# The Latest Advances in CAR T-Cell Therapy for Refractory and Relapsed Lymphomas and Leukemias

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Author's disclosures of potential conflicts of interest are found at the end of this article.

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**Abstract**

While many patients with B-cell leukemias and lymphomas respond to therapy, those with relapsed or refractory disease often have poor outcomes and need more effective treatment options. The clinical development of tumor-targeted chimeric antigen receptor (CAR)–modified T cells has demonstrated the potential of this therapy for such difficult-to-treat hematologic malignancies. CAR T-cell therapies can be directed against the CD19 B-cell antigen, which is expressed on many leukemias and lymphomas. This article discusses the design of first- and second-generation CARs and their proposed mechanism of action. Recent clinical trial results in patients with relapsed or refractory B-cell malignancies treated with CD19-targeted, CAR-modified T cells are presented, including factors that may affect efficacy. The article also discusses key associated toxicities including cytokine-release syndrome, neurologic toxicities, and B-cell aplasia, as well as recommendations on management of these adverse events. As clinical use of this technology progresses, advanced practitioners will need to understand the biology underlying CAR T-cell therapy and be aware of its growing role in the treatment of relapsed/refractory leukemias and lymphomas. Advanced practitioners will also play crucial roles in identifying individuals at risk for treatment-related toxicities, grading adverse events, and managing toxicities.

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B-cell malignancies represent a diverse collection of diseases including many types of leukemias and lymphomas. Specific types of these cancers reflect their transformed cell of origin, with B-cell acute lymphoblastic leukemia (B-ALL) arising in bone marrow, while diffuse large B-cell lymphoma (DLBCL)—the most common type of high-grade non-Hodgkin lymphoma (NHL)—originates in the cells of the lymph nodes. Despite significant therapeutic advances over the past decade, including the

use of monoclonal antibodies such as rituximab (Rituxan), treatment of patients with relapsed or refractory B-cell leukemias and lymphomas remains challenging and outcomes are often poor. For patients with B-ALL, standard of care consists of induction and consolidation chemotherapy (including central nervous system prophylaxis), followed by several years of maintenance chemotherapy. However, relapse is common, and disease-free survival for those with relapsed/refractory B-ALL is less than 40%, making curative allogeneic stem cell transplantation a treatment goal for patients who achieve a complete response (CR) with chemotherapy (Hahn et al., 2006). Standard of care for DLBCL involves a regimen of R-CHOP (rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone). Patients with relapsed/refractory DLBCL (representing approximately one-third of all such cases) typically receive high-dose chemotherapy followed by autologous stem cell transplantation (ASCT), but long-term survival is poor, especially for those who received prior rituximab (Friedberg, 2011). More effective treatment options are clearly needed for individuals with relapsed/refractory B-ALL and DLBCL.

## CHIMERIC ANTIGEN RECEPTOR T CELLS

Chimeric antigen receptors (CARs) targeting CD19 represent a novel type of cellular immunotherapy that allows reprogramming of the specificity and function of T cells for treatment of B-cell malignancies. CARs are hybrid antigen receptors in which an extracellular single-chain antigen-binding domain is fused to an intracellular signaling domain (Figure 1). The antibody single-chain variable fragment (scFv) is responsible for T-cell binding to a selected tumor antigen, while the intracellular domain (composed of costimulatory and CD3ζ endodomains) triggers T-cell activation; these components are linked by transmembrane domains. Second-generation CARs differ from their predecessors by an additional costimulatory domain (e.g., 4-1BB, OX40, CD28, or ICOS) to further enhance cytokine production and antitumor activity upon antigen stimulation and demonstrate improved persistence of CAR T cells in animal models (Davila, Sauter, & Brentjens, 2015; Frey & Porter, 2016). These customized receptors can be introduced into T cells by lentiviral or gammaretroviral gene transfer or electroporation. Following administration of a cyclophosphamide-based

