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Review

Exploring the mechanisms of CD19 CAR T-cell failure and salvage strategies in B-cell lymphoma

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Abstract

Chimeric antigen receptor (CAR) T-cell therapy has emerged as a potential treatment for patients with B-cell lymphoma in whom standard therapy has failed. The U.S. Food and Drug Administration (FDA) has approved anti-CD19 CAR T-cell products for B-cell lymphoma. However, growing experience has shown that treatment has limitations, such as relapses due to tumour mutations or CD19 antigen loss, unexpanded CAR T-cells, and/or poor persistence of CAR T-cells. Understanding the limitations of CAR T-cell therapy is essential to achieve the full potential of this therapeutic strategy. In this review, we analyse factors potentially affecting the efficacy of CAR T-cell therapy, explore the mechanisms of resistance to CD19 CAR T-cell therapy in B-cell lymphoma, and summarise potential strategies to overcome treatment barriers.

Keywords: Anti-CD19 CAR T-cell failure, salvage strategies, B-cell lymphoma

1. INTRODUCTION

CD19 is present on the surfaces of all B lineage cells except plasma cells. Patients with relapsed/refractory (R/R) B-cell lymphoma have poor prognosis [1]. CD19 is a transmembrane protein that is largely restricted to B-cells and most B-lineage malignancies, and plays a critical role in B-cell development and maturation [2, 3]. Anti-CD19 chimeric antigen receptor (CAR) T-cells are an effective treatment for R/R B-cell lymphomas that are CD19 antigen positive. CAR T-cells, unlike normal T-cells, recognise lymphoma independently of the human leukocyte antigen system and then destroy tumours [4, 5].

Axicabatagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with refractory or relapsed disease after two previous treatment regimens for aggressive B-cell non-Hodgkin's lymphomas (NHLs) [6, 7]. Although spectacular results have been achieved with CAR T-cell therapy in the treatment of R/R B-cell lymphoma, with overall response rates ranging from 40% to 83% reported in trials (ZUMA1, TRANSCEND, and JULIET) and real world cohorts, 30–50% of patients eventually develop disease progression or relapse after infusion, usually within 1 year of treatment [8, 9]. In addition, nearly 10–20% of patients do not achieve remission after treatment with anti-CD19 CAR T-cells [8-11]. As CAR T-cell therapies become more common, their limitations must be understood. In this review, we discuss factors influencing the persistence of CAR T-cells, as well as salvage strategies after CD19 CAR T-cell therapies fail.

2. CURRENT STATUS OF CD19 CAR T-CELLS IN THE TREATMENT OF B-CELL LYMPHOMA

The multicentre, single-arm phase I/II study of axi-cel for relapsed or refractory B-NHL (ZUMA-1) showed a treatment objective response rate (ORR) of 83%, including a complete remission rate (CR) of 58%. After a follow-up period of longer than 4 years, the median overall survival (OS) was 25.8 months, with a 4-year OS rate of 44%. The 4-year OS for patients with an event-free survival (EFS) event after month 12 (EFS12; n=57) was 7% (95% confidence interval [CI], 2–16), and that for patients without EFS12 (n=44) was 91% (95% CI, 78–97) [12]. As compared with the ZUMA-1 research baseline, real world research data on axi-cel in Center for

International Blood and Marrow Transplant Research (CIBMTR) groups include a greater proportion of older patients with poor physical fitness scores among 1343 cases of diffuse large B-cell lymphoma (DLBCL), more patients with double-or triple-hit lymphoma, and more patients who had previously received autologous stem cell transplant (ASCT). Curative effects were observed, with an ORR of 73.6% and a CR of 56.1%. The JULIET study data from tisagenlecleucel and CIBMTR (tisa-cel real world study) data show an ORR of 52–59.4% and CR of 40% for R/R B-cell lymphoma. The median follow-up was 40.3 months (n=115), and the progression-free survival (PFS) rates were 33% and 31% at 24 and 36 months, respectively [13]. The results of the NHL001 transfer study of lisocabtagene maraleucel showed an ORR of 73% and a CR rate of 53%.

