activity of T cells (183). These CAR-T cells include 1) CAR-T cells that target several cancer antigens simultaneously, such as CD19 and CD22, which prevents antigen loss (255), 2) CAR-T cells that directly suppress immune checkpoints (254), 3) CAR-T cells that use gene editing to insert the CAR gene in a position that enhances activation and reduces T cell exhaustion (256), 4) CAR-T-cells secreting cytokines such as IL-12 which may impair the suppressive

function of the tumor microenvironment (257, 258). Finally, new allogeneic products are likely to replace autologous CAR- T cells. Autologous T cell products have limitations such as poor T cell health derived from patients who have already received lymphoma treatments, the time-consuming production process in patients with R/R high-grade lymphoma, and costly process apheresis, bridging, and construction. Allogeneic CAR-T cells may overcome these barriers by using gene-editing technology by removing the T cell receptor from the healthy donor T cell by inserting the CAR gene against the target tumor antigen (259). Allogeneic CAR-T cells are presently being studied in early-stage clinical trials in lymphoma patients. Finally, the possibility of using CAR-T cell technology in T cell lymphoma and solid tumors is expanding. It is important to select a target antigen that is tumor-specific enough because less specific markers increase the destructive immunological attack on healthy tissues from which the malignancy has developed.

CONCLUSION

The current advances in CAR-T cell therapy have presented us with highly efficient solutions aimed at treating patients with NHL. Although the efficacy of CAR-T cells has been proven in previous studies, it is still possible to further improve the effectiveness and speed up the response time. Besides,

neurotoxicity and CRS induced by CAR-T treatment can cause considerable morbidity in patients receiving this type of treatment. Therefore, the use of new treatment strategies such as T cell engagers, targeted molecular therapies, checkpoint inhibitors, and antibody-drug compounds in the conjunction with CAR-T cell treatment not only reduces side effects but also generates positive changes in the treatment of hematologic malignancies like the NHL creates.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and the main idea of the work. FM, SI, HS, MA, KS, WS, WA, MM, NS, and AH drafted the main text, figures, and tables. M.J supervised the work and provided the comments and additional scientific information. MA, MY, RM, YP, and A.C-A also reviewed and revised the text. All authors contributed to the article and approved the submitted version.

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