Review Article

Exploring CD19-targeted Immunotherapy Strategies for Human B-cell Lymphoma

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How to cite this article: **Sasan Salehi Nezamabadi, Arash Safari Sabet, Sana Sadat Peighambardoust, Sadra Behrouzieh, Seyed Reza Banihashemi, Saeid Amanpour. Exploring CD19-targeted Immunotherapy Strategies for Human B-cell Lymphoma. Archives of Razi Institute. 2025;80(2):301-312.** DOI: 10.32592/ARI.2025.80.2.301

Article Info:
Received: 13 February 2024
Accepted: 1 June 2024
Published: 30 April 2025

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ABSTRACT

B-cell lymphomas (BCLs) encompass approximately 40 subtypes arising from the malignant transformation of mature B-cells. The management of BCLs varies according to the specific type and stage of lymphoma. A plethora of therapeutic options are available, encompassing chemotherapy, immunotherapy, radiation therapy, targeted therapy, and stem cell transplantation. Among these approaches, targeted therapy has demonstrated considerable promise in terms of its potential to enhance safety and efficacy in treatment regimens. The field of targeted therapies encompasses a range of treatments that are designed to target specific molecules and pathways involved in various diseases. These therapies include monoclonal antibodies, nanobodies, CAR-T cell therapies, and bispecific T-cell engager (BiTE) molecules. These therapeutic agents operate through various mechanisms, targeting a variety of molecules and receptors associated with different diseases, such as CD79b, CD20, CD30, CD52, and CD19. CD19 is an immunoglobulin superfamily transmembrane glycoprotein of type I, which is necessary for setting intrinsic B-cell signaling thresholds by tempering both receptor-dependent and receptor-independent signaling. Conventional therapeutic interventions and other targets have demonstrated limitations, suggesting that CD19 is a viable target for lymphoma treatment. There are several FDA-approved anti-CD19 CAR-T cells, including Axicabtagene Ciloleucel, Tisagenlecleucel, and Lisocabtagene Maraleucel, as well as anti-CD19 monoclonal antibodies (mABs), such as loncastuximab tesirine and tafasitamab. These agents have demonstrated efficacy in numerous clinical trials. Blinatumomab, the inaugural FDA-approved antibody to be produced using BiTE technology, has demonstrated notable benefits in clinical trials investigating its use in the treatment of B-cell acute lymphoblastic leukemia (B-ALL). Single-domain antibodies (sdAb) or nanobodies represent the nanoscale VHH fragments of heavy chain-only antibodies (HcAbs). These have been utilized in conjunction with CAR T-cells, yielding promising outcomes. In this review, we sought to explore the potential of CD19 as a promising therapeutic target for lymphoma. Furthermore, we engaged in a discourse on the various treatment options concerning CD19 targeting, accompanied by an exposition of the pertinent clinical studies. In this regard, the efficacy, safety, and limitations of each option were thoroughly delineated.

Keywords: CD-19 Antigen; Molecular Targeted Therapy; Lymphoma; CAR-T Cell; Monoclonal Antibody,