However, some patients did not achieve remission. A multicentre study has reported outcomes of axicabtagene treatment failure. The median follow-up period was 12.9 months, and disease progression (progressive disease [PD]) occurred in 136 of 275 patients (49%), primarily in patients who did not respond to CAR T-cells, had severe cytokine release syndrome (CRS), and had previously received bridging therapy (BT) [14]. In a study at the Fred Hutchinson Cancer Research Center, the OS was 5.3 months after CAR T-cell failure. The overall prognosis was poor, particularly for patients who experienced disease progression within 30 days of CAR T-cell infusion [15].

3. KILLING MECHANISMS OF CAR T-CELLS

CAR T-cells are have specific antigen receptors whose function is independent of T-cell receptor/peptide-MHC (TCR/pMHC). CAR T-cells permanently attack tumour cells through T-cell activation signals and the CD28 or 4-1BB structural domain [16]. CAR T-cells use three mechanisms to attack cancer cells. Through Fas/Fas ligand mediated lysis of tumour cells and cleavage of granzyme and perforin, activated CAR T-cells perform cytokine-induced killing and enhance anti-tumour activity [17, 18].

4. RESISTANCE MECHANISMS TO CAR T-CELL THERAPY

4.1 T-Cell

4.1.1 CAR T-cell exhaustion. Sustained antigen stimulation leads to T-cell exhaustion, defined as inhibition of T-cell proliferation and effector function, thus resulting in failure of CAR T-cell therapy [19, 20]. CAR T-cell exhaustion may cause CAR T-cell therapy resistance. An increase in exhausted $CD8^+$ T-cells in the apheresis lymphocyte product is associated with non-response and relapse after CAR T-cell treatment [21-23]. High expression of lymphocyte-activated gene-3 (LAG-3) and TIM domain-containing protein-3 (TIM-3) in CAR T-cell infusion products correlates with decreased response to CD19 CAR T-cell therapy and early relapse of DLBCL [22]. In addition, an increase in the frequency of cells expressing LAG-3 and a decreased ability to secrete cytokines after stimulation may decrease antileukemic efficacy and lead to CD19-positive relapse [23]. These results suggest combination opportunities with immuno-oncology agents, such as checkpoint inhibitors, tyrosine kinase inhibitors, and immunomodulatory agents, that could revive persistent CAR T-cells [24].

4.1.2 CAR T-cell phenotype. Initial T-cell phenotype, such as the percentages of $CD4^+$ and $CD8^+$ CAR T-cells, determines the persistence of CAR T-cell responses [25-28]. According to some studies, a 1:1 ratio of $CD4^+CD8^+$ T-cells is optimal for CAR T-cell products [29, 30]. Detailed analysis in the ZUMA-1 trial of axi-cel in large B-cell lymphoma (LBCL) has indicated that the limited number of $CCR7^+CD45RA^+$ or $CD8^+$ T-cells relative to tumour burden is associated with failure to achieve a durable response. Moreover, the number of infused $CCR7^+CD45RA1^+$ T-cells is associated with objective response and peak CAR T-cells [31]. CAR T-cell production can be optimised by selection and enrichment of T-cells before production of CAR T-cells [32-34].

4.1.3 Other possible influencing factors. Other factors that may influence the persistence of CAR T-cell expansion in vivo include aberrant signalling pathways within CAR T-cells and the interaction between CAR T-cells and tumour cells [35, 36]. Abnormal apoptotic pathways are another mechanism affecting CAR T-cell toxicity. In addition, T-cell subpopulations continue to change with age [37, 38].

4.2 CAR construct design

CAR construct design is another parameter likely to affect the properties of CAR T-cell products, and their expansion kinetics and duration of persistence in vivo [39].

The four major components of CARs are the extracellular antigen-binding domain, the hinge region, the transmembrane domain, and the intracellular signalling domain. The targeted antigen-binding domain of CARs requires high affinity but cannot induce toxicity in T-cells [40, 41]. The hinge region is also important, and its composition and length affect the recognition of antigenic epitopes [42, 43]. CAR transmembrane structural domains affect CAR expression and stability [44-46]. Intracellular signalling domains significantly affect the persistence of cellular products [39]. CD28 and 4-1BB are the two co-stimulatory structural domain choices used in most preclinical and clinical studies. CD19-28ζ T-cells exhibit strong functional potential and expansion, but are rapidly depleted after expansion, whereas CD19-BBζ T-cells have better persistence. The median CD19-BBζ and CD19-28ζ $CD19^+$ relapse rates are 16.7% and 22.7%, respectively [47].

