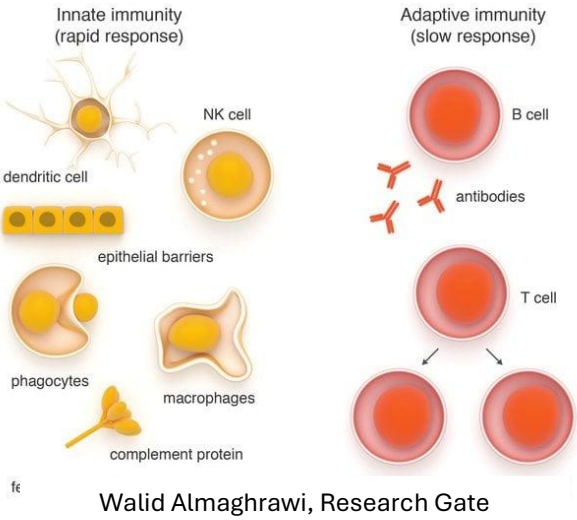
Immunotherapy for Cancer

What is Immunotherapy in Cancer Treatment?

Immunotherapy boosts or restores the patient's own immune system to improve its ability to destroy cancer cells. Our immune system includes both our innate (generalized protection such as skin, mucous membranes, fever production, inflammation and neutrophil response) and our adaptive (targeted or specific response including antibodies and T cells).

There are numerous immunotherapies that can target the immune response. This document will review therapies targeting Immune Effector Cells.



Walid Almaghrawi, Research Gate

What are Immune Effector Cells (IECs)?

Immune effector cells are specialized white blood cells that are activated to eliminate pathogens, including cancer. Examples of IECs include CD4 T cells (helper T cells), CD8 T cells (killer T cells), Natural Killer (NK) cells and plasma B cells. IEC Therapy is a broad term for therapies that use a patient's own immune system to fight cancer. IEC Therapy is divided into non-cell and cell-based therapies.

Non-Cell Based Immune Effector Cell (IEC) Therapy

Non-cell Based IEC therapy influences the way the patient's own T cells work when the drug is present in the patient's system. They can help T cells or Natural Killer Cells (NK) to identify, attach and destroy cancer cells. This therapy does not modify the patient's own cells outside of the body. Examples include Bispecific T-cell Engager (BiTEs) or other bispecific antibodies.

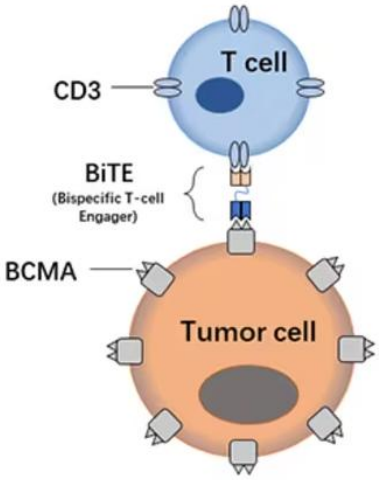
Cell-Based Immune Effector Cell (IEC) Therapy

Cell-based IEC therapy uses the patient's own cells. These are collected from the patient, modified in an external lab and then reinfused about 1 week later. Modification augments the patient's own immune cells, helping them to destroy cancer cells. Examples of cell-based IEC therapy include the Chimeric Antigen Receptor Therapy (CAR-T) therapy.

Bispecific T-Cell Engagers (BiTEs)

What is BiTE therapy?

BiTE therapy is a **non-cell-based IEC** therapy that provides targeted immunological treatment to individuals with certain hematological and solid tumors.