1. Context

According to the 2017 World Health Organization (WHO) classification system, there are over 80 mature lymphoma subtypes that are categorized into three main groups: Hodgkin lymphomas (HL), B-cell neoplasms, and NK cell and T-cell neoplasms (1). B-cell lymphomas (BCLs) are a diverse group of over 40 subtypes of neoplasms with diverse physiological and clinical statuses. They are caused by the malignant transformation of mature B-cells, most frequently during the germinal center (GC) stage of development. Mantle cell lymphoma (MCL), follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, and chronic lymphocytic leukemia are the most prevalent types of adult B-cell malignancies. As is the case with most cancers, the development of these tumors is attributable to specific mutations in tumor suppressor genes (TSGs) and oncogenes (2). According to GLOBOCAN, 544,352 cases of non-Hodgkin lymphoma (NHL) were diagnosed in 2020, and it is estimated that this number will increase by 53.1 percent by 2040 (3). The National Institutes of Health (NIH) has reported that NHL is a prevalent form of cancer in the United States, accounting for approximately 4% of all malignancies. According to the American Cancer Society (ACS), the incidence of non-Hodgkin's lymphoma (NHL) is projected to total approximately 80,550 cases (44,880 in men and 35,670 in women) in 2023, while the mortality rate is estimated to be 20,180 (11,780 in men and 8,400 in women). The lifetime risk of developing NHL is approximately 1:43 and 1:53 for males and females, respectively (4). According to data from the American Cancer Society (ACS), B-cell lymphoma (BCL) constitutes approximately 85% of all non-Hodgkin's lymphoma (NHL) cases in the United States. The most prevalent form of B-cell lymphoma (BCL) is diffuse large B-cell lymphoma (DLBCL), which manifests in approximately 30% of cases. This is followed by follicular lymphoma, which occurs in about 20% of cases (4). DLBCL has the capacity to affect patients of any age; however, it is predominantly prevalent among the elderly. The average age at diagnosis is approximately 65 years. The onset of the disease is characterized by the rapid development of a palpable mass in the chest and abdominal deep lymph nodes or the neck and armpit palpable lymph nodes. The onset of this condition can occur in various anatomical locations, including the gastrointestinal system, the musculoskeletal system, and even the central nervous system. DLBCL is classified as an aggressive lymphoma; however, it generally exhibits a positive response to treatment (4). The average age of patients diagnosed with follicular lymphoma is approximately 60. This phenomenon is rarely observed in young children. Typically, this lymphoma affects numerous lymph nodes, as well as the bone marrow. Despite the fact that follicular lymphomas generally exhibit a favorable response to treatment, they continue to present significant therapeutic challenges. At the time of initial diagnosis, these lymphomas may not necessitate treatment. Conversely, treatment may be postponed until the lymphoma begins to manifest symptomatically. It has been established that, over time, certain follicular lymphomas have the potential to evolve into a rapidly progressing diffuse large B-cell lymphoma (DLBCL). Although most cases of follicular lymphoma are characterized by a slow growth pattern, referred to as "indolent," some cases exhibit rapid progression. The management of B-cell lymphomas (BCLs) is subject to variation based on the specific type and stage of the lymphoma. Treatment modalities encompass a range of options, including chemotherapy, immunotherapy, radiation therapy, targeted therapy, and stem cell transplantation. Chemotherapy is the primary treatment for most individuals diagnosed with non-Hodgkin lymphoma (NHL), and it can be administered as a standalone therapy or in combination with immunotherapy or radiation therapy. The concurrent administration of medications from different classes is a common practice in clinical settings. CHOP is one of the most frequently utilized combinations, comprising Cyclophosphamide, Doxorubicin (also known as Hydroxydaunorubicin), Vincristine (Oncovin), and Prednisone (4). Rituximab, a chimeric anti-CD20 antibody, has been shown to expand treatment options for patients with B-cell lymphoma (BCLs) and is often administered in conjunction with chemotherapy (5). Immunotherapy has the capacity to either enhance the patient's own immune system or utilize synthetic versions of natural immune system components to kill or hinder the growth of lymphoma cells. A plethora of immunotherapy drugs has been developed, including monoclonal antibodies, immune checkpoint inhibitors (ICIs), chimeric antigen receptor T-cells (CAR-T cells), and immunomodulating drugs (4). Radiation therapy employs high-energy rays to eradicate cancer cells. In the early stages of the disease, this therapy is frequently employed as the primary treatment option, as these tumors exhibit a high degree of responsiveness to it. In more advanced cases, it is sometimes used in conjunction with chemotherapy. Radiation therapy is a treatment option that may be employed to mitigate the symptoms of lymphoma that have metastasized to internal organs, such as the brain or spinal cord. It can also be utilized when a tumor is causing discomfort due to nerve compression (4). There are several types of targeted therapies that act in various ways, including monoclonal antibodies, CAR-T cell therapies, bispecific T-cell engager (BiTE), and nanobodies.These medications exhibit a broad spectrum of targets, including proteasomes, histone deacetylases (HDACs), Bruton's tyrosine kinase (BTK), and phosphatidylinositol 3-kinases (PI3Ks). A variety of targets have been identified for the treatment of multiple myeloma, including EZH2 (a kind of methyltransferase), CD20, CD19, CD52 (alemtuzumab), CD30 (brentuximab vedotin), CD79b (polatuzumab vedotin), and nuclear export proteins (SINEs) (4).Monoclonal antibodies that are directed against the CD20 antigen include Rituximab (Rituxan), Obinutuzumab, Ofatumumab, and Ibritumomab

tiuxetan. Each of these antibodies has a distinct mode of action, and they are indicated for a certain type of BCL. Rituximab is frequently used in combination with chemotherapy for the treatment of certain types of non-Hodgkin's lymphoma (NHL). However, it may also be administered as a standalone treatment (4). Rituximab has been demonstrated to exert direct cytotoxic effects via complement-dependent and antibody-dependent cell-mediated mechanisms. In addition to these direct effects, the drug has also been shown to elicit indirect cytotoxic effects through structural alterations, cancer cell sensitization to chemotherapy, and apoptosis (6). The potential for these CD20-targeting drugs to reactivate latent hepatitis B infections has been demonstrated, with the consequence of severe or life-threatening liver complications. Furthermore, there is a possibility that they may elevate the risk of certain severe infections for a period of several months following their withdrawal. A plethora of other minor adverse effects have been documented in relation to the aforementioned pharmaceuticals (4). Notwithstanding the substantial advancements in BCL therapy, there are still some limitations, including low efficacy and high toxicity. Moreover, there is a necessity for more precise targets, particularly those associated with BCL, to achieve enhanced efficacy and reduced toxicity. CD19 is a type I transmembrane glycoprotein that belongs to the immunoglobulin superfamily. This molecule is necessary for establishing intrinsic B-cell signaling thresholds by influencing both receptor-dependent and receptor-independent signaling. CD19 is imperative for the body's optimal immunological response. It has been demonstrated to interact with BCR and other surface molecules, thereby facilitating the recruitment and binding of several downstream protein kinases in both direct and indirect manners. A notable observation is the sequence in which these genes are expressed during the differentiation of B cells. Specifically, CD19 is expressed earlier than CD20, a finding that merits further investigation. CD19 expression is found to be three times more abundant in mature B-cells compared to immature B-cells. Furthermore, B1 cells exhibit slightly higher levels of CD19 expression compared to B2 (typical B) cells. The surface biomarker under consideration is characterized by its high degree of accuracy in the identification of B lymphocytes. Its expression is observed in pre-B cells until the differentiation of plasma cells, at which point its expression is maintained in both aggressive and indolent subtypes of non-Hodgkin's lymphoma (7). Given the limitations of conventional BCL treatments, particularly antibodies and multiple therapeutic products engineered against CD20, and the encouraging results of studies regarding CD19, the primary objective of this review is to introduce the various types of targeted therapy methods that target CD19 molecules in BCL patients. The efficacy, safety, and limitations of these methods will be discussed, and relevant clinical studies will be examined in order to achieve a comprehensive understanding of the research objectives.

2. Data Acquisition

A comprehensive literature search was conducted in PubMed to identify relevant studies about CD19-targeted immunotherapy strategies for human B-cell lymphoma. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and keywords related to CD19 antigen, molecular targeted therapy, cancer, CAR-T cell therapy, BiTE, nanobodies, monoclonal antibodies, and B-cell lymphoma. The search was constrained to articles published in the English language. Furthermore, reference lists of relevant articles and review papers were manually screened to identify additional studies that were not captured by the initial search strategy.