4.3 CAR immunogenicity

Compared with mouse-derived CAR T-cells, humanised CAR T-cells have similar anti-tumour effects but are less immunogenic and more durable [48-50]. Moreover, CAR immunogenicity can be decreased by modification of the hinge region and transmembrane structural domains [49, 51].

4.4 Tumour mutations

CD19 antigen-negative recurrence may be associated with tumour mutations in response to immune stress. The mechanisms are as follows:

- Acquired CD19 shift mutations [52]
- Selective splicing of CD19 antigen [53]
- Downregulation of CD19 antigen density [54]
- CD19 negative subclones already present at diagnosis; recurrence of negative subclones when CD19 positive clones are cleared [39]
- Altered tumour spectrum [55]

4.5 Immunosuppressive microenvironment

Systemic inflammation is likely to be due to immune system dysregulation caused by tumours and the tumour microenvironment (TME), inadequate expansion of axial cells, and ultimately treatment failure. In the TME, many cell types, including myeloid-derived suppressor cells (MDSCs), regulatory T-cells, and tumour-associated macrophages, can cause immune suppression [56]. Programmed cell death protein-1 (PD-1) on the surfaces of tumour-specific T-cells binds programmed cell death-ligand 1 (PD-L1) on the surfaces of tumour-associated macrophages or MDSCs in the TME, thus triggering apoptosis and depletion of lymphocytes in tumour tissue [57]. Studies have shown that CAR T-cell expansion and a low sustained response rate may be associated with high IFN signalling in the TME and high levels of circulating MDSCs [58].

4.6 Recipient-associated factors

4.6.1 Tumour burden. Disease burden may positively influence the degree of cell expansion [10, 11] and the immunological microenvironment [39, 58]. A study by the American CAR T-Cell Consortium has suggested that high preinfusion lactate dehydrogenase (LDH) levels significantly contribute to poor survival outcomes [59]. Published data from ZUMA-1 suggest that a high baseline tumour burden decreases durable response rates [60]. A retrospective multivariate study conducted in France has found that patients with LBCL with extensive disease (metabolic tumour volume, mean tumour volume (MTV) greater than 80.42 ml) and two or more extranodal lesions are more likely to experience disease progression than those without these two factors after treatment with CAR T-cell therapy (axi-cel and tisa-cel) [61]. In another study, 273 adults with R/R LBCL from two centres were treated with CD19 CAR T-cells with axi-cel [98, 36%], tisa-cel [76, 28%], and lisocabtagen-maraleucel [28, 10%]. In multivariate analysis, bulky disease at apheresis (HR 2.05 [1.07–3.95], P=0.031) has been associated with poorer OS [62].

4.6.2 Bridging therapy (BT). Patients requiring BT have poorer PFS and OS without relapse and increased mortality. Possible reasons include more advanced disease condition in patients receiving BT, e.g., more patients with stage III/IV, International Prognostic Index (IPI) score ≥3, elevated LDH and extensive disease [63, 64]. Immunosuppression is further aggravated by haemocytopenia after BT [63].

4.6.3 Lymphodepletion before CAR T-cell infusion. Lymphodepletion is also important for CAR T-cell expansion, and certain chemotherapeutic agents such as fludarabine may be effective in lymphodepletion [29].

4.6.4 Previous treatment. Cytotoxic therapy before CAR T-cell therapy results in lymphopoenia: sufficient T-cells for CAR T-cell therapy cannot be collected in 79% of patients [65]. In addition, chemotherapy before CAR T-cell therapy may disrupt the metabolic pathways of T-cells in vivo, thus further affecting the durable persistent reactivity of CAR T-cells [66]. Clinical studies have shown that the use of cytarabine and cyclophosphamide decreases early phenotypic T-cell subsets, and differences in T-cell subsets are associated with expansion of CAR T-cells [65].

4.6.5 Severe cytokine release syndrome and other toxicities. Severe CRS and other toxicities pose obstacles to the efficacy of CAR T-cell therapy. Whether long-term steroid use affects the efficacy of CAR T-cell therapy in patients who experience severe CRS reactions requires further investigation [39].

5. CURRENT SALVAGE STRATEGIES FOR CD19 CAR T-CELL FAILURE

Currently, no standard regimen exists for LBCL after CAR T-cell failure.