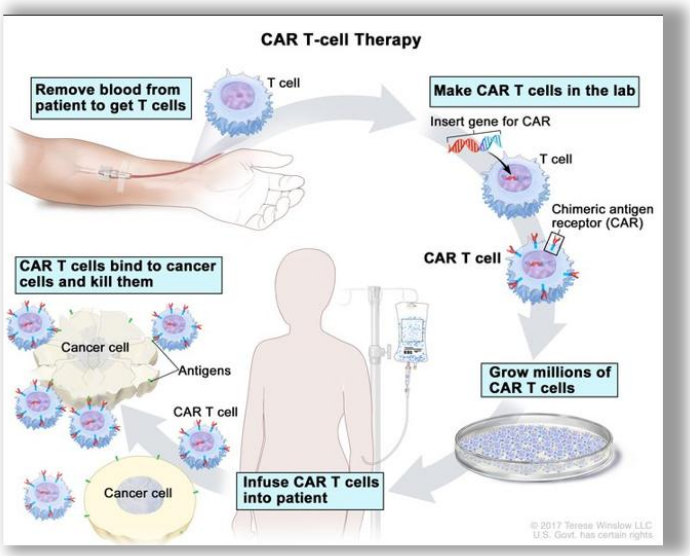
How does it work?

There are several BiTE therapies currently offered at LHSC and are administered as a continuous infusion. The infusion contains bi-specific antibodies that function by binding to both the CD3 receptor on T-cells as well as antigens on specific malignant cells. As a result, the BiTE physically links the T-cell to the malignant cell which will activate the T-cell to destroy it.

Chimeric Antigen Receptor T-Cell (CAR-T) Therapy

What is CAR-T therapy?

CAR-T therapy is a new **cell-based IEC** therapy available to individuals with certain hematologic malignancies, such as B cell acute lymphoblastic leukemia, multiple myeloma, and diffuse large B cell lymphoma.



How does it work?

The patients' own (autologous) T-cells are collected through apheresis and then sent to a lab to be genetically modified to express chimeric antigen receptors (CAR). Once reinfused, the modified T-cells will multiply, and the CAR will recognize and destroy malignant cells.

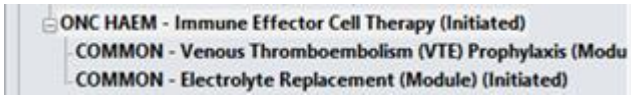
What is the role CCTC?

Two notable side effects of both BiTE and CAR-T therapies are cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS). Both can lead to severe complications but are reversible if identified and treated early. CRS and/or ICANS may develop in 50-60% of patients who receive IEC therapy. CAR-T therapy is associated with more severe CRS/ICANS symptoms. Among patients who receive CAR-T therapy and develop ICANS, 25% may need CCTC admission.

CRS: *an exaggerated systemic inflammatory response following therapy due to a surge of cytokines release. Similar to other inflammatory processes, fever, hypoxemia and hypotension are early indicators. Severity can progress to multi-organ failure. Onset is between Day 1-7, with the peak risk phase between Day 7-14*

ICANS: *a cytokine-mediated disruption of the blood–brain barrier, which can progress to cerebral edema, seizures, and coma. This may present initially as expressive aphasia, disorientation, apraxia, and inattention. This can progress to cerebral edema and death. ICANS can develop in the first week post administration, with the peak risk phase between day 7-14. Symptoms can also develop weeks later.*

Immune Effector Cell Admission Checklist

❑	Notify Haem-Onc fellow or consultant to perform in-person evaluation of the patient if it was not already completed before transfer. This is a requirement for both management of CRS and ICANS to determine grades and direct management.
❑	If ICANS Grade 2 or higher, ensure Neurology has been consulted.
❑	Management of patient is to be between CCTC fellow or consultant and Haem-Onc fellow or consultant.
❑	Ensure "**ONC - Syndrome Management Immune Effector Cell**" care set is initiated by CCTC fellow or Haem-Onc fellow or consultant, based on CRS and/or ICANS grades. These care sets will include necessary medications, monitoring, and other interventions. 
❑ - -	Ensure CCTC fellow or consultant reviews "**ONC HAEM – Immune Effector Cell Therapy**" care set with Haem-Onc fellow or consultant. Do not discontinue this without the Haem-Onc team's review. There are a number of important medications that should continue. 
❑	Review interventions and monitoring requirements from care set(s).
❑	Ensure "Immunological Effector Cell Encephalopathy (ICE)" is on view. See slide show for details.
❑	Document admission ICE with standard neurological and vital sign assessment. Reassess and document Q1H until Haem-Onc/CCTC determines deescalation is appropriate.
❑	Monitor for CRS including temperature, vital signs, SpO2, blood gases, lactate and organ function per CCTC standard care.