3. Results

3.1. Anti-CD19 Chimeric Antigen Receptor (CAR) T-cells

Chimeric antigen receptor T (CAR-T) treatment represents a particularly rapidly evolving and frequently utilized branch of cellular immunotherapy, particularly in the context of anticancer therapies. This relatively novel method has had a profound impact on the field of hematological malignancies. This approach accounts for over 50% of all cell therapies currently being researched or on the market (8). In this approach, T lymphocytes are extracted from the bloodstream and engineered to produce chimeric antigen receptors (CARs). These modified T lymphocytes are capable of identifying and targeting cancer cells independently of the major histocompatibility complex (MHC). These cells are subsequently reintroduced to the patient following in vitro proliferation to stimulate anticancer immune responses (9). The initial generation of CARs comprised three distinct components: the external domain, which facilitates binding to antigens; the transmembrane domain; and the intracellular portion of CD3, which functions as a signaling mechanism that results in the proliferation of T-cells and the subsequent release of cytokines (10). Subsequently, the second generation of CARs is produced through the integration of co-stimulatory molecules, such as 41-BB or CD28, into the first generation. This integration facilitates the survival of CAR-T cells (11). The third generation is composed of the pairing of both co-stimulatory molecules. Recently, CAR-T cells have been engineered to release cytokines, such as interleukin-12 (IL-12), for various purposes, including improving T-cell survival and enhancing safety and potency by attraction and activation of additional immune cells (Figure 1) (8). A substantial body of research has been conducted on CAR-T cells that target CD19 for the treatment of hematologic CD19+ malignancies. Axicabtagene Ciloleucel, Tisagenlecleucel, and Lisocabtagene Maraleucel are FDA-approved and the most well-known of them (Table 1).

3.1.1. Axicabtagene Ciloleucel

xicabtagene Ciloleucel (Axi-cel) is a type of CAR-T cell that encodes anti-CD19 CARs. In October 2017, the FDA granted regular approval to a new treatment called Axicabtagene Ciloleucel for the treatment of refractory/relapsed (R/R) large B-cell lymphoma (LBCL) in adult patients who have been administered at least two lines of systemic therapy (FDA approved 10/18/2017).The composition of the CAR-T cell is initiated with the concentration of T cells from apheresis peripheral blood. Subsequently, stimulation is induced through the administration of recombinant human interleukin-2 (IL2) and anti-CD3 antibodies. Thereafter, transduction occurs via a retroviral vector that is incompetent for replication and carries the anti-CD19 CAR transgene. A murine single-chain variable segment specific for CD19 is coupled to two costimulatory domains generated from human CD3-z and CD28 genes in the CAR protein (12). In a multicenter, phase two trial, 111 patients with refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma, or transformed follicular lymphoma were enrolled. A total of 101 subjects were administered Axi-Cel, and 82 percent of them exhibited an objective response. Furthermore, 54 percent of the subjects demonstrated a complete response (CR). While the majority of patients exhibited CRs during the initial 30-day period, 23 patients demonstrated CRs after a 15-month interval. In the context of initial evaluations, it would have been judicious to monitor patients lacking a CR, thereby offering them the opportunity to demonstrate improvement. The responses to therapy, including those that are still ongoing, demonstrated consistency across significant variables. At baseline, the eight patients with CD19-negative disease exhibited response rates analogous to those observed in patients with CD19-positive disease, thereby indicating that challenges in CD19 detection rather than the presence of actual CD19 negativity were the predominant factors. The findings of this trial suggest that Axi-cel can be safely administered in medical institutions that perform transplants, even in those with no prior expertise in CAR T-cell treatment. Despite the theoretical concern regarding the use of immunosuppressive medications to treat cytokine release syndrome (CRS) or neurological episodes (NEs), tocilizumab or glucocorticoids did not appear to compromise the overall response (OR) in these patients (13). In a separate multicenter, phase two trial of 17 patients with R/R LBCL, 16 of the patients received Axi-cel. A total of 86.7% of the 15 efficacy-evaluable patients exhibited an objective response, 4 (26.7%) patients demonstrated a complete response (CR), and 9 (60.0%) exhibited a partial response (PR). The study's findings revealed that all 16 patients (100%) exhibited grade 3 treatment-related adverse events (AEs). The most prevalent AEs were neutropenia (81.3%), lymphopenia (81.3%), and thrombocytopenia (62.5%). In 13 cases (81.3%), CRS occurred, including 12 cases of grade 1 or 2 and 1 case of grade 4. No neurological events were observed (14). The ZUMA-1 trial was a multicenter, single-arm, and registrational study. It was conducted at 22 sites in Israel and the USA and enrolled patients who met specific criteria. These patients were at least 18 years of age and had confirmed LBCL, as determined by histological analysis. Between May 19, 2015, and September 15, 2016, the study enrolled 119 patients in phases 1 and 2, with 108 of these patients receiving Axicabtagene Ciloleucel. As of August 11, 2018, 101 patients who were assessed for phase 2 activity had been followed for a median period of 27.1 months, with 84 (83%) demonstrating an objective response and 59 (58%) achieving a complete response (CR). The mean response time was 11.1 months. The median overall survival was not attained, whereas the median progression-free survival was 5.9 months. In phases 1 and 2, 52 (48%) of the 108 patients evaluated for safety experienced significant AEs of grade 3 or higher. Twelve patients (11%) exhibited grade 3 or worse CRS, while 35 patients (32%) demonstrated grade 3 or worse neurological events (15). In order to mitigate the toxicity associated with the treatment, several investigative safety management cohorts were incorporated into ZUMA-1. The primary objective of Cohort 6 was to investigate the utilization of preventive corticosteroids, early corticosteroids, and tocilizumab intervention for the management of CRS and NEs. The findings from cohort 6 suggest that individuals treated with Axi-cel may benefit from preventive corticosteroids, early corticosteroids, and/or Tocilizumab intervention, even in the absence of randomized data. The findings are encouraging, as no patients who received prophylactic corticosteroids experienced grade 3 or higher CRS, and the median CRS duration was reduced, with a delay in CRS onset. Furthermore, in cohort 6, 68% (n=27/40) of patients did not experience NEs or CRS within the first 72 hours after Axi-cel infusion, which may allow for improved corticosteroid use and an increase in the proportion of patients who can be managed as outpatients. The findings indicated that corticosteroid prophylaxis or early interventions with corticosteroids and Tocilizumab did not appear to adversely affect the efficacy of Axi-cel (16).