5.1 Combination therapy with targeted agents

A small sample study has indicated that in patients with PD after CAR T-cell therapy, five patients who received BTK inhibitors (BTKi) had non-germinal center B-cell (non-GCB) cells of origin. The ORR and CRs were 50% and 38% for BTKi. The median PFS was 1.2 mo for BTKi (n=8). BTKi may be attributed a immunomodulatory effect on previously CARTs [67]. The exact mechanism of the synergistic effects of BTKi and CAR T-cells is unclear. Ibrutinib treatment significantly increases the implantation and expansion of CAR T-cells, decreases expression of immunosuppressive PD-1 and CD200, and enhances their cytotoxic activity [68].

5.2 Immunomodulatory therapies

5.2.1 Immune checkpoint inhibitors. Preclinical data have shown that PD-1/PD-L1 inhibitors increase the

efficacy of CAR T-cell therapy [69, 70]. Blocking the PD-1/PD-L1 pathway helps restore the functions of $CD8^+$ effector T-cells, while inhibiting the function of regulatory T-cells and MDSCs and enhancing the anti-tumour effects [57]. One study has reported an ORR of 27% (one partial remission (PR) and two CR cases) in 11 cases of lymphoma relapsed after CAR T-cell treatment after a single infusion of pembrolizumab, and the American CAR T-cell Consortium has reported a similar trend [15]. This previous study showed that the median time to the first dose of pembrolizumab was 3.3 months (range: 0.4–42.8 months). Of 12 patients, nine had a re-expansion peak of CART19 cells in peripheral blood (CART19 transgene copy number) between days 2 and 14 (median 3 days) after the first pembrolizumab dose. Responsive patients had more than one re-expansion peak during pembrolizumab treatment, whereas non-responsive patients had only a single re-expansion peak or no expansion after the first pembrolizumab dose. After treatment with pembrolizumab, grade 3 CRS occurred in one patient, and grade 3 neutropoenia was observed in three patients [15]. The ZUMA-6 study is a phase I study evaluating the PD-L1 inhibitor atezumab in combination with axi-cel at different time points. However, no positive results have been found to date [61]. Clinical studies have examined cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibodies, such as ipilimumab, for their role in enhancing the efficacy of CAR T-cell therapy [71].

5.2.2 Lenalidomide-based therapies. Combined use of lenalidomide (LEN) at the time of cell expansion after CAR T-cell transfusion increases the efficacy of CAR T-cell treatment in patients at high risk of relapse. One study has reported failure in 59 patients after CAR T-cell infusion including tisa-cel (n=33) or axi-cel (n=26). A higher ORR (7/11, 63.6%) and CR rate (4/11, 36.4%) have been observed in 11 patients receiving combined LEN within day (D) 15 after CAR T-cell infusion. In addition, six of the evaluable patients with LEN (≤D15) had a higher expansion rate of CAR T-cells in the blood in the first 28 days after CAR T-cell infusion (P=0.042) than the other patients, including patients with combined treatment with LEN after D15 (P=0.033) [72].

Another study has reached a similar conclusion: among the 36 patients who relapsed after CAR T-cell infusion in the first month, LEN was initiated in 17 patients before D15. The PFS was significantly longer than that in other patients, with a median of 68 days (95% CI, 52, not reached) compared with 35 days (95% CI, 28–70) (P=0.035). In univariate analysis, 13 patients with early combination LEN had higher CAR T-cell expansion in the blood during the first 28 days than the other patients [73].

In a National Cancer Institute study, several drugs including venetoclax, ibrutinib, obinutuzumab, and LEN (Vipor) have been combined for six cycles of 21 days each to assess the efficacy. The following treatments were administered: venetoclax at four dose levels (200 mg, 400 mg, 600 mg and 800 mg) peros (PO) on D2–14, ibrutinib 560 mg PO on D1–14, prednisolone PO 100 mg on D1–7, obinutuzumab IV 1000 mg on D1–2, and LEN 15 mg PO on D1–14. The ten patients in whom CAR T-cell therapy failed had an ORR of 40% and a CR of 30% [74].