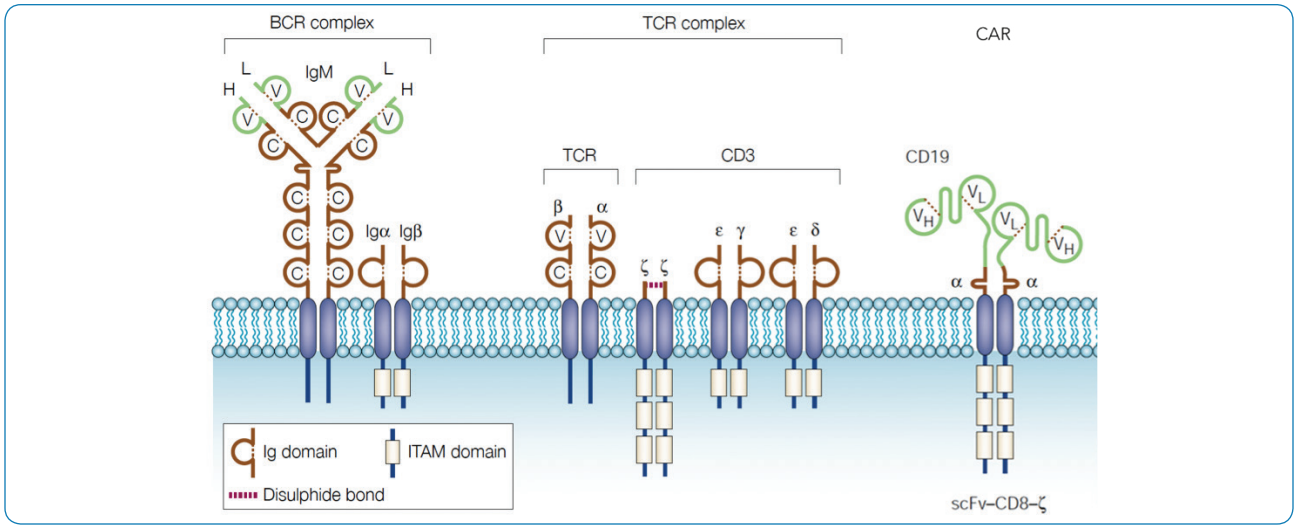


**Figure 1.** Physiologic and chimeric antigen receptors. Structures of the normal B-cell and T-cell receptor complex are shown at left. Chimeric antigen receptors (CARs; at right) are composed of a single-chain fragment variable (scFv) domain that binds a specified antigen; hinge and transmembrane domains to anchor to the cell membrane; and an intracellular CD3ζ immunoreceptor tyrosine-based activation motif (ITAM) component that functions in T-cell signal transduction upon antigen binding. Second-generation CARs have an additional costimulatory domain(s) attached to the CD3ζ to enhance T-cell function in vivo. BCR = B-cell receptor; TCR = T-cell receptor; CAR = chimeric antigen receptor. Adapted with permission from Sadelain, Riviere, and Brentjens (2003).

conditioning chemotherapy regimen, the modified immune cells are adoptively transferred back into the patient to mount an antitumor response against the preselected tumor antigen. CD19 can serve as a therapeutic target in these disorders because this antigen is expressed on the majority of B-cell malignancies and functions as a critical co-receptor for B-cell antigen receptor (BCR) signal transduction (Naddafi & Davami, 2015). Furthermore, because normal expression of CD19 is restricted to the B-cell lineage, any on-target, off-tumor toxicities would be limited to B-cell aplasia.

CARs differ from normal T-cell receptors (TCRs) in several important ways. In contrast with TCRs, CARs are not human leukocyte antigen–restricted but are limited to presentation of only extracellular antigens. Unlike TCRs, CARs do not require peptide processing for antigen presentation and can even be used to generate immune responses against non-peptides such as glycolipids. However, immunogenicity can occur with CARs due to the inclusion of murine antibody domains.

## CLINICAL TRIAL DATA

Clinical trials of CAR T-cell therapy have been conducted for a variety of hematologic malignancies that express CD19 including B-ALL, chronic lymphoid leukemia (CLL), mantle cell lymphoma (MCL), small lymphocytic lymphoma, follicular lymphoma (FL), DLBCL, Burkitt lymphoma, Hodgkin lymphoma, multiple myeloma, and others. Results from studies of CAR T cells in B-ALL and DLBCL are highlighted here.

Multiple clinical trials in both children and adults with B-cell ALL and NHL have evaluated various CAR constructs and vectors, doses, and conditioning regimens (Tables 1 and 2; Davila et al., 2014; Lee et al., 2015; Maude et al., 2014; Turtle et al., 2016a). Although most B-ALL studies have been small (≤ 30 patients each), all have reported CR rates of 70% to 93%, with complete molecular response (CRm) rates of 60% to 86%. Figure 2 shows examples of overall and disease-free survival observed in these trials, and Figure 3 provides responses to CAR T-cell therapy in patients with chemorefractory lymphoma.