Cytokine Release Syndrome (CRS)

CRS is an exaggerated systemic inflammatory response following Immune Effector Cell (IEC) therapy. CAR-T therapy is associated with more severe CRS due to a surge of cytokines released by activated immune cells. For monitoring, nurses are expected to conduct frequent vital sign assessments (with temperature) and labs, at the frequency indicated in the care set or according to CCTC nursing standards. Monitor for fever, hypotension, hypoxemia and signs of organ dysfunction as with other severe inflammatory responses.

CRS Grading System:

CRS is graded from 1 (least severe) to 4 (most severe). At each grade, there is a specific care set that outlines medical management and monitoring. Patients with Grade 2 CRS will have CCOT consulted and may require admission to CCTC if their risk for deterioration is predicted by Haem-Onc to be high. Patients with Grade 3 CRS require transfer to CCTC for vasopressor support and/or positive pressure ventilation.

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature greater or equal to 38C	Temperature greater or equal to 38C	Temperature greater or equal to 38C	Temperature greater or equal to 38C
WITH				
Hypotension	None	Not requiring vasopressors	Requiring 1 vasopressor (+/- vasopressin)	Requiring 2 or more vasopressors excluding vasopressin
AND/OR				
Hypoxia	None	Requiring low-flow nasal cannula	Requiring HFNC, facemask, venturi or non-rebreather	Requiring positive pressure (CPAP, BiPAP, mechanical ventilation)

Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

ICANS is caused by cytokine-mediated disruption of the blood–brain barrier. The Immunological Effector Cell Encephalopathy (ICE) assessment is used to determine ICANS grade.

Immune Effector Cell Encephalopathy (ICE) Assessment:

Orientation	Assess the patients' orientation to year, month, city, and hospital.	1 point for each correct answer.
Naming	Assess expressive aphasia by pointing to 3 objects and having the patient name the 3 objects.	1 point for each correct answer.
Following Commands	Assess receptive aphasia by instructing the patient to follow a simple command (e.g. show 2 fingers)	1 point for correctly following command.
Writing	Assess apraxia by having the patient write a sentence on the specified writing document (CAN0259-OND) and compare to previous.	1 point for writing that is comparable to previous.
Attention	Assess attention by instructing the patient to count backwards from 100 by increments of 10.	1 point for correctly and entirely counting backwards from 100 to 0.

ICANS Grading System:

ICANS is graded from 1 (least severe) to 4 (most severe). At each grade, there is a specific care set that outlines medical management and monitoring. Patients with Grade 2 ICANS will have CCOT and Neurology consulted and may require admission to CCTC if their risk for deterioration is predicted by Haem-Onc to be high. Grade 3 ICANS will need transfer to ICU for monitoring and management of cerebral edema

Neurotoxicity Domain	**N/A**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
ICE Score	10	7-9	3-6	0-2	0 (patient unarousable and unable to perform that is not attributed to another cause)
Depressed LOC	N/A	Awaken 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	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 min): or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	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

Verspeeten Family Cancer Centre
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Immune Effector Cell-Associated Encephalopathy: Writing Assessment

ADDRESSOGRAPH

Write the following sentence at each visit to the chemotherapy suite and at your clinic follow-up appointments. Keep this sheet on you for all visits, thank you!	**Date** (YYYY/MM/DD)
Hello, my name is _____ *First Name* *Last Name*	

Copies of this form are available in file folder at the front desk.

Continue documenting the patient's handwriting on the form from Haem-Onc.

If another form is needed, go to "Programs and Services" and chose "Forms Management". Search the "Forms Catalogue". Enter form number CAN0259 and download another copy. The owner is Cancer Care Ontario.

Have patient write the sentence "my name is x x" on the line below the previous entry. Time the entry and compare the handwriting quality/characteristics with the previous entry.