Commentary

Chimeric antigen receptor (CAR) T cells were first clinically tested in trials against metastatic solid tumors without therapeutic benefit; however, these efforts established the necessary domains that are required for a functional CAR T-cell. With the characterization of cells within the immune system, the expression of CD19 was found to dictate B cell lineage that remains present on normal and malignant B cells [1,2]. Having such profound tissue specificity, this identified CD19 served as a promising target for antigen-specific CAR T-cell development [3]. The first clinical success was in 2010 with an advanced follicular lymphoma patient who received anti-CD19 CAR T-cell treatment with a durable response reported at 39 weeks [4]. This was rapidly followed by a separate report of treating a refractory chronic lymphocytic leukemia (CLL) patient with an anti-CD19 CAR T-cell therapy [5].

Thus began the era of CD19 CAR T-cell therapy leading to several clinical trials and the FDA approval of Yescarta® (axicabtagene ciloleucel), Kymriah® (tisagenlecleucel), Tecartus® (brexucabtagene autoleucel), and Breyanzi® (lisocabtagene maraleucel). The approved indications for these CD19 CAR T-cell therapies were for relapsed/refractory (r/r) diseases, specifically B cell acute lymphoblastic leukemia (ALL), follicular lymphoma, diffused large B-cell lymphoma, and mantle cell lymphoma [6]. What is studiously absent is CLL, one of first B cell malignancies that was a target for CD19 CAR T-cells.

CLL is the most common adult leukemia in Western populations, and although CLL can be observed in young adulthood, the disease is mostly observed at an average age of 72, with incidence increasing with increasing age [7]. With the rising numbers of “baby boomers,” there may soon be an increase in CLL numbers [8]. Chronic lymphocytic leukemia (CLL) is a complex progressive disease that can minimally affect patients before progressing to a degree where therapy is required and finally advancing to an aggressive disease that demands therapeutic intervention [9]. The precise etiology of CLL remains to be definitively explained. Genetic factors appear to strongly affect the genesis of CLL as evidenced with familial linkages and a history of challenges to the immune system (e.g., viral infections, history of atopic conditions, autoimmune phenomena) [9-12]. There are also specific chemical exposures that are correlated with CLL (herbicide exposure and tobacco usage) [9,11].

CLL is characterized by an accumulation of mature but dysfunctional B lymphocytes [7,13]. CD19 participates with the B cell receptor (BCR) to maintain a survival signal for the B cell which also results in propagation of malignant B cells. Inherited susceptibility has been localized to genes that control B cell development [9,14], whereas noninherited CLL has mutations in several pathways that are associated with aging with the mutational status of the immunoglobulin heavy variable gene as a critical differentiator for disease characterization [9,13,14]. The signaling threshold of the BCR is modulated by CD19 with the BCR/CD19 complex initiating a protein kinase driven signaling cascade [15]. Both CD19 and the BCR interact with Bruton tyrosine kinase. Initial treatment options for CLL include BTK inhibitors, phosphatidylinositol 3-kinase inhibitors, and the B-cell lymphoma 2 inhibitors, alone or combined with CD20 monoclonal antibodies [16]; however, r/r disease can
occur which requires more creative treatments. CAR T-cell therapy was originally pioneered to target CLL; however, robust effects were not noted, and CAR T-cell therapy was more successfully applied to other B cell malignancies like acute lymphoblastic leukemia with blazing successes of complete remissions in over 90% of cases [17-19]. Although the currently FDA approved CD19 targeted CAR T-cell therapies have been applied to CLL, durable antitumor responses have been reported in only 26% of patients [20].

As is the case with many biochemically critical systems, B cell proliferation and activation are modulated by other receptor pathways that are also associated with the BCR, the B-cell activating factor receptor (BAFF-R)/BAFF cascade. We submit that BAFF-R is an ideal target for CAR T-cells, specifically since BAFF-R is consistently observed in CLL [21]. BAFF-R is essential for B lymphocyte development and mature B-cell survival as well as clonal progression of malignant CLL B cells [22]. Qin et al. reported the first BAFF-R targeting CAR T-cell therapy, showing the CAR T-cells were active against several cell lines with known BAFF-R expression [23] as well as in xenograft models with the same cell lines as well as in models to mimic CD19 antigen relapse [24]. This BAFF-R CAR design, which contains a CD8 transmembrane domain and the 4-1BB and CD3 zeta costimulatory domains, is currently under evaluation in a clinical trial (NCT05370430).