### Axicabtagene Ciloleucel

Axicabtagene ciloleucel (KTE-C19) is an autologous CD3ζ/CD28-based anti-CD19 CAR T-cell therapy. A pivotal phase I/II trial (ZUMA-1) was conducted to evaluate its safety and efficacy in patients with chemorefractory aggressive NHL (Locke et al., 2017a, 2017b). A total of 101 patients were treated, including those with DLBCL, primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (tFL). The primary analysis indicated that the trial met its primary endpoint of objective response rate (ORR). Complete or partial response was observed in 82% of patients after a single infusion, including a 54% CR rate (Table 2). Subgroup analysis indicated an ORR of 83% in patients with PMBCL or tFL (n = 24) and 82% in those with DLBCL (n = 77). These results are substantially better than those seen in the SCHOLAR-1 retrospective study of refrac-

**Table 1. Published Clinical Trials of CD19-Targeted CAR T-Cell Therapy in B-ALL**

| Trial | N | ScFv | CAR design | Vector | Conditioning chemotherapy | Dose (CART/kg) | CR | CRm |
|---|---|---|---|---|---|---|---|---|
| NCI (Lee, 2015) | 20 peds | FMC63 | CD28-ζ | Retrovirus | Flu/Cy | 1–3 x $10^6$ | 70% | 60% |
| UPENN (Maude, 2014) | 25 peds 5 adults | FMC63 | 4-1BB-ζ | Lentivirus | Varied | 8 x $10^5$ to 2 x $10^7$ | 90% | 79% |
| MSKCC (Davila, 2014) | 16 adults | SJ25C1 | CD28-ζ | Retrovirus | Cy | 3 x $10^6$ | 88% | 75% |
| FHCRC (Turtle, 2016a) | 30 adults | FMC63 | 4-1BB-ζ | Lentivirus | Flu/Cy vs. Cy | 2 x $10^5$ to 2 x $10^7$ | 93% | 86% |

*Note.* CAR = chimeric antigen receptor; B-ALL = B-cell acute lymphoblastic leukemia; ScFv = single-chain fragment variable; CR = complete response; CRm = complete molecular response; NCI = National Cancer Institute; peds = pediatric; Flu = fludarabine; Cy = cyclophosphamide; UPENN = University of Pennsylvania; MSKCC = Memorial Sloan Kettering Cancer Center; FHCRC = Fred Hutchinson Cancer Research Center.

**Table 2. Published Clinical Trials of CD19-Targeted CAR T-Cell Therapy in NHL**

| Trial | N | Disease | ORR | CR |
|---|---|---|---|---|
| UPENN (Porter, 2015) | 14 | CLL | 57% | 29% |
| FHCRC (Turtle, 2016b) | 32 | NHL (no CLL) | 50% | 8% |
| Locke, 2017a | 101 | R/R DLBCL | 82% | 54% |

*Note.* CAR = chimeric antigen receptor; NHL = non-Hodgkin lymphoma; ORR = overall response rate; CR = complete response; UPENN = University of Pennsylvania; CLL = chronic lymphoid leukemia; FHCRC = Fred Hutchinson Cancer Research Center; R/R = relapsed/refractory; DLBCL = diffuse large B-cell lymphoma.

tory DLBCL in which the CR was 7% (Crump et al., 2017). In 93 patients treated with axicabtagene ciloleucel who had at least 1 month of follow-up, the most common grade 3 or higher adverse events were neutropenia (63%), anemia (42%), leukopenia (40%), febrile neutropenia (29%), thrombocytopenia (26%), encephalopathy (19%), and hypophosphatemia and decreased lymphocyte count (17% each). There were three deaths due to treatment-emergent adverse events (hemophagocytic lymphohistiocytosis, cardiac arrest in the setting of cytokine release syndrome [CRS], and pulmonary embolism). Axicabtagene ciloleucel has been filed for approval by the US Food and Drug Administration (FDA) with indications for the treatment of refractory DLBCL, PMBCL, and tFL and has received Breakthrough Therapy designation for these indications.

### Tisagenlecleucel-T

Tisagenlecleucel-T (Kymriah; CTL019) is a CD19-directed CAR lentiviral vector. In a phase I/IIa study, 30 children and adults with relapsed/refractory ALL were infused with CTL019 (Maude et al., 2014). One month after the initial infusion, 27 patients (90%) had achieved CR, including 15 patients who had undergone SCT. Remissions were sustained, and the overall survival rate was 78%. Immune activation as manifested by severe CRS (see section on treatment-related toxicities and management) developed in 27% of patients and was associated with a higher baseline disease burden; this was effectively treated with tocilizumab (Actemra). Tisagenlecleucel-T has recently been approved by the FDA for use in pediatric and young adult patients with B-ALL that is refractory or in second or later relapse. It has also shown clinical efficacy in relapsed/refractory CLL and multiple myeloma (Garfall et al., 2015; Porter et al., 2015). Interim analysis of a phase II trial (JULIET) in relapsed/refractory DLBCL reported an ORR of 59%, including a 43% CR rate, with durable responses (Schuster et al., 2017). This agent recently received FDA Breakthrough Therapy designation for the treatment of adult patients with relapsed/refractory DLBCL, and a biologic license application for approval has been filed with the FDA.