5.3 Noncellular immunotherapeutic approaches

5.3.1 Loncastuximab. Loncastuximab tesirine is a humanised anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine dimer toxin as an antibody drug conjugate (ADC). The open-label, single-arm LOTIS-2 trial applied loncastuximab tesirine monotherapy to 145 patients with R/R LBCL. The recommended dosage was 0.15 mg/kg every 3 weeks for two cycles, and 0.075 mg/kg every 3 weeks for each subsequent cycle. Of particular note, the ORR in 13 patients in whom CD19 CAR T-cell therapy failed was 46.2%. Among all patients, adverse events such as anaemia and neutropoenia, and non-haematological events such as fatigue and nausea, were common after administration [75, 76]. Because biopsy to assess CD19 expression was required in patients who had previously received CD19-targeted therapy, these preliminary results are limited to patients in whom CD19 expression was maintained [75].

5.3.2 Polatuzumab vedotin. Polatuzumab vedotin (PV) is an ADC consisting of an anti-CD79b mAb and an antimitotic agent called mono-methyl auristatin E, which has been approved for patients with R/R LBCL. Studies of CD19 CAR T-cell treatment failure have shown that, among all patients receiving further treatment, PV-based therapy was associated with the highest ORR (52–73%) and CR(35–40%) in patients with PD [67, 77]. Chemotherapy was associated with the poorest survival (6-month OS 25%; 95% CI, 11–59), whereas PV-based treatment was associated with a survival of 67% (50–89%) [77]. The median PFS was highest with polatuzumab vedotin combined with bendamustine and rituximab (PBR) (8.9 months, n=14) [67, 77]. The three factors associated with OS prognosis were age ≥65 years, bulky disease at apheresis, and CAR T-cell refractory disease [77]. A multicentre retrospective analysis has assessed the efficacy of PV-based treatment in 57 patients with LBCL who relapsed or progressed after CAR T-cell therapy. Patients received PV 1.8 mg/kg intravenously (IV) every 3 weeks, and the number of patients treated with the combination of PV and rituximab or PV and bendamustine was 45 (95%) and 35 (61%), respectively. Treatment was effective in 25 patients (44%), of whom 8 (14%) achieved CR. The median follow-up was 47 weeks (95% CI, 40–54), and the median PFS was 10 weeks (95% CI, 5–15). Multifactorial analysis showed that the two factors associated with shorter PFS were bone marrow involvement (HR 5.2; 95% CI, 1.8–15; P=0.003) and elevated LDH (HR, 5.0; 95% CI, 1.4–16; P=0.01) [78].

5.3.3 CD22-ADC. TRPH-222 contains an antibody directed against CD22 and the antimitotic agent metformin, which has been tested in R/R LBCL. TRPH-222-100 was an open-label, multicentre dose-escalation study followed by a dose-extension phase (from 0.6 to 10 mg/kg). A total of 22 patients were enrolled in the study, including four previously treated with CAR T. Five CR and one PR were observed at doses ranging from 0.6 to 5.6 mg/kg at the end of cycle 6. TRPH-222 was well tolerated and caused a low incidence of adverse reactions including thrombocytopoenia, neutropoenia, and peripheral neuropathy [79].

5.3.4 CD3-CD20 bispecifc antibody. CD3-CD20 bispecifc antibodies have relatively long half-lives and appear to offer higher response rates in R/R B-cell lymphomas [80]. In addition, CD3-CD20 bispecifc antibodies have the potential to circumvent the shortcomings of CAR T-cells while achieving high response rates. Mosunetuzumab is a full-length, fully humanised IgG1 bispecific antibody targeting both CD3 and CD20. GO29781 is an open-label, multicentre, phase I/Ib study in R/R B-cell NHL, administering mosunetuzumab with step-up dosing on days 1, 8, and 15 of cycle 1, and then on D 1 of each subsequent 21-D cycle. A total of 16 patients who had received prior CAR-T therapy were evaluable for efficacy (seven DLBCL, five transformed follicular cell lymphoma [tr FL], and four follicular cell lymphoma [FL]). The ORR and CR rates were 43.8% (7/16) and 25.0% (4/16, two DLBCL, and two FL), respectively. Quantitative PCR detected the expansion of prior CAR T-cells after administration. CRS was observed in 28.4%, and Gr 3 CRS occurred in 1.4% of patients. Neurological adverse events were reported in 44% of patients (Gr 1, 28.0%; Gr 2, 12.8%; Gr 3, 3.2%) [80]. Another study targeting the CD3-CD20 antibody (REGN1979) included three cases of DLBCL that had relapsed after CAR T-cell treatment, thus resulting in two of three CRs with REGN1979 at doses of 80/160/320 mg, consisting of 12 weekly IV doses followed by administration at 2-week intervals for 12 doses (36 weeks total) [81]. Gloftamab (RG6026) is also a candidate for the treatment of CD19 CAR T-cell failure [61]. Epcoritamab (GEN3013) has been reported to elicit three objective responses in four relapsed DLBCL cases after CAR T-cell therapy [82].

