Section Editors: Christopher J. Campen and Beth Eaby-Sandy

Axicabtagene Ciloleucel: The First FDA-Approved CAR T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma

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Authors' disclosures of conflicts of interest are found at the end of this article.

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https://doi.org/10.6004/jadpro.2019.10.8.9

Abstract

Axicabtagene ciloleucel (axi-cel) is an anti-CD19 CAR T-cell therapy that has demonstrated efficacy in relapsed and refractory diffuse large B-cell lymphoma (DLBCL) patients who have had suboptimal responses to conventional therapies. The immune activation that confers the efficacy of axi-cel comes at the price of potentially devastating adverse phenomena: cytokine release syndrome and neurotoxicity. This article serves as an overview of axi-cel, including a review of the available clinical evidence, mechanism of action, and management of some of the unique toxicities of axi-cel.

Recent advances in cancer immunology have led to novel developments in chimeric antigen receptor (CAR) T-cell therapy.

The immune system provides defense against a host of potential insults, including malignancy. T cells are integral to the immune response to malignancy; they express tumor antigen–specific receptors that lead to the ultimate destruction of tumor cells.

In the case of hematologic malignancy, the immunosuppressive tumor microenvironment, inadequate number of T cells, and activation of immune checkpoints by tumor cells significantly impair the ability of endogenous T cells to completely eradicate tumor cells.

Chimeric antigen receptors are a therapeutic modality in the armamentarium of immunotherapy and have been developed to overcome the limitations of the immune system. They are immune receptors that are synthetically designed to recognize a tumor cell surface protein and enhance endogenous T-cell activity independent of conventional mechanisms, providing a novel therapeutic option for cancer patients (Jackson, Rafiq, & Brentjens, 2016; Yang, 2015).

J Adv Pract Oncol 2019;10(8):878–882

Non-Hodgkin lymphoma (NHL) comprises a heterogenous group of disorders. Diffuse large B-cell lymphoma accounts for approximately 32.5% of all NHL cases diagnosed annually, making this subtype the most common lymphoma (National Cancer Institute, 2018).

Although many are cured with initial standard chemoimmunotherapy, a select group of patients may experience primary refractory disease or relapse. Patients who fail treatment may receive salvage therapy as a bridge toward an autologous stem cell transplant (ASCT). Patients with comorbidities deemed unfit for ASCT or those with suboptimal response to salvage therapy encompass an underserved population (Chaganti et al., 2016).

Employment of anti-CD19 CAR T-cell therapy, specifically axicabtagene ciloleucel (axi-cel), has demonstrated efficacy in relapsed and refractory B-cell lymphoma patients (Chaganti et al., 2016; Neelapu et al., 2017).

PHARMACOLOGY AND MECHANISM OF ACTION

Axi-cel is a genetically modified, autologous, anti-CD19 CAR T-cell therapy. Axi-cel is currently U.S. Food & Drug Administration (FDA) approved for the treatment of adult patients with relapsed/refractory large B-cell lymphoma, with the exception of primary central nervous system lymphoma, after two or more lines of systemic therapy.

CD19 is an antigen expressed on malignant and normal B cells, but is absent on other normal cells. After axi-cel binds to CD19-positive cells, the CD28 and CD3ζ costimulatory domains result in T-cell activation, proliferation, and secretion of inflammatory cytokines; this leads to the destruction of CD19-positive cells. Peak elevation of cytokines has been observed within the first 2 weeks postinfusion and generally trend down within 28 days. Emerging data suggest the ability of CARs to remain in circulation postinfusion lends to durable remissions. This concept, known as persistence, may vary based on disease pathology and CAR construct.

Axi-cel is manufactured from patients' own peripheral blood through leukapheresis. Activated T cells are transduced with an incompetent retroviral vector and are then further expanded.

The target dose is 2×10^6 of CAR-positive viable T cells per kg of body weight, with a maximum of 2×10^8 CAR-positive viable T cells. To facilitate and optimize the expansion of axi-cel, lymphodepleting therapy with cyclophosphamide at 500 mg/m^2 and fludarabine at 30 mg/m^2 are given on the fifth, fourth, and third day prior to CAR T-cell infusion (Kite Pharma, Inc., 2018; Kochenderfer et al., 2015; Neelapu et al., 2017).

CLINICAL EVIDENCE

U.S. Food & Drug Administration approval was based on the results of a phase II, multicenter trial (ZUMA-1). The trial included relapsed or refractory patients with DLBCL, primary mediastinal B-cell lymphoma (PMBCL), or transformed follicular lymphoma (TFL).

Patients were enrolled into two cohorts consisting of those with DLBCL (N = 77) in cohort one and those with PMBCL or TFL (N = 24) in cohort two. Patients received conditioning with concurrent cyclophosphamide at 500 mg/m^2 and fludarabine at 30 mg/m^2 for 3 days followed by axi-cel at a target dose of 2×10^6 CAR T cells/kg. The primary endpoint was objective response rate (ORR; calculated as the combined rates of complete response and partial response) in the combined DLBCL, PMBCL, and TFL population. Key secondary endpoints were duration of response (DOR), overall survival (OS), and frequency of adverse events (AEs).