### JCAR015 and JCAR017

Another series of anti-CD19 CAR T cells is being developed for treatment of various hematologic as well as solid tumor indications. However, a clinical trial of one of these agents, JCAR015, for relapsed/refractory B-ALL was halted following several deaths on study (DeFrancesco, 2017). It is not yet clear whether these deaths resulted from CAR T-cell therapy itself or the inclusion of fludarabine in the preconditioning regimen. Another anti-CD19 CAR T-cell construct, JCAR017, was evaluated in a phase I study (TRANSCEND) in patients with DLBCL, MCL, and FL. It is unique among CD19 CAR T products because it is infused in a 1:1 ratio of CD4:CD8 T cells. An 80% ORR was reported, with 60% of patients achieving a CR (Abramson et al., 2017). JCAR017 received a Breakthrough Therapy designation from the FDA for NHL. Trials of other CAR T-cell therapies within this class for treatment of B-cell malignancies, pediatric ALL, and adult NHL are ongoing.

### Response to CAR T-Cell Therapy

Response to CAR T cells appears to be determined by multiple factors, including the tumor type, dose of infused cells, CAR design, and preconditioning therapy (Almåsbak, Aarvak, & Vemuri, 2016). In patients with B-ALL and other hematologic malignancies, response correlates with the degree of clonal T-cell expansion as well as their duration of persistence. Responders were shown to have significantly higher

