

Essential Nursing Considerations:

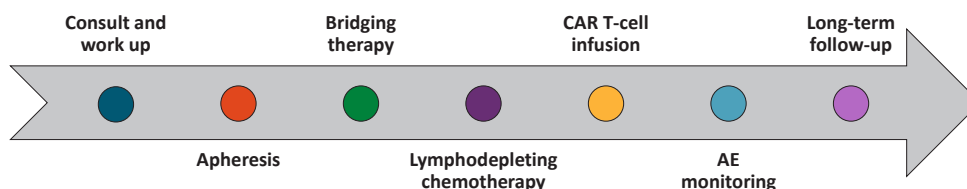
CAR T-Cell Therapy



CLINICAL CARE OPTIONS®
ONCOLOGY

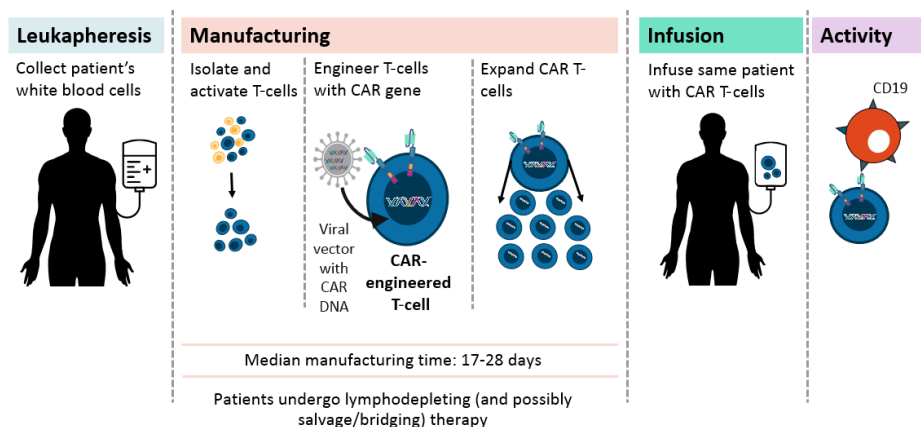
THE CAR T-CELL THERAPY JOURNEY

- CAR T-cell therapy consists of multiple stages



CONSULT AND WORKUP

- Patients are generally referred to an authorized CAR T-cell therapy center (ATC) by their primary oncologist for initial consult and workup to determine eligibility for CAR T-cell therapy
- Nursing considerations^[1]
 - Understand the principles of CAR T-cell therapy and eligibility requirements for approved treatments or clinical trials
 - Assist in obtaining and reviewing patient information to determine eligibility for treatment (eg, medical history, physical exam, performance status, and baseline laboratory studies)
 - Communicate with members of the ATC care team and referring center regarding eligibility
 - Provide education to patients and caregivers in verbal and written form regarding eligibility for CAR T-cell therapy and the process, goals, and risks
- Key elements of knowledge and education
 - Overview of CAR T-cell therapy^[2,15]



- Indications for FDA-approved CAR T-cell therapy
 - Currently approved CAR T-cell therapies (May 2020) target cancer cells expressing the CD19 antigen

Therapy	Indications
Tisagenlecleucel ^[3]	- Patients aged up to 25 years with B-cell precursor ALL that is refractory or in second or later relapse - Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy, including: - DLBCL NOS or arising from follicular lymphoma - High-grade B-cell lymphoma
Axicabtagene ciloleucel ^[4]	- Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy, including: - DLBCL NOS or arising from follicular lymphoma - High-grade B-cell lymphoma - Primary mediastinal large B-cell lymphoma

ALL, acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; NOS, not otherwise specified; R/R, relapsed/refractory.

- Key trials and data supporting the use of CAR T-cell therapy: lymphoma
 - Lisocabtagene maraleucel and KTE-X19 are CD19-targeting agents currently under FDA priority review for R/R DLBCL and mantle cell lymphoma, respectively

	ZUMA-1^[5,6]	JULIET^[7]	TRANSCEND NHL 001^[8]	ZUMA -2^[9]
CAR T-cell agent	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel	KTE-X19
Study phase	II	II	I	II
Population	Adults with refractory DLBCL	Adults with R/R DLBCL	Adults with R/R DLBCL	Adults with R/R mantle cell lymphoma
Pheresed/ treated, n	111/101	165/111	344/269	74/68
ORR, %	82	52	73	85
CR, %	54	40	53	59
1-yr OS/PFS, %	59/44	40/--	58/44	83/61

