REVIEW

The breakthrough and the future: CD20 chimeric antigen receptor T-cell therapy for hematologic malignancies

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Abstract
Chimeric antigen receptors (CAR) T-cell therapy is one of the most effective treatments in curing hematologic malignancies. Besides the four CD19 CAR T-cells therapy recently approved by the US Food and Drug Administration (FDA), CD20 CAR T-cell therapy is now another effective treatment option for relapsed or refractory non-Hodgkin lymphoma (NHL). CD20 CAR T-cell infusion has achieved remarkable clinical outcomes in patients with B-cell malignancies. This review will cover the current situations, advantages, limitations, prospects, and application of CD20 CAR T-cell therapy.

KEYWORDS
CD20, chimeric antigen receptor (CAR) T-cells, immunotherapy, non-Hodgkin lymphoma (NHL)

1 INTRODUCTION

In recent years, targeted therapies and immunotherapy, especially chimeric antigen receptor (CAR) T-cell therapy, have been widely introduced to cure hematological cancers. Nearly half of the clinical CAR-T trials are conducted in China. The first US Food and Drug Administration (FDA)'s approved treatment is CD19 CAR T-cells to treat acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL). The other target CAR antigens like CD20, CD22, CD30, CD33, CD123, and BCMA are currently being studied.

One of the most common B-cells hematologic malignancies, non-Hodgkin lymphoma (NHL) (accounted for approximately 85%), is characterized by high fatality and a dismal prognosis. More recently, CD20 CAR T-cells have effectively treated relapsed or refractory NHL patients. CD20 is a tetra-transmembrane protein that primarily expresses on mature B-cells and malignant B-cells but not in early B-cell progenitors or later mature plasma cells. CD20 plays a vital role in developing B-cells’ differentiation and development into plasma cells, which actively participate in B-cell activation and proliferation. It presents in more than 90% of B-cell lymphomas, making it a perfect target molecule for NHL.

The standard regimen, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), benefited almost 50% of the newly diagnosed NHL patients. However, at least one-third of the patients remained in partial remission (PR), relapsed, or refractory due to cancer stem cells' resistance to standard chemotherapy. Fortunately, CD20 CAR T-cell therapy works effectively for relapsed or refractory NHL patients who have failed the previous chemotherapy. Therefore, CD20 CAR T-cell is efficient in fighting hematological malignancies.

Nevertheless, the CD20 CAR T-cell therapy has several limitations in its modality and some foreseen obstacles to overcome to improve its clinical efficacy and usage. In this review, we will further discuss the advantages of CD20 CAR T-cell, the limitation of CD20 CAR T-cell therapy, the adverse effects of this treatment, and its future perspectives.

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CAR-T CELL THERAPY: HOW DOES IT WORK?

The CAR-T CELL are genetically engineered T-cells to target receptor proteins expressed explicitly on tumor cells. They are chimeric as each of the receptors combines the T-cell activation and antigen-binding sites. These receptors efficiently direct T-cells to tumor cells' surface antigens to initiate cytotoxic activity.

The ideal targets for CAR-modified T-cells are those receptor proteins expressed on tumor cells but not normal cells. CD19 mainly appears on B-lymphocyte, while CD20 on 90% of B-cell lymphomas. Thus, CD19 and CD20 are the perfect targets for B-cell malignancies treatment due to their specificity in B cell lineage. It is worth noting that other target antigens such as CD30 and CD138 are proved to be valid. CARs targeting CD20, CD22, CD30, and κ light chains are aimed to treat patients with Hodgkin lymphoma, T-cell lymphoma, or CD19-negative B-cell lymphoma.

In a study conducted by Locke et al., the long-term follow-up of phase I/II ZUMA-1 clinical trial using Axicabtagene ciloleucel has reported an objective response rate (ORR) of 83% and a complete response rate (CRR) of 58% in relapsed/refractory DLBCL for more than 2 years. However, some clinical cases reported the emergence of CD19 (−) negative tumor cells as they are vulnerable to antigen escape. Therefore, new multi-targeted CARs are invented to prevent resistance. The outcomes in the studies are satisfying for patients with relapsed, refractory B-cell NHL, multiple myeloma (MM), and B-cell ALL.

UNDERSTANDING CD20 CAR T-CELL THERAPY AND ITS ADVANTAGES

CD20 CAR T-cell therapy has been widely introduced as CD20 is one of the pan-B cell markers that appear in more than 90% of B-cell lymphomas. The available CAR T-cell clinical trials mainly emphasize CD19 and CD20 antigens as the target molecules in B cell malignancies. Unlike CD19, CD20 does not express on early B-cell progenitors or later mature plasma cells. However, CD20 antigen expression is remained controversial due to its prognostic value. Though the exact role of CD20 remains unclear, it helps exhaust the B-cell compartment, so it has become a cornerstone in treating B-cell lymphoma.