At the date of data cutoff for primary analysis, 101 patients received axi-cel. The median age was 58 years (range: 23–76). The ORR in the intention-to-treat (ITT) analysis was 82%, with a complete response (CR) rate of 54% and partial response (PR) rate of 28%. The median time to response was approximately 1 month (range: 0.8–6). The overall median DOR was 8.1 months (95% confidence interval [CI] = 3.3–could not be estimated). The median OS had not yet been reached at the time of analysis, with OS rates of 78% (95% CI = 69%–85%) at 6 months, 59% (95% CI = 49%–68%) at 12 months, and 52% (95% CI = 41%–62%) at 18 months. Responses were consistent across key covariates, including disease subtype, age, use of tocilizumab and/or glucocorticoids, and degree of refractory disease.

The most common grade ≥ 3 AEs were neutropenia (78%), anemia (43%), and thrombocytopenia (38%). Grade ≥ 3 cytokine release syndrome (CRS) and neurotoxicity (NTX) occurred in 13% and 28%

of patients, respectively. Twenty-seven percent of patients received glucocorticoids and 43% of patients received tocilizumab for the management of CRS and/or NTX, neither of which appeared to adversely impact response rates based on subgroup analyses. Three deaths were attributed to axi-cel use in the primary analysis, including two deaths related to CRS and one death secondary to pulmonary embolism (deemed not related to axi-cel).

As of August 11, 2018, the 101 patients were followed up for a median of 27.1 months. 84 (83%) of 101 patients had an objective response to axi-cel: 59 (58%) complete responses and 25 (25%) partial responses. The median duration of response for all 101 patients was 11.1 months (95% CI = 4.2–not estimable). The median duration of response for participants with complete responses was not reached (95% CI = 12.9–not estimable). Median progression-free survival was 5.9 months (95% CI = 3.3–15.0). The safety profile at the 2-year mark was very similar to earlier findings. Grade ≥ 3 CRS occurred in 12 (11%) patients and grade ≥ 3 neurologic events occurred in 35 (32%); all these events were manageable and largely reversible. 18 (17%) of 108 patients had grade ≥ 3 cytopenias at 3 months or later, including 12 (11%) with neutropenia, eight (7%) with thrombocytopenia, and three (3%) with anemia. At 9 months, 20 (61%) of 33 assessable patients had detectable B cells, and at 24 months, 24 (75%) of 32 assessable patients had detectable B cells. 50 patients have died from progression of disease. No new axi-cel related deaths occurred since the initial analysis.

Axi-cel has demonstrated efficacy in refractory NHL patients, providing rapid and durable responses in a historically difficult-to-treat population, with a manageable safety profile (Kite Pharma, Inc., 2018; Kochenderfer et al., 2015; Locke et al., 2017, 2019; Neelapu et al., 2017). Further analysis is warranted to confirm the OS results reported and how these translate to improved quality of life.

CYTOKINE RELEASE SYNDROME AND NEUROTOXICITY

The intense immune activation that confers axi-cel efficacy has resulted in potentially devastating adverse phenomena: CRS and NTX. Axi-cel is only available through a restricted program under a risk evaluation and mitigation strategy (REMS) called the "Yescarta REMS" (Kite Pharma, Inc., 2018).

Cytokine Release Syndrome

Improved costimulatory signaling throughout the generations of CAR-T cell therapy have translated to improved T-cell activation/expansion, cytokine production, and efficacy. This advancement comes with a cost, demonstrated by the risk of CRS following CAR T-cell administration.

Definitions, grading, and even symptoms of CRS have varied among institutions throughout the years. Generally, symptoms of CRS include fever, hypotension, respiratory insufficiency, and capillary leak syndrome. The ASTCT (American Society for Transplantation and Cellular Therapy) recently published consensus guidelines in an effort to synchronize various grading systems. They defined CRS as a supraphysiologic response that leads to the activation or engagement of T cells. Cytokine release syndrome must include a fever and may include hypotension, hypoxia, end-organ dysfunction, and capillary leak. The grade of CRS is determined by the most severe event (Table 1). Early recognition, appropriate grading, and continued supportive care are essential in the successful management of CRS.

Following the diagnosis of CRS, the goal is to find a balance between mitigating the physiologic consequences of aberrant immune activation and salvaging efficacy. At the first sign of CRS, recommendations are to immediately institute appropriate supportive care measures (e.g., antibiotics, vasopressors, fluids) and consider administration of the interleukin 6 receptor antagonist, tocilizumab, and/or corticosteroids such as dexamethasone or methylprednisolone. The REMS program for axi-cel mandates at least two doses of tocilizumab are available onsite prior to axi-cel infusion.