3.1.2. Tisagenlecleucel

Tisagenlecleucel is a second-generation anti-CD19 CAR-T cell that incorporates the co-stimulatory domain 4-1BB. In May 2018, tisagenlecleucel received approval from the FDA for the treatment of relapsed/refractory (R/R) large B-cell lymphoma (LBCL) in adult patients, following at least two courses of systemic therapy (FDA approved 05/01/2018). The primary target of this therapeutic intervention is CD19+ B-cells. Tisagenlecleucel was subjected to a phase 2, multicenter, global, pivotal trial, which revealed a significant rate of durable response in adult patients with R/R DLBCL (17). According to the findings of preceding studies, the medication has been shown to have a high degree of efficacy and a favorable safety profile in young adults and children suffering from relapsed/refractory acute lymphoblastic leukemia (R/R ALL) (18). The Tisagenlecleucel chimeric antigen receptor

(CAR) comprises an extracellular antigen-binding domain capable of recognizing CD19, as well as 4-1BB costimulatory and CD3-z chain signaling domains (18). A single-group, open-label, multicenter, international phase 2 study enrolled 135 patients with relapsed or refractory DLBCL who were at least 18 years old and had previously undergone two or more courses of treatment, including rituximab and one type of anthracyclines. A total of 111 patients were administered tisagenlecleucel. The results of the efficacy analysis revealed an overall response rate of 52 percent among the 93 patients, which was the most significant rate observed among the study participants. The participants were divided into two groups: one that had three months or more of follow-up and another that had previously discontinued their participation in the research. Furthermore, 40% of patients demonstrated complete remission (CR), while only 12% exhibited partial remission (PR). In the third month, the observed and controlled rates were 38% and 32%, respectively; and at the conclusion of the sixth month, 33% and 29% were documented. In this trial, adults with R/R DLBCL who had been extensively pretreated exhibited a high incidence and durability of response to Tisagenlecleucel treatment (17). A phase 2, single-cohort, 25-center, global study of Tisagenlecleucel was conducted on 75 children and young adults with CD19+ R/R B-cell acute lymphoblastic leukemia (ALL). In a period of three months, the total remission rate was documented to be 81%, and all patients who had exhibited a positive response to the therapeutic regimen did not manifest any evidence of minimum residual illness, as determined by means of flow cytometry. In the sixth month, the event-free rate was 73%, and the overall survival rate was 90%. At the conclusion of the 12-month period, these rates had decreased to 50% and 76%, respectively. The presence of tisagenlecleucel was detected in the bloodstream for a period of up to 20 months. It is noteworthy that 73% of patients experienced grade 3 or 4 adverse events (AEs) that were assumed to be associated with Tisagenlecleucel. CRS has been documented in approximately 77% of patients, 48% of whom have been administered tocilizumab. Furthermore, 40% of patients exhibited neurological complications (18). JULIET (NCT02445248) is a phase 2, single-arm, open-label, multicenter study. This study focuses on adult patients diagnosed with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). These patients are either those who have relapsed following autologous stem cell transplantation or were deemed ineligible for such a procedure. A recent study has indicated that Tisagenlecleucel demonstrates acceptable effectiveness and safety in the Japanese subgroup. A total of 17 patients were enrolled in Japan, and Tisagenlecleucel was administered to 9 of them who had completed more than 3 months of follow-up. The optimal overall response rate was determined to be 77.8%, with five patients (55.6%) demonstrating complete remission (CR) and two (22.2%) exhibiting partial remission (PR). The development of CRS was observed in six individuals (66.7%), with two patients experiencing grade 3 of CRS (19).

3.1.3. Lisocabtagene Maraleucel

Lisocabtagene maraleucel, also known as liso-cel, is an autologous, CD19-directed chimeric antigen receptor (CAR) T-cell product with a 4-1BB co-stimulatory domain. It is administered as a sequential infusion of two components containing CD8+ and CD4+ CAR-T cells at equal doses (20). On February 5, 2021, the FDA approved Liso-cel, marketed under the name Breyanzi®, as a treatment option for adult patients with R/R LBCL after at least two courses of systemic therapy (FDA approved 02/05/2021). A multicenter study was conducted, enrolling 344 patients with relapsed/refractory lymphoblastic cell lymphoma (R/R LBCL). Of these patients, 269 received one or more doses of liso-cel. The investigation revealed that the dosage level did not have a significant impact on the overall safety or activity of liso-cel. The target dosage of 100×10^6 CAR+ T-cells was determined to be the optimal concentration for the treatment. Within the efficacy-evaluable group, 186 patients (73%) exhibited an objective response, while 136 patients (53%) demonstrated a complete response (CR). The most prevalent grade 3 or more severe adverse events (AEs) were neutropenia (60%), anemia (37%), and thrombocytopenia (27%). Furthermore, the incidence of any grade CRS and neurological events was documented in 113 (42%) and 80 (30%) patients, respectively. Grade 3 or worse CRS and neurological events were reported in six (2%) and 27 (10%) patients, respectively. Nine patients (6%) experienced dose-limiting toxicity, including one patient who died as a result of widespread alveolar injury after receiving 50×10^6 CAR+ T cells (20). A longitudinal, unmasked, non-randomized clinical trial is currently underway to assess the impact of CAR-T cell therapy utilizing liso-cel on the health-related quality of life (HROoL) and associated symptoms of patients diagnosed with relapsed/refractory lymphoblastic cell lymphoma (R/R LBCL). The results indicate a clinically significant improvement in quality of life. No substantial alterations in physical performance or pain levels were observed at the 2nd, 12th, and 18th months; however, a notable reduction in fatigue was documented. Moreover, a higher proportion of patients who exhibited a positive response to the treatment demonstrated clinically significant improvements in their global health status and QoL in comparison to those who did not respond to the treatment (21).