CD20 CAR T-cells have been used in patients with advanced B-cell lymphomas and have achieved excellent outcomes. For instance, the second-generation CD20 CAR T-cells containing co-stimulatory endodomain, CD28 or 4-1BB, were used in another pilot trial by Till et al. Based on the clinical observations in this pilot trial, three patients remained stable, and there were only minimal lesions observed in these patients. It affirmed the effectiveness of CD20 CAR T-cells.

Moreover, in the phase IIa trial, 11 patients with refractory or relapsed CD20 positive B-cell lymphoma were enrolled. Seven received conditioning therapy to deplete the body's lymphocytes before the autologous anti-CD20 CAR T-cells were administered. According to the study, six patients achieved complete remission (CR), and another three achieved PR. The overall ORR was 81.8%, and no severe toxicity was observed. Furthermore, one of the patients continuously achieved 27 months of CR, and the median progression-free survival for the rest of the patients persisted for more than 6 months. Besides, Till's team has also conducted a pilot clinical trial with third-generation CD20 CAR T-cell coupled with co-stimulatory domains CD28 and 4-1BB in patients with relapsed indolent B-cell and mantle cell lymphomas. Two patients remained progression-free for 1 and 2 years, respectively.

Besides its effectiveness in treating B-cell malignancies in those proven studies, CD20 CAR-T cells therapy is also proven to be easily recognized even in considerably low antigen expression. It only required a minimum number of antigen molecules to activate CAR-T cells. Therefore, CD20 CAR T-cells therapy may work efficiently for patients with CD20 downregulated lymphoma or those with refractory to CD20 monoclonal antibodies (mAbs) therapy. The ongoing and completed clinical trials of single CD20 CAR T-cell therapy for hematologic malignancies are summarized in Table 1.

THE LIMITATIONS OF CD20 CAR T-CELL THERAPY

There are some limitations in CD20 CAR T-cells therapy worth noting. Firstly, CAR T-cell therapy is usually applied to patients with refractory or relapsed hematologic cancers. Thus, most patients had undergone various therapies before administering CAR T-cells into their bodies. CD20 CAR T-cells therapy is effective for NHL patients. The R-CHOP treatment regimen has prominently improved the overall survival (OS), complete response (CR), and event-free survival (EFS) in these patients with NHL. However, about 30%–40% of patients experienced relapse or progression of the disease, though R-CHOP was prescribed.

The anti-CD20 mAb, namely rituximab, is being conventionally added to the R-CHOP chemotherapy regimen. This anti-CD20 antibody therapy may exhaust normal CD20 positive B cells and reduce circulating B-cell numbers. Also, it might be concerning as rituximab would induce CD20-negative tumor cell production. The CD20 antigen loss or reduction might lead to CD20 CAR T-cell treatment resistance. Nevertheless, some studies depicted that the number of CD20+ B-cells remained stable or slightly increased, although B-cell counts fluctuated during CAR T-cell infusions. However, the mechanism of the antigen loss is yet to be investigated.

Secondly, CD20 antigens are predominantly expressed on mature B-cells and malignant B-cells but are less likely to be exhibited on early B-cell progenitors or later mature plasma cells. Thus, its treatment efficacy might be limited due to its antigen nature. The limitation of CD20 antigen presentation might restrict the establishment of CD20 CART therapy in certain hematologic diseases. For instance, the CD20 antigen is highly expressed in NHL patients. Thus, CD20 CAR T-cells work perfectly for NHL. Meanwhile, for ALL patients, the CD20 antigen presentation is relatively low. Therefore, CD20 CART therapy is not recommended for ALL patients.
### TABLE 1  Recruiting and completed CD20 CAR-T clinical trials for hematological malignancies