Expert consensus generally advises reserving tocilizumab for patients with at least grade 2 or greater CRS without overt concern for overlapping neurotoxicity (Genentech, Inc., 2018; Lee et al., 2014, 2019).

The dosing recommendations for tocilizumab are 8 mg/kg in patients over 30 kg and 12 mg/kg in patients under 30 kg given intravenously, with the option for subsequent dosing if there is a lack of clinical improvement. The interval between consecutive doses should be at least 8 hours, with a maximum of 4 total doses. Doses above 800 mg per infusion are not recommended for the treatment of

Table 1. American Society for Transplantation and Cellular Therapy (ASTCT) Cytokine Release Syndrome Grading

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever (temperature ≥ 38°C)	Yes	Yes	Yes	Yes
Hypotension	None	Not requiring vasopressors	One vasopressor with or without vasopressin	Multiple vasopressors (excludes vasopressin)
Hypoxia[a]	None	Low-flow nasal cannula or blow-by	High-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask	Positive pressure (e.g., mechanical ventilation, intubation, BiPAP, CPAP)

Note. BiPAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure. [a]Low-flow nasal cannula: oxygen ≤ 6 L/min; high-flow nasal cannula: oxygen > 6 L/min. Information from Lee et al. (2019).

CRS (Jackson et al., 2016; Kite Pharma, Inc., 2018; Lee et al., 2014, 2019).

Dosing and choice of corticosteroids should be administered based on patient characteristics. Expert opinions suggest methylprednisolone or dexamethasone if concordant neurologic symptoms exist or if CRS is refractory to tocilizumab. This dosing is followed by a taper over several days, with duration contingent upon clinical resolution.

Corticosteroids have widespread consequences on the immune system and may mitigate the antitumor effect of adoptively transferred T cells; thus, this intervention should be reserved for CRS refractory to tocilizumab (Kite Pharma, Inc., 2018; Lee et al., 2014; Neelapu et al., 2017).

Neurologic Toxicity

Similar to the discordant categorization of CRS, the ASTCT has recently established definitions in an attempt to harmonize definitions and grading for neurologic toxicity (Tables 2 and 3). Neurologic toxicity, also now termed ICANS (immune effector cell–associated neurotoxicity syndrome), encompasses several different symptoms. It can be concurrent with CRS, independent of CRS, or follow the resolution of CRS. It may manifest as delirium, tremor, seizures, aphasia, or encephalopathy.

Table 2. American Society for Transplantation and Cellular Therapy (ASTCT) Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS) Consensus Grading for Adults

Clinical event	Grade 1	Grade 2	Grade 3	Grade 4
ICE[a] score	7–9	3–6	0–2	0 (unable to score secondary to patient inability to communicate)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	None	None	Any clinical seizure (focal or generalized) that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min) or repetitive clinical or electrical seizures without return to baseline in between
Cerebral edema, elevated intracranial pressure	None	None	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad
Motor findings	None	None	None	Deep focal motor weakness such as hemiparesis or paraparesis

Note. EEG = electroencephalogram. Information from Lee et al. (2019).
[a]See Table 3 for ICE score.

Table 3. Immune Effector Cell Scoring (ICE)[a]

Orientation: 4 points *Orientation to year, month, city, hospital*
Naming: 3 points *Ability to name 3 objects (e.g., point to clock, pen, button)*
Following commands: 1 point *Ability to follow simple commands (e.g., "Show me 2 fingers" or "Close your eyes and stick out your tongue")*
Writing: 1 point *Ability to write a standard sentence (e.g., "Our national bird is the bald eagle")*
Attention: 1 point *Ability to count backwards from 100 by 10*

Note. Information from Lee et al. (2019).
[a]For grading, see Table 2.

Most often, NTX occurs within 8 weeks of axi-cel infusion, with a median time to onset of 4 days. Manufacturer and expert recommendations for the management of NTX include high-dose corticosteroids, and prophylactic antiepileptic medications, in addition to general supportive care.

Tocilizumab may be ineffective or potentially worsen isolated NTX. If there is a suspicion for concurrent CRS, consider the employment of corticosteroids and/or tocilizumab per previous discussions (Genentech, Inc., 2018; Kite Pharma, Inc., 2018; Lee et al., 2014, 2019; Neelapu et al., 2017, Santomasso et al., 2018).

SUMMARY AND IMPLICATIONS FOR THE ADVANCED PRACTICE PROVIDER

The appropriate management and early recognition of CRS and NTX/ICANS are integral attributes to the successful clinical application of axi-cel. Axi-cel is an effective therapeutic option for adults with DLBCL who have failed conventional therapies, including transplant. Available data for axi-cel are promising; however, longer follow-up is necessary to determine its true place in therapy. To allow patients to derive optimal efficacy, providers should be cognizant of significant and unique adverse events. The prompt implementation of supportive care strategies and appropriate management strategies for NTX and CRS are integral to the care of these patients.

Disclosure

Dr. King has served on an advisory board for Genentech. Dr. Orozco has no potential conflicts of interest to disclose.

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