3.1.4. Challenges and Recent Advances

Notwithstanding the substantial progressions in cancer therapy and CAR-T cell therapy, residual limitations persist. For instance, numerous intrinsic and extrinsic factors have the potential to induce failure in this therapeutic modality. Intrinsic factors, such as the short persistence of CAR-T cells, and extrinsic factors, such as the tumor inhibitory microenvironment (22), must be considered. The limitations of the aforementioned treatment include safety concerns, high cost, labor-intensive

production, and a prolonged production period (8).The focus has now shifted to the Universal CAR-T (UCAR-T) cell treatment, which is expected to improve the current situation. To mitigate the risk of severe alloimmune rejection triggered by MHC mismatch between the donor and recipient, all currently available or in development CAR-T cell products are autologous, meaning they are produced using T cells from the same patient. It has been posited that UCAR-T cells may also be composed of allogeneic CAR-T cells acquired from healthy donors. UCAR-T cells are produced via different techniques, and they have different safety concerns and applications. However, they have the same killing mechanisms. Additionally, it is characterized by its cost-effectiveness and immediate availability. Presently, CAR-T cells that utilize nanobody approaches are also receiving significant attention, a topic that will be addressed subsequently.

3.1.5. Safety and Toxicity

Despite the evident clinical efficacy of CAR-T cells in the context of cancer therapy, their widespread utilization is constrained by a range of toxicities that are attributable to the stimulation of tumor-reactive T-cells. This stimulation leads to a substantial release of cytokines, which in turn precipitate cardiovascular, pulmonary, and neurological adverse effects. These side effects, known as CRS and/or neurotoxicity (NT), are a leading cause of morbidity and mortality in certain individuals (23). A retrospective observational study was conducted on all reports in the EU (EudraVigilance, EV) and US (FAERS) databases of adverse drug reactions regarding Axi-cel and Tisagenlecleucel. Among the 1,426 reports, the most common adverse reaction was CRS, which was documented in 185 cases for Tisagenlecleucel, 462 cases for Axi-cel in FAERS, and 137 and 498 cases in EudraVigilance, respectively. A comparative analysis of the two medications and databases revealed that they had a higher percentage of male patients. This observation does not suggest that male patients are more susceptible to adverse drug reactions (ADRs); rather, it is associated with the prevalence of the underlying disease being treated. Research indicates that males exhibit a marginally elevated propensity to develop acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL) compared to females (24). A study that followed 100 patients from PLAT-02 or PLAT-03 phase 1/2 trials found that the severity of clinical neurotoxicity during electroencephalogram (EEG) recording after CD19-directed chimeric antigen receptor (CAR)-T cell treatment can be accurately reflected by EEG background patterns (25). Despite the potential for CAR-T cells to induce toxicities, there are ongoing studies aimed at reducing, monitoring, and diagnosing them in a timely manner.

3.2. Anti-CD19 Monoclonal Antibodies (mABs)

Anti-CD19 monoclonal antibodies (mABs) are meticulously engineered to exhibit augmented Fc functionality. Following binding to their receptors, these immunoglobulins (Ig) can directly induce signaling pathways that culminate in the demise of tumor cells. Furthermore, by attracting other immune mechanisms, they contribute indirectly to complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) (26).

3.2.1. Complement-Dependent Cytotoxicity (CDC)

The C1q's interaction as a member of complement proteins and the Fc region of mABs activates membrane attack complex (MAC). Subsequently, MAC perforates the cellular membrane, leading to cell death following lysis of the targeted cell. The extent of the complement response on tumor cells dictates the manner in which cell death ensues. In addition to MAC activation, cell death can occur through the recruitment of macrophages, which facilitate the destruction of opsonized targeted cells (26).

3.2.2. Antibody-Dependent Cellular Phagocytosis (ADCP)

In contrast, the operator cells of ADCP express a wide range of FcγR molecules, including activating molecules FcγRIIIa, FcγRIIa (CD32A), and FcγRIIIb (CD16b) and inhibitory molecule FcγRIIb (CD32b). The combined effect of these factors is to either induce the ADCP or not. In this particular case, the predominant mode of action of macrophages is phagocytosis, as opposed to the release of cytotoxic agents (26, 27).

3.2.3. Antibody-Dependent Cellular Cytotoxicity (ADCC)

Natural killer (NK) cells, which play a pivotal role in ADCC, are the sole cells among macrophages and monocytes that express FcγRIIIa exclusively. FcγRIIIa, also known as CD16a, is an activating member of the FcγR molecule family. Upon activation, it initiates a series of events that culminate in the release of perforin and granzyme granules, thereby leading to the elimination of tumor cells (26, 28).