| No. | Topics                                                                 | Clinical trial number | Conditions                                                                 | Interventions                                               | Status       | Phase       | Sponsors                                                   |
|-----|------------------------------------------------------------------------|------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------|--------------|-------------|------------------------------------------------------------|
| 1.  | The Clinical Study of CD20 CAR-T Cells in Patients with Relapsed and Refractory B Cell Non-Hodgkin Lymphoma | NCT04169932            | Relapsed and refractory B cell lymphoma or non-Hodgkin lymphoma             | Biological: CD20 CAR-T                                       | Recruiting   | Early Phase 1 | Shanghai Longyao Biotechnology Inc., Ltd.                  |
| 2.  | Sequential Treatment with CD20/CD22/CD10-CART after CD19-CART Treatment Based on MRD in Relapsed/Refractory B-ALL | NCT03407859            | Therapy related leukemia                                                   | Biological: Sequential Treatment With different CART         | Recruiting   | Early Phase 1 | Zhujiang Hospital, Nanfang Hospital of Southern Medical University |
| 3.  | CAR-T Immunotherapy Targeting CD19-ALL                                  | NCT04016129            | B-cell leukemia                                                            | Biological: 4SCAR-CD22/CD123/CD38/CD10/CD20/TSLPR           | Recruiting   | Phase 1/Phase 2 | Shenzhen Geno-Immune Medical Institute                     |
| 4.  | DALY 2.0 USA/MB-CART2019.1 for DLBCL                                    | NCT04792489            | Diffuse large B-cell lymphoma (DLBCL)                                       | Biological: MB-CART2019.1                                    | Recruiting   | Phase 2      | Miltenyi Biomedicine GmbH                                |
| 5.  | Decitabine-primed Tandem CD19/CD20 CAR T Cells Plus Epigenetic Agents in Aggressive r/r B-NHL with Huge Tumor Burden | NCT04553393            | Refractory or relapsed aggressive r/r B-NHL with huge tumor burden         | Drug: Chidamide, Decitabine, Chidamide and Decitabine        | Recruiting   | Phase 1/Phase 2 | Chinese PLA General Hospital                              |
| 6.  | Decitabine-primed Tandem CD19/CD20 CAR T Cells Treatment in r/r B-NHL  | NCT04697940            | Relapse and refractory B-cell non-Hodgkin’s lymphoma                       | Biological: Decitabine-primed Tandem CAR19/20 engineered T cells | Recruiting   | Phase 1/Phase 2 | Chinese PLA General Hospital                              |
| 7.  | Efficacy and Safety of MB-CART2019.1 vs. SoC in Lymphoma Patients       | NCT04844866            | Diffuse large B-cell lymphoma                                              | Genetic: MB-CART2019.1|Drug: R-GemOx or BR plus polatuzumab vedotin | Recruiting   | Phase 2      | Miltenyi Biomedicine GmbH/ICON plc                        |

(Continues)
| No. | Topics                                                                                                                                  | Clinical trial number | Conditions                                                                                                                             | Interventions                                                                                                           | Status       | Phase    | Sponsors                                                                                           |
|-----|----------------------------------------------------------------------------------------------------------------------------------------|------------------------|---------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|--------------|----------|--------------------------------------------------------------------------------------------------|
| 8.  | Safety of Autologous Humanized Anti-CD19 and Anti-CD20 Dual Specific CART Cells in Adult Patients with Diffuse Large B-cell Lymphoma         | NCT04215016            | Relapsed or refractory DLBCL patients with either CD19 or CD20 positive                                                          | Biological: Autologous humanized anti-CD19 and anti-CD20 dual-specific CART Cells                                      | Recruiting   | Phase 1  | Fujian Medical University                                                                       |
| 9.  | CAR-T CD19/CD20 for Patients with Advanced CD19/CD20+ B Cell Line Recurrent or Refractory Hematological Malignancies                   | NCT04700319            | Relapsed or refractory CD19/CD20 positive B cell line hematological malignancies                                                    | Drug: CD19/CD20 CAR-T cell infusion                                                                                   | Recruiting   | Early Phase 1 | PersonGen BioTherapeutics (Suzhou) Co., Ltd/Anhui Provincial Hospital |
| 10. | Modified Immune Cells (CD19/CD20 CAR-T Cells) in Treating Patients with Recurrent or Refractory B-Cell Lymphoma or Chronic Lymphocytic Leukemia | NCT04007029            | CD 19 positive/CD20 positive recurrent chronic lymphocytic leukemia, recurrent diffuse large B-cell lymphoma, recurrent mantle cell lymphoma, recurrent primary mediastinal (thymic) large B-cell lymphoma, recurrent small lymphocytic lymphoma, refractory chronic lymphocytic leukemia, refractory diffuse large B-cell lymphoma, refractory follicular lymphoma, refractory mantle cell lymphoma, refractory primary mediastinal (thymic) large B-cell lymphoma, refractory small lymphocytic lymphoma | Biological: Chimeric Antigen Receptor T-Cell Therapy|Drug: Cyclophosphamide|Drug: Fludarabine|Phosphate|Biological: Tocilizumab                                                                             | Recruiting   | Phase 1  | Jonsson Comprehensive Cancer Center/Parker Institute for Cancer Immunotherapy                 |
| 11. | Multi-CAR-T Cells Targeting B Cell Lymphomas                                                                                           | NCT04429438            | B cell lymphoma (BCL)                                                                                                               | Biological: 4SCAR19 and 4SCAR20/22/70/PSMA/13/79b/GD2                                                              | Recruiting   | Phase 1/Phase 2 | Shenzhen Geno-Immune Medical Institute, The Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen Children's Hospital |
Moreover, the efficiency of CD20 CAR-T is hugely influenced by the tumor microenvironment of the T-cells, especially for solid tumors. These tumor cells are highly heterogeneous. Worse still, these negative influences such as the upregulation of the immune target molecules like PD-1/PD-L1 and PD-L2, the presence of suppressive cytokines (TGF-β, etc.), tumor-associated fibroblasts and macrophages, the expression of myeloid-derived suppressive cell and regulatory T-cells, poor vascularization, and hypoxic conditions of the cells might blunt the immune responses exerted by the CAR T-cells as they prevent CAR T-cells migration to the tumor sites.