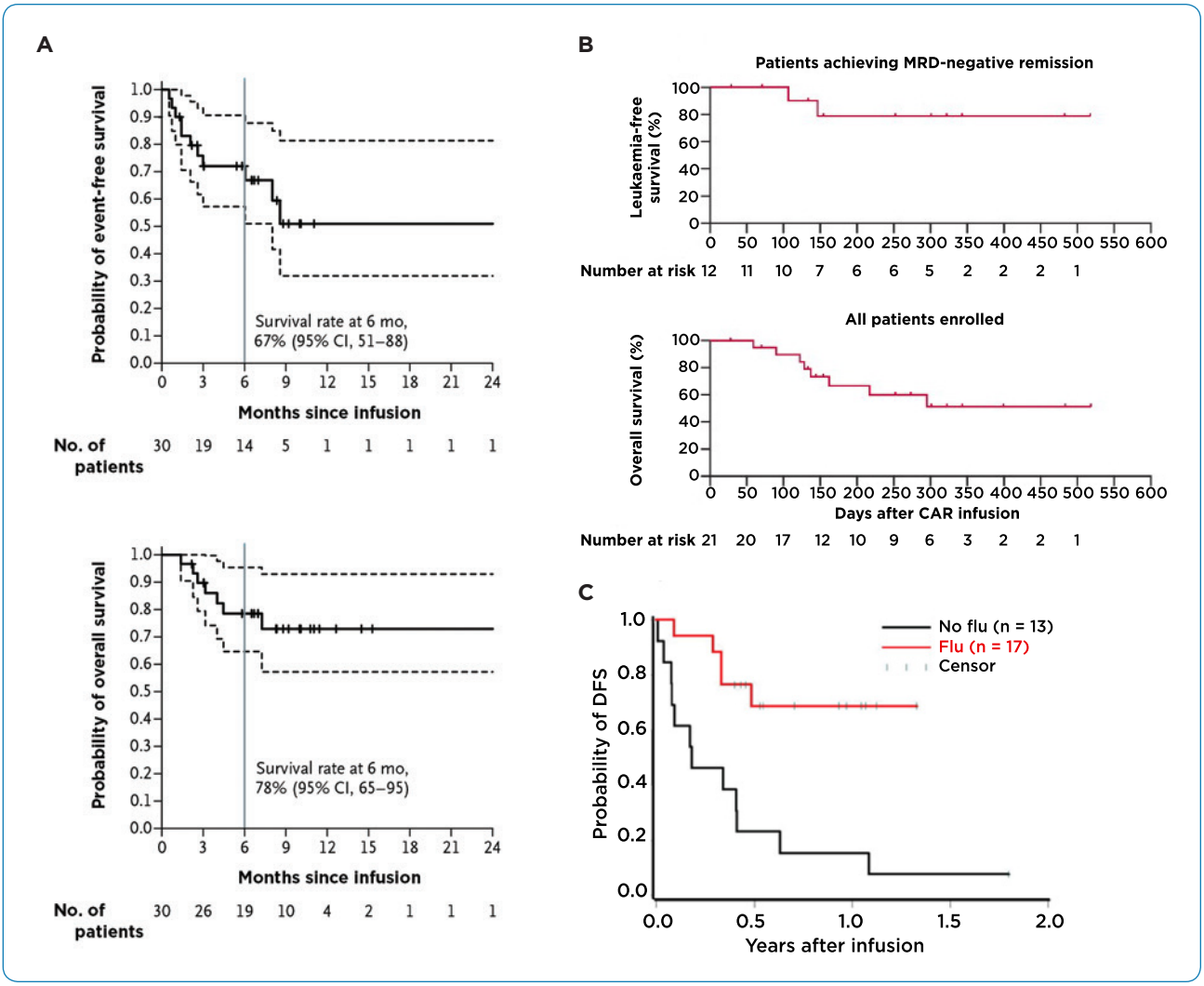


**Figure 2.** Survival of B-ALL patients following treatment with CD19-targeted CAR T cells. B-ALL = B-cell acute lymphocytic leukemia; CAR = chimeric antigen receptor; CI = confidence interval; MRD = minimal residual disease; DFS = disease-free survival; Flu = fludarabine. Used with permission from (A) Maude et al. (2014); (B) Lee et al. (2015); and (C) Turtle et al. (2016a).

numbers of circulating CAR T cells compared with nonresponders. In the CLL study, expansion of CAR T cells (seen in all responding patients) occurred in conjunction with the development of CRS in most patients, supporting the potential of CRS as a predictive biomarker of response (Porter et al., 2015).

Long-term persistence of CAR T cells appears to be a critical factor for sustained remission and is therefore an important treatment goal. In theory, patients with leukemia who are not candidates for curative ASCT might be able to achieve long-term disease control with CAR T-cell therapy alone, but this may depend on the persistence of anti-CD19 CAR T cells. However, persistence of adoptively transferred T cells seems to vary substantially between studies. CAR T cells could not be detected past 42 days postinfusion in one study (Lee et al., 2015), whereas detection at 9 to 11 months or longer has been reported by other investigators (Locke et al., 2017a; Maude et al., 2014). Reasons for this variability are unclear but could be related to the nature of the costimulatory domain, manufacturing process, CAR T-cell dose, initial tumor burden, the myeloablative conditioning regimen used, transgene immune response, and the method for CAR T-cell detection (Turtle et al., 2016a). In some studies, the median peak blood CAR T-

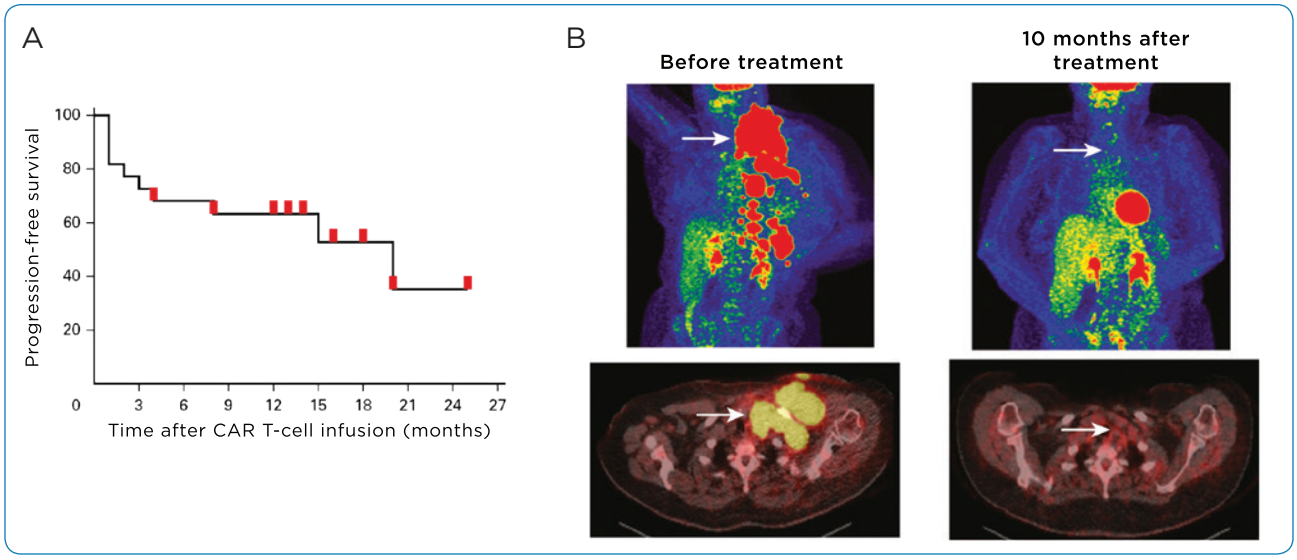


**Figure 3.** Responses to CAR T-cell therapy in chemotherapy-refractory lymphoma. (A) Progression-free survival. (B) PET/CT scans showing response to CAR T-cell therapy in a patient with chemotherapy-refractory diffuse large B-cell lymphoma. White arrows indicate sites of lymphoma. Residual red areas in post-treatment images reflect normal findings in the brain, heart, kidneys, and bladder. Following CAR-19 T-cell infusion, this patient entered an ongoing complete remission. CAR = chimeric antigen receptor; PET = positron emission tomography; CT = computed tomography. Information from Kochenderfer et al. (2017).

cell level was found to be higher in patients with lymphoma who achieved remission compared with those with lower levels (Kochenderfer et al., 2017). In this trial, high serum levels of the cytokine interleukin-15 (IL-15) were significantly associated with elevated peak blood CAR-positive cell levels and remissions. At present, the optimal duration of persistence required for all patients who receive CAR T-cell therapy is unknown.