3.2.4. Loncastuximab Tesirine (ADCT-402)

Loncastuximab Tesirine (also known as Zynlonta® and ADCT-402) received accelerated approval from the FDA on April 23. Loncastuximab Tesirine, an antibody-drug conjugate (ADC), consists of an anti-CD19 humanized mAB and a pyrrolobenzodiazepine (PBD) dimer toxin that functions as a DNA-alkylating factor. This is attached by a cathepsin-cleavable valine-alanine linker. The PBD-linker compound is known as Tesirine (29). The PBD dimer warheads contained in Loncastuximab Tesirine function as cytotoxic sequence-selective DNA crosslinking agents. The crosslinks formed by these agents result in minor disturbances in the structure of DNA, thereby hindering the detection system's capacity to activate repair mechanisms and conferring enhanced biological activity to PBDs in targeted tumor cells. The distinguishing characteristic of PBD dimers is their non-disturbing effect on DNA structure, which differentiates them from conventional chemotherapeutic agents such as nitrogen mustard (e.g., cyclophosphamide) and platinum drugs (30). A phase 1 study was conducted employing a 3+3 dose-escalation

design, which was subdivided into two parts. The objective of this study was to ascertain the sufficient dose. Patients received Loncastuximab Tesirine intravenously once every 21 days as one cycle. Of the 69 patients who received a dose of ≥120 µg/kg of loncastuximab tesirine, 40.6% (28 patients) achieved a complete response (CR), and 18.8% (13 patients) achieved a partial response (PR). The inclusion criteria for this study required that all patients be at least 18 years of age and have relapsed or refractory B-cell non-Hodgkin lymphoma (NHL) that was validated histologically. The exclusion criteria included patients who could not tolerate conventional therapies, those for whom the treatment had failed, and those without access to other therapy choices (29). In a phase 2 clinical trial, 35 of the 145 patients who were initially enrolled exhibited complete remission (CR), while 35 patients demonstrated partial remission (PR). This resulted in an overall response percentage of 48.3%. The patients in this trial met the following criteria: they were at least 18 years of age, and they had R/R DLBCL after receiving two or more multi-agent systemic treatments. The patients were administered 150 µg/kg of Loncastuximab Tesirine intravenously once every three weeks for two cycles, followed by a subsequent administration of 75 µg/kg for additional cycles. The most prevalent grade 3 or higher treatment-emergent adverse events (TEAE) were neutropenia (26%) and thrombocytopenia (18%), and serious adverse events (AEs) were observed in 39% of 145 patients (31).

3.2.5. Tafasitamab

Tafasitamab (MOR208 monoclonal antibody or XMAB-5574) is a humanized anti-CD19 monoclonal antibody engineered to possess enhanced Fc function, thereby augmenting its ability to induce ADCP and ADCC. The alterations made to the structure have been shown to increase the FcγRIIIa receptor binding, which is expressed by natural killer (NK) cells. Consequently, the interaction between the Fc domain of the monoclonal antibody and the FcγRIIIa receptor is augmented substantially (a 70-254-fold increase compared to the same interaction with a standard Fc domain) to a degree that is crucial for the efficacy of mABs (32). A number of studies have been conducted on the efficacy of Tafasitamab monotherapy. In a study from 2018, Tafasitamab was prescribed for 35 patients aged at least 18 years old with R/R DLBCL for whom one or more regimens including rituximab have been prescribed previously. Tafasitamab was administered at a dosage of 12 mg/kg via intravenous injection in two stages: an initial 8-week period followed by a subsequent 4-week period. This dosing regimen was implemented only for patients who had attained a stable stage of disease. The prevalence of CR and PR has been documented in two and seven patients, respectively. The objective response rate was 26% and 36% among all patients and only assessable patients, respectively (33). Lenalidomide, an immunomodulatory drug, has received approval for the management of multiple myeloma. This approval is based on studies that have evaluated its efficacy when administered as a single agent. The single-agent efficacy of lenalidomide has been a point of concern in other studies regarding its application in the treatment of R/R indolent lymphoma (34, 35). The combination of Tafasitamab and lenalidomide received its initial approval in 2020 for patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) (US-FDA, First Approval. Drugs. July 2020). An investigation of 80 patients who received tafasitamab in conjunction with lenalidomide revealed that 48 patients exhibited objective responses. Of these, 34 demonstrated complete responses (CRs), while 14 exhibited partial responses (PRs), resulting in a response rate of 60% and 43%, respectively. Furthermore, 59 out of 80 patients (74%) exhibited disease control (36). The effects of tafasitamab have been the focus of other studies concerning other types of B-cell non-Hodgkin lymphoma (NHL). These studies have included an exploration of the potency of tafasitamab in the therapeutic regimen of relapsed/refractory (R/R) B-precursor cell acute lymphoblastic leukemia (ALL), which was discontinued due to the low rate of responses to monotherapy with tafasitamab (37).

3.2.6. DI-B4

DI-B4 is another humanized anti-CD19 mAb that, despite its reduced CDC features, exhibits potent ADCC. An ongoing Phase 1, multicenter clinical trial is in progress to ascertain the maximum safe dose and the recommended dose for the subsequent phase of the trial. The administration of DI-B4 to patients was initiated intravenously, with the dosage administered on a weekly basis for a period of four weeks. The patients in this trial have the following conditions: The subject is suffering from R/R CD19 positive indolent B-cell lymphoma, chronic lymphocytic leukemia (CLL), or Waldenström macroglobulinemia (ClinicalTrials.gov Identifier: NCT01805375).