Besides, CAR T-cells tend to accumulate in the organs like the spleen and liver and eventually cause severe adverse effects in patients. Subsequently, delayed toxicities related to CAR-T cell infusion correlate to heavy tumor burden. The delayed toxicities comprised the tumor lysis syndrome, cytokine release symptoms (CRS), massive gastrointestinal hemorrhage, or intrapulmonary infection. They tend to damage normal tissues in tumor localized areas. Thus, extra care should be emphasized to specific sites, for instance, the lung tissues and the submucosa of the gastrointestinal tract, before the infusion of CD20 CAR T-cells to prevent further damage.

5 | THE ADVERSE EFFECTS OF CD20 CAR-T CELL THERAPY

Cytokine release syndrome (CRS), or cytokine storm, is the most common side effect of CAR T-cells treatment. In cytokine release syndrome, clinical symptoms like elevated ferritin, high-grade fever, serous cavity effusion, or capillary leak syndrome might occur in some patients. However, there are significant differences between hemophagocytic lymphohistiocytosis (HLH) and CRS, although their clinical symptoms seem similar. HLH is pathophysiologic immune dysregulation that results in excessive inflammation and abnormal activation of macrophages/T cells. CRS is due to a high level of immune activation and massive release of lymphocytes, macrophages, or myeloid cells, which lead to hypotension, renal failure, shock, or even death. It usually begins on the second or third day after CART infusion and persists for 7–10 days. Nonetheless, most of CRS’s clinical symptoms could be resolved by prescribing tocilizumab, corticosteroid, and/or etanercept (anti-TNFα). The evidence of delayed toxicities to various organs by CD20 CAR T-cells therapy was fully displayed and illustrated in the study conducted Wang et al.

Next, another side effect of CD20 CAR T-cells treatment is CAR T-cell-related encephalopathy syndrome (CRES), or immune effector cell-associated neurotoxicity syndrome (ICANS). CRES is neurotoxic and can present with neurologic signs and symptoms, including tremors, mild aphasia, apraxia, dysgraphia, and lethargy. These symptoms may progress to delirium, including hallucinations, severe aphasia, encephalopathy, rarely seizures, coma, and fatal cerebral edema over hours to days. CRES may coincide with other symptoms or may appear after other symptoms have resolved. It typically starts around the fifth day after the CART infusion. CRES typically lasts between 2 and 4 days and is entirely reversible. However, CRES’s pathophysiology, management, and long-term effects remained unclear.

6 | MULTI-TARGETED CD20 CAR-T CELL THERAPY: TWO IS BETTER THAN ONE?

CD19 and CD20 target B-cell antigens in CAR T-cell therapies as they are broadly expressed on malignant B-cells. Hence, CD19 or CD20 CAR T-cells are clinically applicable. CD19 or CD20 CAR-T cell therapy may reach a 41%–54% of CR rate. Nonetheless, according to the recent research on the CD19 CAR-T therapy approved by the FDA, about 65% of the patients encountered a disease relapse after CD19 CART treatment due to the variability of mono-target antigen in the tumor cell and CD19 antigen loss. Other interventions with alternative checkpoint inhibitors need to be studied as soon as possible for these patients who failed to obtain early CR (<90 days).