The majority of patients who respond to an anticancer therapy with a single mechanism of action eventually relapse, and this appears to be true with CAR T-cell therapy as well. Relapses occurring after CD19-directed T-cell immunotherapies (i.e., antigen escape) have been described (Grupp et al., 2013; Maude et al., 2014; Wang, Wu, Liu, & Han, 2017), and in one study loss of CD19 expression was observed in half of all patients with relapsed disease (Grupp et al., 2014). CD19 antigen escape is thought to occur by at least two mechanisms: alternative splicing of *CD19* exons that affect expression of a critical epitope, and a lineage switch from lymphoid to myeloid cell (e.g., clonal switch from B-ALL to acute myelogenous leukemia; Gardner et al., 2016; Sotillo et al., 2015). The frequency of such antigen escape in CAR T cells, development of resistance, and approaches to limit their occurrence are areas of high clinical interest.

In other CD19-positive malignancies, early studies of CD19-targeted CAR T-cell therapy have also demonstrated efficacy, although CR rates were lower compared with those in B-ALL studies. Of four NHL studies published prior to 2014, CR rates ranged from 0% to 12% in three trials (Brentjens et al., 2011; Kochenderfer et al., 2012; Savoldo et al., 2011) and reached 67% in another small study (Kalos et al., 2011). Subsequent modifications to CAR construct, gene delivery methods, and trial design including the chemotherapy conditioning regimen have resulted in higher CR rates (e.g., 8% in NHL and 29% in CLL [Porter et al., 2015; Turtle, Riddell, & Maloney, 2016]). In the CLL trial in heavily pretreated patients, the ORR was 57%, with durable responses. A phase II trial of CAR T cells in DLBCL reported an ORR of 82% and a 54% CR rate, suggesting that this type of malignancy may be more sensitive to CAR T-cell therapy than CLL (Locke et al., 2017b).

Recent studies have attempted to reduce the rate of relapses by inhibiting host immune response against the CAR T cells. Intensifying the immunodepletion regimen by adding fludarabine to cyclophosphamide was shown to enhance both peak

CAR T-cell levels and persistence in patients with B-ALL compared with those who received cyclophosphamide alone (Turtle et al., 2016a). Notably, 16 of 17 patients (94%) who received cyclophosphamide/fludarabine prior to CAR T cells had a CR. In patients who underwent lymphodepletion and had no detectable residual disease, three of four individuals who received prior cyclophosphamide (alone or in combination with etoposide) subsequently relapsed compared with zero of six patients who had received cyclophosphamide/fludarabine lymphodepletion. Improved efficacy and persistence also were reported for patients with NHL who received this conditioning combination regimen (Turtle et al., 2016b). Thus, incorporation of fludarabine as part of a low-dose conditioning regimen is now recommended with CAR T-cell therapy, at least for CARs employing the 4-1BB costimulatory domain.

## TREATMENT-RELATED TOXICITIES AND MANAGEMENT

CAR T-cell therapy can result in a clinical benefit in many patients, but clinicians must be aware that it may also produce a range of toxicities of varying severity and duration. The most clinically significant toxicity that occurs following infusion of CAR T cells is the systemic inflammatory response of CRS. Cytokine-release syndrome develops when large numbers of activated lymphocytes release inflammatory cytokines that recruit and activate other immune cells and also exert direct physiologic effects. Cytokine-release syndrome has been previously reported to occur following infusion of adoptive cellular immunotherapy, including CAR T cells (Brentjens, Yeh, Bernal, Riviere, & Sadelain, 2010; Davila et al., 2014; Grupp et al., 2013).

Cytokine-release syndrome is typically accompanied by a constellation of inflammatory toxicities. Fever is usually the first clinical sign, but cardiovascular dysfunction (e.g., tachycardia, hypotension), respiratory disorder (e.g., tachypnea, hypoxia), renal and hepatic failure, disseminated intravascular coagulation, other organ toxicities, and even death can occur (Davila et al., 2014).

