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An Overview of Approved CAR-T Cell Therapeutics

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Key Points

- CAR-T Cell therapy is an adoptive immunotherapy option for certain disease processes.
- Two FDA-approved options, Axicabtagene ciloleucel and Tisagenlecleucel are approved for relapsed/refractory diffuse large B-cell lymphoma (DLBCL).
- Tisagenlecleucel is also approved for acute lymphoblastic leukemia (ALL) in patients up to age 25.
- Treatment with CAR-T cell therapy can be complicated by cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

Background: Chimeric Antigen Receptor-T Cells (CAR-T Cells) are an adoptive cellular immunotherapy consisting of autologous mononuclear cells harvested from the patient via leukapheresis collection. This product undergoes a T Cell enrichment step followed by CAR gene transduction via a viral vector[1]. A T cell expansion step follows which may be achieved either with soluble anti-CD3 antibody or IL-2 with or without a costimulatory signal either from co-culture with dendritic cells or anti-CD3/anti-CD28 antibodies[2].

The CAR consists of: (1) an extracellular antigen recognition domain, (2) a hinge region linking the recognition site to the transmembrane domain, and (3) an intracellular domain expressing the CD3ζ chain, which is critical for T cell receptor signaling and activation[3]. In the first-generation CAR-T Cell products, the intracellular CD3ζ chain was unmodified. In subsequent-generation CAR-T Cell constructs, the CD3ζ chain has been augmented with additional costimulatory molecules such as CD28 or CD137 (4-1BB) to improve signaling, expansion and persistence.

In 2nd generation CAR-T Cell products, signaling endo-domains of costimulatory molecules, such as CD28, CD134 (OX-40), or CD 137 (4-1BB), are inserted proximal to the CD3ζ chain[4]. In 3rd generation products, CD28 and CD137 (4-1BB) are inserted proximal to the CD3ζ chain. 4th generation products further modify the 3rd generation constructs to incorporate transgenes permitting CAR-inducible cytokine secretion or expression of additional costimulatory ligands[4,5].

What's available now: Currently approved CAR-T Cells are Axicabtagene ciloleucel (Axi-Cel; Yescarta – Gilead/Kite) and Tisagenlecleucel (Kymriah – Novartis). Both are approved for relapsed/refractory diffuse large B-cell lymphoma (DLBCL), with the latter also approved for relapsed/refractory acute lymphoblastic leukemia for children and adults up to age 25. Both express an antigen-recognition domain consisting of a single-chain variable fragment (scFV) derived from a monoclonal antibody targeting CD19. The former incorporates CD28 as a costimulatory molecule whereas the latter incorporates 4-1BB[3].

Summary of research (focusing on efficacy and toxicity):

The retrospective SCHOLAR1 study[6] provided a more precise understanding of response rates and overall survival in patients with refractory DLBCL (none received CAR-T Cell therapy). Results showed an objective response rate of 26%, complete response rate from 2%-15% (pooled complete response 7%) with median survival of 6.3 months and 1-, and 2-year survival of only 28% and 20%, respectively.

Participants with relapsed/refractory DLBCL receiving Tisagenlecleucel in the JULIET study experienced overall (i.e. complete & partial response) and complete response rates of 52% (48/93) and 40% (37/93), respectively. The median overall survival among patients who received an infusion was 12 months. The estimated probability of survival at 12 months was 49% among all patients and 90% among patients with a complete response. Most common adverse events included cytokine release syndrome, anemia, pyrexia, neutropenia, thrombocytopenia leukopenia and diarrhea. Three patients in this study died, however, none were attributed to CAR-T Cell therapy[7].

Participants with refractory large B cell lymphoma subtypes (including DLBCL, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma) receiving Axicabtagene ciloleucel in ZUMA-1 experienced an 52% (53/101) objective response rate (i.e. complete & partial response) and a 54% (54/101) complete response rate. The median time to response was rapid (1.0 month; range 0.8-6.0 months) and the median duration of response was 8.1 months. All 101 patients who received Axicabtagene ciloleucel experienced some types of adverse events ranging from pyrexia, neutropenia, anemia, thrombocytopenia or cytokine release syndrome. Forty-four patients died in this study, two were due to cytokine release syndrome associated with CAR-T Cell therapy[8].

The most significant CAR-T Cell-related toxicities include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). CRS is a systemic inflammatory response due to the release of cytokines that can affect any organ system with manifestations that may include fever, myalgia, rigors, headache, tachypnea, tachycardia, hypotension, rash, and/or hypoxia[9]. Neurologic manifestations from ICANS may include tremor, dysgraphia, altered level of consciousness, seizures, and expressive aphasia (the latter being a fairly characteristic feature). The median onset in JULIET and ZUMA-1 trials was 5 days post-treatment (range 1-17 days) with median resolution 14-17 days. A biphasic onset of ICANS may be seen, with phase I occurring concurrently with CRS (typically within the first 5 days) while phase II occurs after CRS subsides.

In the JULIET[7] study, neurologic events within 8 weeks of infusion occurred among 23/111 (21%): the median duration was 14 days and among the 13 (12%) with grade 3-4 neurologic events, the majority had resolved by data cutoff. In ZUMA-1[8], neurologic events had median resolution by day 17 with 1 patient having resolution of memory impairment after data cutoff and resolution of all other neurologic events except for four, which were ongoing at time of death (two deaths for progressive disease and two from adverse events unrelated to neurologic events).