- Key trials and data supporting the use of CAR T-cell therapy: leukemia

	ELIANA^[10] (N = 75)
CAR T-cell agent	Tisagenlecleucel
Study phase	II
Study population	Pediatric/young adults with R/R B-cell ALL
CR, %	Measurable residual disease negative: 81
Median OS, mos	19.1
Median follow-up, mos	13.1

- See final table for key emerging investigational CAR T-cell therapies and trials

LEUKAPHERESIS

- Takes approximately 3-6 hours; after which T-cells are labeled, packaged, and shipped to the manufacturing facility^[1,2]
- Nursing considerations:
 - Review the procedure with patients and caregivers, including catheter placement and potential adverse events (eg, hypocalcemia)
 - Review medications to identify risk for bleeding and hypotension
 - Provide a copy of and review the consent for apheresis

BRIDGING THERAPY

- Several weeks may pass between leukapheresis and the administration of CAR T-cells; bridging therapy may be administered to palliate symptoms, debulk the primary tumor, or preserve functional status to safely administer CAR T-cells^[1]
- Regimens vary among institutions but may consist of chemotherapy, steroids, radiation therapy
- Nursing considerations:
 - Understand the rationale for bridging therapy
 - Be aware of regimens used at their institution and the associated adverse events
 - Be able to participate in symptom management and teach patients and caregivers to notify the treatment team when symptoms occur

LYMPHODEPLETION

- Used to deplete the patient's regulatory T-cells and create a favorable environment for CAR T-cells^[1]
- Regimens vary; approved product labels recommend fludarabine and cyclophosphamide for adults^[3,4]
- Nursing considerations:
 - Provide education on regimen and associated adverse events
 - Be able to participate in symptom management and teach patients and caregivers to notify the treatment team when symptoms occur
 - Guide patients through logistics of treatment (ie, location, infusions, additional prophylactic medications)

CAR T-CELL INFUSION

- Nursing considerations^[1]
 - Check patient suitability (central line requirement, vital signs/labs, any signs/symptoms of active infection)
 - If infusing CAR T-cell therapy, demonstrate competence in administering cellular therapy products
 - Check that emergency equipment is at bedside, including 2 doses of tocilizumab
 - Provide education on the infusion process, including potential adverse events
 - Provide a wallet card to the patient with details regarding the patient's CAR T-cell therapy and key contact information

POSTTREATMENT MONITORING AND MANAGEMENT OF ADVERSE EVENTS (AES)

- Key AEs with CAR T-cell therapy: cytokine-release syndrome (CRS) and neurotoxicity^[11,12]
 - CRS: potentially life-threatening toxicity caused by immune activation of T-cells, resulting in elevated inflammatory cytokines and activation of other immune cells; key symptoms include fever, hypotension, hypoxia
 - Neurotoxicity: likely related to T-cell activation; key symptoms include diminished attention, language disturbance, confusion, disorientation, agitation, aphasia, tremors, seizures, encephalopathy
 - Longer-term AEs: cytopenias, B-cell aplasia/hypogammaglobulinemia, infections
 - Higher-grade adverse events may warrant escalation of care to an Intensive Care Unit
- Nursing considerations^[1]
 - Understand how to monitor for, assess, and manage CRS, neurotoxicity, and other CAR T-cell therapy-associated AEs
 - Provide education to patients and caregivers regarding CAR T-cell therapy-associated AEs
- Key elements of knowledge and education
 - Patients should be monitored daily at the ATC for the first week following CAR T-cell infusion; patients should remain within proximity of the certified healthcare facility for at least 4 weeks^[3,4]
 - Timing of CRS and neurotoxicity
 - CRS grading: American Society for Transplantation and Cellular Therapy guidelines^[11]

Number of Days (Range)	CRS		Neurologic AEs	
	Median Time to Onset	Median Duration	Median Time to Onset	Median Duration
Axicabtagene ciloleucel ^[4]	2 (1-12)	7 (2-58)	4 (1-43)	17
Tisagenlecleucel ^[3]	3 (1-51)	8 (1-36)	6 (1-359)	ALL: 6; DLBCL: 14

- Neurotoxicity grading: immune effector cell-associated encephalopathy (ICE) score and American Society for Transplantation and

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	≥ 38°C	≥ 38°C	≥ 38°C	≥ 38°C
with				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
and/or				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.