The incidence and severity of CRS toxicities generally correlate with tumor burden as well as the level of inflammatory cytokines. In support of the central role of cytokines as mediators of CRS, this syndrome could be abrogated by prior treatment with the IL-6 receptor inhibitor tocilizumab in patients with ALL who received CAR T-cell therapy (Teachey et al., 2016). Serum levels of C-reactive protein (CRP) and ferritin may serve as a surrogate marker for CRS but cannot predict development of severe CRS. Interestingly, in one study, peak levels of 24 cytokines, including IL-6 and interferon gamma (IFNγ), during the first month following CAR T-cell infusion were highly associated with severe CRS, suggesting potential as a predictive biomarker (Teachey et al., 2016).

Although several grading systems for CRS have been described, a modified grading system has been proposed to better aid clinicians in diagnosis and guide treatment decisions (Lee et al., 2014). According to this classification, CRS is defined as mild, moderate, severe, or life threatening. For grade 1 CRS, for example, symptoms are not life threatening, whereas grade 3 CRS may be associated with grade 3/4 toxicities and requires aggressive interventions. Lee et al. (2014) have proposed an algorithm for the management of CRS based on this grading system. Appropriate treatments are recommended based on the severity of the symptoms (e.g., supportive care for grade 1 CRS or use of tocilizumab [possibly with corticosteroids] for more severe toxicities, particularly if comorbidities are present). The general trend is to intervene with tocilizumab earlier (i.e., grade 2/3) to prevent development of grade 4 CRS (Lee et al., 2014). Close monitoring for significant adverse events is required when using tocilizumab, as this agent has a black-box warning regarding risk of serious infections in patients with rheumatologic disease.

Reversible neurologic toxicities can be observed during the first few weeks of CAR T-cell therapy. They include signs such as aphasia, obtundation, tremors, and seizures, ranging from mild to severe, including death. Symptoms can include headache, altered cognitive function, and confusion or hallucinations (Lee et al., 2014). Such toxicities are common among patients with B-ALL: severe (grade > 3) toxicities were noted in 15 of 30 patients treated at the Fred Hutchinson Cancer Research Center and in 6 of 17 patients at Memorial Sloan Kettering Cancer Center (Davila et al., 2014; Turtle et al., 2016a). Such neurologic toxicity may be distinct from that seen with CRS, as other investigators

### Implications for Advanced Practice: A Conversation With Pamela Hallquist Viale

*JADPRO Editor-in-Chief Pamela Hallquist Viale, RN, MS, CNS, ANP, discussed with Dr. Davila how CAR T-cell therapy might impact advanced practitioners (APs).*

**Ms. Viale:** *What adverse effects associated with CAR T-cell therapy should APs be aware of, and how should they be managed?*
**Dr. Davila:** The two major toxicities that APs should be aware of when managing patients who receive CAR T-cell therapy are cytokine-release syndrome (CRS) and neurologic toxicities. Both have been associated with death in some patients, and failure to recognize and manage these issues appropriately can cause these manageable toxicities to become very dangerous. The main criteria used to manage CRS are those proposed by Lee et al. (2014), which call for early intervention with cytokine-blocking agents and steroids for patients who are refractory to cytokine blockers. At present, it is unclear whether corticosteroids will suppress the efficacy of CAR T-cell therapy. Data (presented at the American Society of Hematology Annual Meeting in 2016) suggest that early intervention with steroids does not appear to affect efficacy. However, this is a single trial in one disease in a cohort of young patients, so it's not certain that we can extrapolate those data to a wider group.

As more patients are treated and live longer, we would expect to see more cases of B-cell aplasia develop. This could result in infectious issues due to hypogammaglobulinemia and a reduced antibody response because B cells are killed. Such patients will have to be managed similar to those who are functionally B-cell–deficient, through the use of antibiotics and gammaglobulin.

**Ms. Viale:** *Do CAR T cells need to be customized for individual patients?*
**Dr. Davila:** CAR T cells are a customized therapy because they are derived from individual patients, so each product is unique. The T-cell preparations have different immune subsets, different gene transfers, and different toxicity and efficacy profiles. This places a substantial burden on the manufacturer to ensure adequate quality control/quality assurance before these products are administered to patients. Early clinical trials suggest an average turnaround time of 2 to 3 weeks from collection to infusion. Unfortunately, some patients may die waiting this long for customized CAR T cells to be prepared, which is the rationale for trying to develop a generic off-the-shelf product that could be administered immediately.

**Ms. Viale:** *How can APs explain this complex treatment to patients and their families?*
**Dr. Davila:** These discussions probably should begin with the concept that one of the critical functions of the immune system is to recognize and eradicate cancer as it develops. When patients develop cancer, it means the malignancy has found a way to evade the immune system. CAR T-cell therapy is a highly personalized treatment in which patients receive a T-cell product that can recognize their cancer and thus avoid the immune escape mechanisms that have been developed by the tumor cells. What we're trying to do in the laboratory is engineer T cells so they can then recognize and kill the cancer again. The T cells already have the programming to do everything they need to do; we're just pointing them to the target.

have noted that CAR-related neurotoxicity did not clearly correlate with CRS severity or kinetics, and these effects could not be prevented by tocilizumab (Maude et al., 2014; Turtle et al., 2016a).