Tocilizumab, a monoclonal antibody directed against IL-6, is used in conjunction with supportive care in the treatment of CRS. It does not, unfortunately, prevent neurologic toxicities. Inactivation of CAR-T Cells (and, thus, reduced efficacy) may result from upfront use of corticosteroids, which are therefore reserved for treatment of life-threatening CRS unresponsive to the first dose of tocilizumab and treatment of neurological toxicities[9].

In the JULIET and ZUMA-1 trials, CRS and ICANS (neurologic events) of grade 3 or higher occurred in 22% and 12%, and 13% and 28%, respectively[7,8]. The American Society for Transplantation and Cellular Therapy (ASTCT) recently published consensus definitions and grading criteria for CAR-T Cell therapy-related ICANS and CRS (See Table 1)[9].

Table 1[9]: ASTCT CRS/ICANS Grading. Grading is based upon the most severe of the three factors.

CRS Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Fever*	Temp ≥38 C	Temp ≥38 C	Temp ≥38 C	Temp ≥38 C
Hypotension	None	No vasopressors	AND vasopressor with/without vasopressin	AND Requiring multiple vasopressors without vasopressin
Hypoxia	None	≤ 6L/min by NC or blow-by	AND/OR >6L/min by HFNC, FM, NRB, Venturi mask	AND/OR requiring positive pressure**
Neurotoxicity Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
ICE Score	7-9	3-6	0-2	0
Depressed consciousness[¥]	Awakens spontaneously	Awakens to voice	Awakens to tactile stimulus only	Unarousable
Seizure	∅	∅	Any seizure activity (resolves rapidly)	Life threatening or prolonged (>5 min)
Motor findings	∅	∅	∅	Deep focal motor weakness
Elevated ICP/cerebral edema	∅	∅	Focal/local cerebral edema	Diffuse cerebral edema

** Fever not attributable to other cause, no longer a diagnostic requirement in patients on antipyretics or being actively treated with tocilizumab. **e.g., CPAP, BIPAP, intubation with mechanical ventilation. NC = nasal cannula. HFNC = high flow NC. NRB = non-rebreather mask. ∅=Not applicable. ICE = Immune Effector Cell-associated Encephalopathy: [¥]Depressed level of consciousness should be attributable to no other cause.*

Median onset of CRS was two days in ZUMA-1 and three days in JULIET whereas median duration was eight days and seven days, respectively.

Cytopenias are also common adverse events. Although febrile neutropenia occurred in 14% (with infections in 20%), and cytopenias lasting >28 days in 32%[7], myeloid growth factors – particularly GM-CSF – are not recommended until CRS has resolved or during the first 3 weeks after Tisagenlecleucel infusion, a period of time during which the risks of CRS or ICANS are greatest[10]. An additional on-target, off-tumor effect includes B-cell aplasia associated hypogammaglobulinemia, which may require downstream supplementation with IVIG.

Due to CRS and ICANS, both Axicabtagene and Tisagenlecleucel are only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Per REMS, patients will be monitored at least daily for seven days at the certified hospitals and clinics following the infusion to monitor for signs and symptoms of CRS[10].

The price tag: Costs associated with CAR-T Cell therapy are significant. In the USA, treatment with Axicabtagene ciloleucel or Tisagenlecleucel costs around $373,000 to $475,000, respectively. When adding in costs associated with hospital stay, supportive care, and physician visits, the price tag can top $1 million[5].

In conclusion, the now-approved CAR-T Cell therapies for refractory DLBCL studied in JULIET and ZUMA-1 provide improved rates of overall response, complete response, and duration of 1-year survival compared to retrospective results in SCHOLAR1. In addition to prolonged cytopenias, risks also include those of prolonged ICANS, and CRS, which appear to respond to glucocorticoids and one or two doses of tocilizumab. The overall cost of CAR-T Cell therapy is high, with at least one estimate placing the overall cost upwards of $1 million dollars or more. Newer CAR-T Cell constructs and applications are in the pipeline.

References

1. Zhu F, Shah N, Xu H, et al. Closed-system manufacturing of CD19 and dual targeted CD20/19 chimeric antigen receptor T cells using the CliniMACS Prodigy device at an academic medical center. Cytotherapy 2018;20:394-406.
2. Highfill SL, Stroncek DF. Overcoming challenges in process development of cellular therapies. Curr Hematol Malig Rep. 2019;14:269-277.
3. Chavez JC, Bachmeier C, Kharfan-Dabaja MA. CAR-T cell therapy for B-cell lymphomas: clinical trial results of available products. Ther Adv Hematol 2019;10:1-20.
4. Zhao Z, Chen Y, Francisco NM, Zhang Y, Wu M. The application of CAR-T cell therapy in hematological malignancies: advantages and challenges. Acta Pharmaceutica Sinica B 2018;8(4):539-51.
5. Subklewe M, von Bergwelt-Baildon M, Humpe A. Chimeric antigen receptor T cells: A race to revolutionize cancer therapy. Transfus Med Hemother 2019;46:15-24.
6. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-Cell lymphoma: results from the international SCHOLAR-1 study. Blood, 2017;130:1800-8.
7. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-Cell lymphoma. NEJM 2019;380:45-56.
8. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. NEJM 2017;377:2531-44.
9. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant, 2019;25:625-38.
10. Tisagenlecleucel package insert available at FDA website, accessed 01/08/20. https://www.fda.gov/media/107296/download.

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