In favor of dealing with the CD19 CART treatment resistance, a dual-targeted CD19-CD20 CAR-T therapy has been invented to prevent antigen escape. Besides, it has been confirmed that the anti-CD19-CD20 dual-specific CAR T-cells attained excellent clinical responsiveness in B-cell malignancies, and it may reduce the relapse risk of the disease in the long term. To prove it further, Wang et al. conducted a study on the bispecific CART, and the overall ORR was 94.4%. Twenty-nine obtained CRs, and another five patients had PRs. No severe toxicity was reported. This bispecific CD19-CD20 CART showed excellent preclinical outcomes, even in tumor cells with no CD19 antigen presentation.

Furthermore, the expression of the CD19-CD20 CART produced lesser cytokines than CD20 CART alone. This dual-target CART enhanced anti-tumor activity. The CD20-CD19 CART made better binding of CD20 peptide and increased the cytotoxic activities in tumor cells. Nevertheless, though bispecific CD19 and CD20 CAR T-cell therapy are highly recommended for refractory or relapsed CD19-B-cell malignancies, the safety of this CART is yet unknown. The debate continues on the robust cytokine release due to increased target antigens of the tumor cells. Increased target antigens in the tumor cells indicate increased cytotoxicity, which may cause a more severe cytokine release syndrome (CRS). Hence, this dual-targeted therapy’s safety is still under investigation.

Despite the drawbacks and concerns raised, bispecific CD19 and CD20 CART T still merit further exploration due to limited toxicity promising ORR and lesser destruction to the healthy cells. Many still prefer CD19 or CD20 CART monotherapy because of the unpredictable clinical consequences of bispecific CAR T-cells. Other than the bispecific CD19-CD20 CAR T-cells, the clinical trials of sequential treatment with CD20 CART after CD19-CART infusion are also being studied for relapsed or refractory B-ALL or DLBCL patients. The outcome of this study is yet to explore.

Recently, in a study conducted by Weinstock et al., the CD20-CD3 bispecific antibody, odronextamab, demonstrated durable responses in patients with NHL in a first-in-human trial (NCT02290951),...
suggesting the dual-targeted odronextamab could be a practical salvage treatment choice for hematological malignancies.  

7 | THE FUTURE PROSPECTS OF CD20 CAR-T CELL THERAPY

Though CD19 CAR-T therapy is most extensively studied, CD20 CAR T-cell therapy is worth focusing on for treating B-cell malignancies. Based on the clinical outcomes of the existing CAR-T treatments, the toxicity of the CD20 CART cells (such as CRS) might be underestimated. Thus, more emphasis and consideration should be included in future research or clinical trials on this matter.

Next, theoretically, the expansion of the CD20 CAR-T efficacy implies an increased risk of immune-related toxicity in patients. So, it is vital to stress the synergistic combination of the immune-modulators or antibody-based therapies with CD20 CAR-T cells to ensure positive clinical outcomes. Besides, despite promising clinical responses in various trials, the results of the first to third-generation CAR T-cells on solid tumors are disappointing. Thus, CAR-T cell design should be improved to tackle tumor antigens’ variability and the complex tumor microenvironment in solid tumors.

Furthermore, allogeneic CAR-T cell is another feasible approach to discover. For those patients with insufficient quality or quantity of autologous cells for CART-cell therapy, allogeneic CAR-T cells should be considered. The graft versus host responses (GVHD) and rejection risks should be evaluated carefully in future studies. The future allogeneic CD20 CAR-T cell products should be more homogenous and well-characterized than current autologous products.

Additionally, the production of any CAR-T cell therapy (CD20 CART therapy) requires ample time and a large amount of financial support. Those patients with symptomatic or rapidly progressive diseases are usually excluded from the trials due to time constraints. Therefore, all relevant stakeholders should devise a decisive plan to build a financially sustainable and patient-oriented CAR-T cell industry.

8 | CONCLUSION

In conclusion, CD20 CART cells are well-tolerated for patients with relapsed or refractory aggressive B-cell malignancies, especially NHL. Despite the fact that CD20 CAR T-cell therapy has achieved tremendous clinical outcomes, its shortcomings should be improved. The CD20 CAR T-cells’ dosage, the side effects, the persistence and expansion of CAR T-cells in the body, and the CAR’s structure and design should be prudently considered to achieve maximal outcomes. Thus, understanding the complex resistance mechanisms in blood cancer and exploring the tumor environment in solid tumors are now significant tasks to broaden the application of CD20 CAR T-cell therapy. In short, CD20 CAR T-cell therapy’s future is promising to improve patients’ quality of life.

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CONFLICT OF INTEREST

The authors declared no conflicts of interest.

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