The mechanism of neurotoxicity has not been established, although CAR T cells can cross the blood–brain barrier. Neurologic toxicity appears to be related to CAR T-cell activation, as such cells are found in cerebrospinal fluid following treatment (Kochenderfer et al., 2015; Maude et al., 2014). Worsening neurotoxicities were found to correlate with increased serum levels of the cytokines IL-6 and IFNγ, which may help predict which patients are at high risk for severe symptoms (Turtle et al., 2016a). A recent study found that peak serum levels of granzyme B, IL-10, and IL-15 were associated with neurotoxicity following CAR T-cell therapy in patients with lymphoma (Kochenderfer et al., 2017).

Optimal management of neurologic toxicity associated with CAR T-cell therapy is not clear. Workup generally includes a neurology consult,

blood and cerebrospinal fluid analyses, neuroimaging, and electroencephalography. Prophylaxis is common, but its efficacy is unknown. The gold standard of treatment is nonspecific immune suppression with systemic corticosteroids (e.g., dexamethasone), because monoclonal antibodies such as tocilizumab may not readily cross the blood–brain barrier.

Significant and prolonged B-cell aplasia is a common toxicity following CAR T-cell therapy due to the persistence of functional CAR T cells, which cause depletion of endogenous CD19-positive B cells and subsequent hypogammaglobulinemia (Frey & Porter, 2016; Kochenderfer et al., 2012; Maude et al., 2014). This represents an example of "on-target, off-tumor" toxicity (i.e., targeting antigens expressed on normal tissues), as CD19 is expressed on developing and mature B cells (Bonifant, Jackson, Brentjens, & Curran, 2016). B-cell aplasia may last from months to 2 years following CAR T-cell infusion (Brudno & Kochenderfer, 2016). It can be detected by measurement of serum immunoglobulins as well as by flow cytometry of blood and/or bone marrow. Hypogammaglobulinemia that can occur following B-cell aplasia is generally managed with intravenous immunoglobulin replacement therapy. Other toxicities resulting from prolonged B-cell aplasia have not yet been described, but as more patients are treated, infections and additional complications should be anticipated. Infections should be managed by antibiotics and/or gammaglobulin. Preclinical studies have demonstrated the feasibility of reversing B-cell aplasia by selectively eliminating CAR T cells following tumor eradication using "suicide gene therapy" or by using coexpressed antigens that can then be targeted by administration of specific antibodies (Casucci & Bondanza, 2011; Paszkiewicz et al., 2016).

Other potential toxicities of CAR T-cell therapy include insertional oncogenesis with activation of cellular proto-oncogenes (resulting in virus-induced tumors) and graft-versus-host disease, although neither has been observed to date. Anaphylaxis due to the immunogenicity of mouse-derived or recombinant proteins is also theoretically possible but has rarely been reported (Bonifant et al., 2016).

## CONCLUSION

Clinical trial data to date have demonstrated the potential of CD19-targeted CAR T-cell therapy for several relapsed/refractory hematologic malignancies. Multiple clinical trials are ongoing or planned to confirm these results and to better define the variables that may affect efficacy such as CAR design, manufacturing processes, viral vector, T-cell dose, and duration of treatment. Investigators are also exploring whether other antigens expressed on B-cell leukemias and lymphomas, such as CD30 and κ light chain, could serve as therapeutic targets (Ramos, Heslop, & Brenner, 2016). Recent data suggest this technology could be useful for the treatment of additional malignancies such as newly diagnosed and relapsed multiple myeloma by targeting B-cell maturation antigen (Ali et al., 2016). CAR T cells targeting antigens expressed on solid tumors, such as EGFR and HER2, are in clinical development as well (Yu et al., 2017). This approach may be more challenging compared with hematologic malignancies because of physical barriers to immune cells imposed by the microenvironment, such as tumor stroma. Lastly, research is ongoing to determine the potential of using a universal "off-the-shelf" preparation of CAR T cells to simplify the manufacturing process and the need to customize therapy for each patient (Almåsbak et al., 2016).

As CAR T-cell therapy moves into clinical use, advanced practitioners will play a key role in the implementation of this technology including early identification of related adverse events, prevention, and management. They will also be essential in helping to educate patients about this type of therapy and make them aware of potential toxicities that may arise. This will help ensure successful adoption of this novel type of immunotherapy and optimize patient outcomes.

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