3.2.7. Safety and Toxicity of Anti-CD19 mABs

The most common adverse effects reported in the study were infusion-related reactions (IRRs). Other documented adverse effects (AEs) included fatigue, hypokalemia, pyrexia, constipation, nausea, hyperglycemia, febrile neutropenia, hyperkalemia, and dyspnea. The most prevalent hematologic AE (hematological adverse event) and the most prevalent grade ≥3 AE (adverse event) was febrile neutropenia. Other hematologic AEs reported in more than two patients included: As indicated by the findings, anemia, a decrease in neutrophil count, and a decrease in platelet count were observed (37). In a separate study, the administration of tafasitamab in conjunction with lenalidomide following the discontinuation of lenalidomide resulted in a reduction in the incidence and severity of treatment-emergent adverse events (AEs) when tafasitamab was administered as a standalone treatment. Specifically, grade 3 or 4 neutropenia was observed in 6% of 51 patients following lenalidomide cessation. During the co-administration of the two drugs, the most common hematologic adverse events (AEs) were neutropenia, anemia, thrombocytopenia, and leukopenia, with these AEs

being reported in five patients or more. The most prevalent non-hematological grade 1-2 events documented were diarrhea (32%), rash (27%), and peripheral edema (22%) (38).

3.3 Bispecific T-cell Engager (BiTE)

As previously indicated, all patients have demonstrated unfavorable prognoses under conventional therapeutic regimens. Consequently, immunotherapy modalities have undergone substantial development in recent years. Recently developed immunotherapeutic agents known as dual bispecific T-cell engaging (BiTE) antibodies have demonstrated encouraging efficacy, particularly in patients with relapsed/refractory leukemia (39). Blinatumomab (BLINCYTO®) represents a pioneering development in the field of antibody engineering, being the first class of antibodies to be formulated using BiTE technology and receiving FDA approval on March 29, 2018. The Blinatumomab molecule is composed of two arms that bind concurrently to CD3 + cytotoxic T-cells and malignant CD19 + B-cells, leading to the induction of cytotoxic T-cell activity, thus resulting in tumor cell lysis (39). The results of clinical trials of blinatumomab have demonstrated encouraging outcomes in patients diagnosed with B-cell acute lymphoblastic leukemia (B-ALL). For instance, in a 2015 phase 2 study comprising 189 patients with relapsed/refractory Philadelphia negative acute lymphoblastic leukemia (R/R ALL), the administration of blinatumomab yielded the following results: 81 patients (43%, 95% CI 36–50) exhibited either complete remission (CR) or complete remission with partial recovery of peripheral blood counts (CRh). Furthermore, 63 patients (33%) demonstrated CR, while 18 patients (10%) exhibited CRh (39). In a 2017 study, Kantarjian et al. examined the overall survival rate of blinatumomab and traditional care in a phase 3 trial. The study included 405 adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL). Patients treated with blinatumomab exhibited a significantly higher overall survival rate of 34% compared to the patients who received chemotherapy, which had an overall survival rate of 16% (40). In a phase 2 study conducted in 2018, Rambaldi et al. demonstrated the superior efficacy of blinatumomab in comparison to standard care, with an odds ratio of 1.54 (95% CI, 0.61-3.89) in patients diagnosed with relapsed/refractory Philadelphia positive B-cell acute lymphoblastic leukemia (41). In a phase 2 study conducted in 2015, Viardot et al. evaluated the effectiveness of the pharmaceutical agent in question in patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). Treatment with blinatumomab resulted in an overall response rate of 43% (complete remission [CR] was 19%) (39). In a subsequent phase 2 study conducted in 2018, Gökbuget et al. observed that adult patients with B-cell acute lymphoblastic leukemia (B-ALL) who had minimal residual disease (MRD) demonstrated enhanced relapse-free survival (RFS) (23.6 vs. 5.7 months; P=.002) and overall survival (OS) (38.9 vs. 12.5 months; P=.002) following the aforementioned treatment (42). Notwithstanding, this pharmaceutical agent has been observed to induce a certain degree of adverse effects, thereby imposing limitations on its utilization. Among these, the most common and vital AEs are CRS and NT (39). Subsequent investigations into the efficacy and adverse effects of blinatumomab are anticipated to facilitate its extensive utilization in the future.

3.4. Single-Domain Antibodies (Nanobodies)

The advent of single-domain antibodies (sdAb) can be traced back to 1993, when a novel antibody was identified in the serum of camelids. Notably, these antibodies lacked light chains, a feature that distinguishes them from conventional human antibodies. These heavy chain-only antibodies (HcAbs) were composed of a mere two heavy chains and a single variable domain (VHH, ~15kDa) for antigen-binding purposes (43). The nanoscale VHH fragments of these molecules were subsequently isolated and observed to be fully capable of interacting with antigens independently of their minuscule size. This observation led to the designation of these molecules as "nanobodies" (Nbs) in 2003 (44). The 2001 article by Desmyter et al. was among the first studies to examine the structural superiority of camelid single-domain antibodies in comparison to human antibodies. The present study revealed that the camelid VHHs benefited from a complementarity determining region 3 (CDR3) of greater length than human VH domains, leading to a higher specificity, affinity, and hydrophilicity (45). This section will elaborate on some of the most pioneering advances in treating different types of B-cell lymphoma with anti-CD19 nanobodies. In 2017, Banihashemi et al. made a significant advancement in this field by employing the phage-display antibody technique to obtain anti-CD19 Nbs from the immune Nb library of a one-humped camel. This procedure resulted in a rich library that could be used to target B-cell malignancies as well as B-cell autoimmunity disorders via CD19 molecules on their surface (46). Furthermore, a number of studies have identified a correlation between nanobodies and CAR T-cells, with certain studies reporting encouraging results. For instance, in a 2021 study, Wang et al. developed CD19 Nb CAR T-cells, CD20 Nb CAR T-cells, and bispecific Nb CAR T-cells. In vitro incubation of these CAR T-cells with lymphoma tumor cells displayed desirable results; however, further in vivo studies are required to ensure the efficacy of using nanobody-armed (Anti-CD19 Nbs in our case) CAR T-cells against B-cell malignancies, such as lymphomas (47). Furthermore, in a study conducted in November 2021, Zhou et al. generated trispecific CD19xCD20xCD22 Nb CAR T-cells (LCAR-AIO), which demonstrated antitumor activity against B-cell tumors with heterogeneous antigen expression in pre-clinical in vitro and in vivo models. In the present study, the concurrent targeting of three antigens was found to reduce immune evasion, thereby suggesting its potential as a treatment option for patients with relapsed B-cell tumors (48). Finally, anti-CD19 Nbs have been developed in conjunction with liposome-based nanocarriers, which hold