5.4 Cellular immunotherapeutic approaches

5.4.1 CD19 CAR T-cell reinfusion. Several studies have shown that the use of an intensive lymphodepletion regimen increases the expansion and persistence of initial CAR T-cells [83]. In ZUMA-1, CD19 CAR T-cells were reinfused in patients who had responded to treatment and were still CD19 positive after relapse. Of the 13 patients, 54% had an ORR, with four CR and three PR. The median time to remission was 81 days, and two patients were still in remission at the last follow-up. The Fred Hutchinson Cancer Research Center has shown an ORR of 39%, with CR achieved in 20% (44 patients) with LCBL after CAR T-cell recurrence. The addition of fludarabine to the second conditioning and the infusion of a higher CAR T-cell dose were both associated with an achievable durable response [84].

5.4.2 Replacement of humanised CD19 CARs. A clinical trial (NCT02374333) is currently underway to humanise CD19 CARs to overcome rejection of the murine-derived anti-CD19 construct [85].

5.4.3 Alternative CARs targeting other B-cell markers. Preliminary results of an autologous 41BB CAR T-cell treatment with LBCL against CD22 have recently been reported. The trial incorporated three patients who relapsed on CD19 CAR T-cell treatment and were treated with a single infusion of autologous 1×10^6 $CAR22^+$ T-cells/kg and showed an ORR of 100%, with one CR and two PRs, at the time of the last follow-up (mean, 7.8 months; range, 6–9.3). CD22 CAR T-cell therapy was well tolerated, without any nonhematologic adverse events higher than grade 2 [86].

CD37 CAR T-cells can be used to treat B-cell lymphomas lacking CD19 antigen expression [87]. Moreover anti-CD38 CAR T-cells exhibit potent cytotoxicity against B-NHL both in vitro and in vivo [88].

5.4.4 Bispecific CARs or dual targeted CAR T-cells. The ORR for CD19-CD22 dual-targeted CAR T-cell therapy in 11 patients with B-NHL (DLBCL, mantle cell lymphoma [MCL], or chronic lymphocytic leukemia [CLL]) has been found to be 82% [89]. AUTO3, also a CD22-CD19 dual-targeted CAR T-cell type, has shown significant activity in a phase I/II study in R/R DLBCL (n=23), with an ORR of 65% (CR=48%) [90]. Multi-target preclinical studies of CAR T-cells have included targeting of CD19-CD20, CD19 and CD22 [91], and several clinical trials of these strategies are ongoing.

5.4.5 Universal CAR T-cell approaches and CAR-NK. If the reason for the failure of CD19 CAR T-cell therapy is a patient's T-lymphocyte dysfunction, universal CAR T-cell salvage therapy may be an option. Several research groups are investigating donor-based CAR T-cell therapy. Donor-derived CAR T-cells and gene-edited "off-the-shelf" universal CAR T-cells are under active development [92, 93]. Results have shown a low incidence of grade III or IV graft-versus-host disease [94-96].

Other potential advantages of include different cytokine responses between CAR natural killer (NK) cells and CAR T-cells [97, 98]. Allogeneic natural killer cells (NK-CARs) are another immune cellular platform that has several advantages over allogeneic CAR T-cells: they can be selected from cord blood or healthy donors who are HLA mismatched with the recipient, do not cause graft-versus-host disease, and are less susceptible to the inhibitory effects of TME [99].