Cellular Therapy guidelines^[11]

- Neurotoxicity is now termed immune effector cell-associated neurotoxicity syndrome (ICANS)

ICE Score
How many of the following is the patient oriented to: year, month, city, hospital (4 points)
Identify 3 objects. How many can the patient name? (3 points)
Can follow commands (1 point)
Can write a standard sentence (1 point)
Can count backwards from 100 by 10 (1 point)

Score 10: no impairment; score 7-9: grade 1 ICANS; score 3-6: grade 2 ICANS; score 0-2: grade 3 ICANS.

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable)
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	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 mins) or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness
Elevated intracranial pressure/cerebral edema	N/A	N/A	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

– Principles of toxicity management by grade^[12,13]

Grade	CRS	Neurotoxicity	CRS + Neurotoxicity
1	Supportive care	Supportive care	Supportive care
2	Tocilizumab	Steroids (dexamethasone or methylprednisolone)	Tocilizumab + steroids (dexamethasone)
3	Tocilizumab	Steroids (dexamethasone)	Tocilizumab + steroids (dexamethasone)
4	Tocilizumab + high-dose steroids	N/A	Deep focal motor weakness

For an interactive, online management decision support tool into which you can enter your patient scenarios and receive recommendations from 5 multidisciplinary experts on managing CAR T-cell therapy-related toxicities, please go to:

www.clinicaloptions.com/CARTool

EMERGING INVESTIGATIONAL CAR T-CELL THERAPIES

- Numerous trials assessing novel CAR T-cell constructs and strategies are ongoing
- Idecabtagene vicleucel is a BCMA-targeted CAR T-cell therapy currently in phase III development for R/R multiple myeloma; encouraging results in phase I trial in this population (ORR: 90%; duration of response: 10.9 months at higher dose range)^[14]

Trial	CAR T-Cell Therapy	CAR T-Cell Target	Phase	Patient Population
KarMMa-3 (NCT03651128)	Idecabtagene vicleucel vs standard triplet therapy	BCMA	III	R/R multiple myeloma
TRANSFORM (NCT03575351)	Lisocabtagene maraleucel vs SoC	CD19	III	R/R aggressive B-cell NHL
BELINDA (NCT03568461)	Tisagenlecleucel vs SoC	CD19	III	R/R aggressive B-cell NHL
OBBERON (NCT03628053)	Tisagenlecleucel vs blinatumomab or inotuzumab ozogamicin	CD19	III	Adults with R/R B-cell precursor ALL
KarMMa-2 (NCT03601078)	Idecabtagene vicleucel	BCMA	II	R/R multiple myeloma
EVOLVE (NCT03430011)	Orvacabtagene autoleucel	BCMA	I/II	R/R multiple myeloma
CARTITUDE-1 (NCT03548207)	LCAR-B38M/JNJ-4528	BCMA	I/II	R/R multiple myeloma
ZUMA-6 (NCT02926833)	Axicabtagene ciloleucel + atezolizumab	CD19	I/II	Refractory DLBCL
PLATFORM (NCT03310619)	Lisocabtagene maraleucel + durvalumab (or other TT)	CD19	I/II	R/R aggressive B-cell NHL

NHL, non-Hodgkin lymphoma; SoC, standard of care; TT, targeted therapy.

References

1. Beupierre. J Adv Pract Oncol. 2019;10(suppl 3):29.
2. Jacobson. Blood. 2011;118:4761.
3. Tisagenlecleucel PI.
4. Axicabtagene ciloleucel PI.
5. Neelapu. NEJM. 2017;377:2531.
6. Locke. Lancet Oncol. 2019;20:31.
7. Schuster. NEJM. 2019;380:45.
8. Abramson. ASH 2019. Abstr 241.
9. Wang. NEJM. 2020;382:1331.
10. Maude. NEJM. 2018;378:439.
11. Lee. Biol Blood Marrow Transplant. 2019;25:625.
12. Neelapu. Nat Rev Clin Oncol. 2018;15:47.
13. MD Anderson. CAR cell therapy toxicity assessment and management. 2017.
14. Raje. NEJM. 2019;380:1726.
15. Figure adapted from Dana-Farber Cancer Institute. How CAR T-Cell therapy works. Available at: <https://www.dana-farber.org/cellular-therapies-program/car-t-cell-therapy/how-car-t-cell-therapy-works/>.