A new monoclonal antibody against BAFF-R has been generated that became the foundation for generation a novel BAFF-R CAR T-cell therapy that utilizes the CD28 transmembrane domain along with the CD28 and CD3 zeta costimulatory domains [25]. These MC10029 CAR T-cells have been rigorously evaluated in both in vitro and in vivo models of leukemia and lymphoma as well as in models to mimic CD19 relapse with MC10029 CAR T-cell antigen specific cytotoxicity and anti-tumor effects confirmed [25]. Aware of the literature cataloguing the limited success of CD19 CAR T-cells against CLL, we turned our attention to applying these BAFF-R targeting CAR T-cells to CLL. Showing antigen specific cytotoxicity was a critical confirmatory set of experiment; however, we were most interested in confirming activity in CLL patient derived cells. Because of reported concerns of insufficient T cells or ineffective CAR T cells in CLL patients, peripheral blood samples from CLL patients were collected and were the source for T cells that were advanced to MC10029 CAR T-cell generation and were also the source for CLL tumor cells. Luo et al. showed the efficacy of CLL patient-derived MC10029 CAR T-cells against autologous CLL tumor cells. This data and the additional data in the approved IND application are leading to a clinical trial at Mayo Clinic Florida (NCT06191887). The original BAFF-R targeting CAR T-cell design is currently in a clinical trial for patients with r/r B cell ALL (NCT04690595) or r/r B-NHL (NCT05370430). Recently, this group reported positive safety and anti-lymphoma activity in three patients with mantle cell lymphoma [26]. These encouraging results, which show that targeting BAFF-R with a CAR T-cell therapy is clinically safe and those that show efficacious and the positive results using CLL patient derived BAFF-R CAR T-cells in an autologous study, support BAFF-R is a solid target for a CAR T-cell therapeutic against CLL.

Since CD19 CAR T-cell therapy was the first-in-class for this type of immunotherapy, CD19 CAR T-cells are responsible for current expectations of durable responses and complete remissions [17-19], and with that, CD19 CAR T-cell therapy has also identified seemingly CAR T-cell specific adverse events (AE) and incidences of neurotoxicity, along the requisite AE treatment strategies. As more CAR T-cell therapies that target new antigens are being generated and approved for clinical application, we will widen and deepen our understanding of the positive and negative effects of CAR T-cells. For instance, with the recent availability of BCMA-targeting CAR T-cells, we are now seeing comparisons of immune effector cell-associated neurotoxicity syndrome (ICANS) for BCMA CAR T-cells that range from 18-20% compared to CD19 CAR T-cell that ranges of 21-60% [27]. These observations along with single-cell RNA sequencing data showing CD19 expression in mural cells may indicate an on-target mechanism for neurotoxicity [28]. Mural cells are part of the cellular network that maintains the integrity of the blood brain barrier (BBB) [29]. Disruption of the BBB may explain the edema, multifocal hemorrhage, and vascular disruption of the brain after CD19 CAR T-cell treatment [28,30]. Conversely, CD19 CAR T-cell therapy has been applied to patients with lymphoma having a secondary central nervous system involvement with favorable results that are similar to typical lymphoma patients [31,32]. This is opening the possibility of CD19 CAR T-cells treatment for primary central nervous system lymphoma (PCNSL), which currently has dismal prognosis [33].

Thus far, CD19 CAR T-cells have been the only option for B cell malignancies or other B cell pathologies and have been invaluable for many patients. With the development and clinical testing of CAR T-cells that target new antigens, we are adding options to the treatment algorithms. CLL patients are typically older patients with comorbidities common to the aging population, like diabetes, hypertension, and vascular disease [34,35]; these comorbidities can impact treatment plans. Caution should be exercised with single-mindedly applying CD19 CAR T-cell therapies when B cell malignancies and the associated patients are complex and diverse. The BAFF-R targeting CAR T-cell therapies that are entering clinical trials offer an alternative that may be ideal for specific r/r patients, like CLL patients, older patients, or patients with vascular concerns where ICANS would be problematic. Additionally, the application of CD19 CAR T-cells for lupus patients [36,37] is opening a new door for CAR T-cell application for diverse pathologies in which B cells play a role. This arena can and should be shared with BAFF-R CAR-T cells to provide additional options for patients.

References