5.5 Allogeneic hematopoietic stem cell transplantation

In one study, 12 patients who relapsed after treatment with CD19 CAR T-cells subsequently underwent allogeneic hematopoietic stem cell transplantation (alloHSCT). The mean age was 59 years (41–68); one patient (8.3%) had already received alloHSCT, and six (50%) had received autologous HSCT. The best response rates of CR and PR to CAR T-cells were 50% and 25%, respectively [67]. Another study has reported high response rates in patients who received alloHCT, because of their young age, with an ORR of 73% and an OS of 70% at 6 months [77]. In a study of CD19 CAR T-cell treatment failure in patients with B-cell acute lymphoblastic leukemia (B-ALL), only 40% of patients responded to salvage treatment, and the remission duration was short, with a median of 5.8 months, despite subsequent consolidative alloHSCT [100]. AlloHCT remains a potentially curative therapy for selected patients, more than half of whom achieve durable remission; however, few patients receive alloHCT.

6. CONCLUSIONS

CAR T-cell therapy is one of the most promising lymphoma treatments ever developed. With the U.S. FDA approval of multiple commercial CAR T-cells for clinical use, the landscape of R/R B-cell lymphoma treatment has evolved rapidly in recent years. As more experience is gained with these therapies, the understanding and treatment of relapse after CAR T-cell therapy will improve. Various aspects of CAR T-cell treatment can be considered to find ways to improve outcomes, such as how to select patients, how to improve CAR T-cell characteristics, and how to improve the potential for subsequent T-cell expansion [39].

Re-biopsy should be the first step after relapse of CAR T-cell therapy, if possible, to confirm the diagnosis and perform evaluation through molecular studies [101-103]. Similarly to multi-agent chemotherapy, strategies targeting multiple antigens could address these relapse mechanisms, thus providing a pathway to more durable remission. CAR T-cell therapy has synergistic effects in combination with immune checkpoint inhibitors or other immunomodulatory therapies, and may clinically improve the speed of response, and the depth and duration of treatment [104].

Pola-BR elicits a high ORR rate and PFS. Loncastuximab tesirine may be available for R/R DLBCL, particularly for patients who relapse after CAR T-cell therapy. Consistently, bispecifc antibodies appear to be effective after CAR T-cell failure. Dual and tandem CAR T-cell therapy has the potential to overcome resistance to CAR T-cell therapy and prolong survival. Allogeneic NK-CARs provide another immune cell platform [13]. Finally, for patients who have regained effective treatment after CAR T-cell failure, consolidation with autologous or allogeneic transplantation may be considered [105, 106]. Future studies should prospectively investigate the optimal sequence of antibody-based and cellular immunotherapies and develop strategies to decrease relapse and increase survival after CD19 CAR T-cell therapy [107, 108].

ABBREVIATIONS

ADC:	antibody drug conjugate
alloHSCT:	allogeneic hematopoietic stem cell transplantation
ASCT:	autologous stem cell transplant
axi-cel:	Axicabatagene ciloleucel
B-ALL:	B-cell acute lymphoblastic leukemia
BT:	bridging therapy
BTKi:	BTK inhibitors
CAR:	Chimeric antigen receptor
CI:	confidence interval
CIBMTR:	Center for International Blood and Marrow Transplant Research
CLL:	chronic lymphocytic leukemia
CR:	complete remission rate
CRS:	cytokine release syndrome
CTLA-4:	cytotoxic T-lymphocyte-associated antigen-4
D:	day
DLBCL:	diffuse large B-cell lymphoma
EFS:	event-free survival
FDA:	Food and Drug Administration
FL:	Follicular cell lymphoma
IPI:	International Prognostic Index
IV:	Intravenous
LAG-3:	lymphocyte-activated gene-3
LBCL:	large B-cell lymphoma
LDH:	lactate dehydrogenase
LEN:	lenalidomide
MCL:	mantle cell lymphoma
MDSC:	Myeloid-derived suppressor cells
MTV:	mean tumour volume
NHL:	non-Hodgkin's lymphoma
NK:	natural killer
ORR:	objective response rate
OS:	overall survival
PD:	progressive disease
PD-1:	programmed cell death protein-1
PD-L1:	Programmed cell death-ligand 1
PFS:	progression-free survival
PO:	peros
PBR:	Polatuzumab vedotin combined with bendamustine and rituximab
PR:	partial remission
PV:	Polatuzumab vedotin
R/R:	relapsed/refractory
TCR/pMHC:	T-cell receptor/peptide-MHC
tisa-cel:	Tisagenlecleucel
TIM-3:	TIM domain-containing protein-3
TME:	tumor microenvironment
tr FL:	Transformed follicular cell lymphoma

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