considerable promise and are anticipated to be discovered in the coming years. In a recent study, Banihashemi et al. developed liposomal nanocarriers that were loaded with anthrax lethal factor (LF) and were armed with anti-CD19 VHHs. The particles' design objective was to identify B-cells and subsequently release LF upon binding to the target, with the critical feature being the precise sparing of normal cells from harm. LF is a mitogen-activated protein kinase (MAPK) pathway inhibitor that functions by obstructing MAPK kinases (MKKs) 1, 2, 3, 4, and 6 (49). The MAPK pathway is comprised of three distinct subgroups, all of which play a pivotal role in the progression and metastasis of tumors. Extracellular signal-regulated kinases (ERKs) have been identified as crucial regulators of B-cell survival, while c-Jun N-terminal kinases (JNKs) and p38-MAPKs have been implicated in the response to cellular stress. Inhibition of these molecules deprives B-cells of the support needed for proliferation, resulting in the apoptosis of tumor cells (50). To demonstrate the variety of CD19 targeted therapies available for B-cell lymphoma, Figure 2 presents an array of treatments, including Anti-CD19 CAR-T cells, mABs, BiTE molecules, and nanobodies. In summary, it is evident that substantial progress has been made in this domain, with numerous advancements yet to be realized. However, the necessity for more comprehensive clinical studies is paramount for these methodologies to attain FDA approval and integration into clinical practice.

4. Conclusion

Despite recent advancements in the treatment of hematological malignancies, there is an ongoing need for improved therapeutic interventions that demonstrate higher efficacy and safety. In the domain of clinical oncology, a range of immunotherapeutic techniques and targeted therapies have emerged in recent decades. The number of patients receiving these treatments is increasing on a continuous basis. CD19 has emerged as a promising target for the treatment of B-cell lymphomas. A multitude of treatment strategies have been developed that target CD19, including but not limited to CAR-T cell therapy, monoclonal antibodies, BiTE, and single-domain antibodies. The efficacy of anti-CD19 CAR-T cells has been demonstrated; however, there are also limitations and adverse effects (AEs) associated with the treatment, including CRS and immune effector cell-associated neurotoxicity syndrome (ICANS). A comparative analysis of FDA-approved CAR-T cells reveals that axicabtagene ciloleucel exhibited a higher incidence of severe immune-related adverse events (IRAs), specifically immune-mediated neurotoxicity (IMN), commonly referred to as "ICANS," when compared with tisagenlecleucel. In contrast, tisagenlecleucel demonstrated a higher prevalence of CRS, or "cytokine release syndrome." Additionally, while the efficacy and safety of Lisocabtagene Maraleucel are well-established, further validation is necessary to ascertain its real-world performance. Monoclonal antibodies have demonstrated considerable promise in a variety of applications, including monotherapies such as loncastuximab tesirine and combination therapy with lenalidomide, as evidenced by studies involving tafasitamab. Nevertheless, further evaluation is necessary for monoclonal antibodies during their developmental process to enhance their effectiveness and reduce adverse events (AEs). Blinatumomab, a pioneering antibody engineered through the BiTE technology, has demonstrated encouraging outcomes in patients diagnosed with B-cell acute lymphoblastic leukemia (B-ALL). However, it is important to note that the agent in question has significant adverse events (AEs), including CRS and neurotoxicity, which are comparable to those observed with CAR-T cells. Pre-clinical studies have demonstrated the efficacy of single-domain antibodies when utilized in conjunction with CAR-T cells or as a standalone modality. As previously mentioned, the extant studies have demonstrated encouraging results for these treatments; however, further research is necessary to ascertain the outcomes of combining different treatment modalities and to investigate the effects in a more heterogeneous patient population with various types of B-cell lymphoma. A range of methodologies for targeting CD19 have demonstrated encouraging outcomes. The implementation of two or more of these methodologies may be a rational approach at this juncture to achieve optimal efficacy. It has been demonstrated that certain of these pharmaceutical agents possess the capacity to interact favorably with other drug classes or cytotoxins. While CD19 appears to be a promising target for BCLs, as evidenced by recent studies, further trials aimed at enhancing these medications may be beneficial. Concurrently, the targeting of CD19 has the potential to enhance the effectiveness of other therapeutic regimens.

Acknowledgment

It should be noted that this review paper does not include any specific acknowledgments.

Authors' Contribution

Conceptualized the review article, conducted the literature review, wrote the main part of the manuscript, and provided critical revisions to the manuscript; S. SN.
Prepared the figures and contributed to the literature review and writing the manuscript; A. SS.
Contributed to the literature review and writing the manuscript; SS. P, S. B.
Provided critical revisions to the manuscript and contributed to writing the manuscript; S R. B.
Took on a supervisory role, managed the project administration, and approved the final manuscript; S. A.

Ethics
It is hereby asserted that all ethical standards have been observed during the preparation of the submitted article.

Conflict of Interest
The authors have no conflicts of interest relevant to the content of this article.

Funding
The authors affirm that no financial resources, grants, or supplementary support were obtained during the preparation of this manuscript.

Data Availability
The data that support the findings of this study are available on request from the corresponding author.

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