LYMPHOMA CANADA

CAR-T: Protocol Overview

Chimeric Antigen Receptor T cell therapy, or CAR-T therapy, is a type of immunotherapy that modifies a patient's T-cells to better detect and destroy lymphoma. A part of the body's immune system, T cells are a type of white blood cell that attacks virus-infected cells, foreign cells and cancer cells. CAR-T therapy enhances the effectiveness of T cells.

The following steps outline the protocol for CAR-T therapy:

1 Screening

Patients must consult with their physician to see if they are medically eligible for CAR-T therapy. There are specific eligibility criteria for each specific therapy, based on what was learned in clinical trials and regulatory approvals.

Generally, patients will be assessed for the following criteria to determine their eligibility for CAR-T therapy:

- Diagnosed with a subtype of lymphoma for which the CAR-T therapy is approved
- Meet regulatory criteria (e.g. relapsed twice and have been previously treated)
- Have tumours that express the specific antigen the therapy targets
- Satisfactory organ function and performance status
- No active infections
- No significant cardiac, neurological or immune dysfunction

Physicians will discuss a patient's eligibility and will send relevant medical records to the specialty cancer centre that performs the CAR-T therapy to be evaluated for treatment.

2 Leukapheresis

Blood is taken from the patient and T cells are isolated and removed in a process called apheresis or leukapheresis. The remaining blood is transfused back to the patient.

To help increase the number of functional T cells the patient's treatment regimen may be changed for a certain time frame. This may include avoiding corticosteroids or salvage chemotherapy for a certain period of time before leukapheresis.

Timeline: The procedure takes 3 – 6 hours

3 T-Cell Engineering

The collected T cells are shipped to a designated laboratory where they are genetically modified. This happens in three steps:

1. **Activation:** The isolated T cells are exposed to antibody-coated beads which activates them.
2. **Addition of the CAR:** The CAR gene is introduced into the activated T cells by using viral vectors. This causes permanent genomic modification and continued CAR expression.
3. **Expansion:** The CAR T cells are then expanded using a culture system to make sure there are enough cells for therapy.

The modified cells are then washed, concentrated and tested for quality. Finally, they are frozen and shipped back to the patient's treatment centre.

Timeline: Approximately 2 – 4 weeks

4 Pre-Treatments

Patients are typically given low-dose chemotherapy called lymphodepleting chemotherapy to reduce their number of immune cells before the CAR-Ts are infused. This helps the CAR-Ts start to grow and multiply within the patient. The patient may receive bridging treatment with steroids, radiation or chemotherapy to help keep their cancer in check while waiting for CAR-T therapy.

Timeline: Approximately 2–14 days before the CAR-T infusion

5 CAR-T Infusion

The modified CAR-T cells are infused into the patient at their treatment centre. The patients' specific treatment protocol can vary to provide maximum efficacy and minimal toxicity and may have different optimal cell doses, number of doses, and timing.

Timeline: 30 - 60 minutes

6 Observation

Patients are monitored regularly to see if the CAR-T therapy is effective and for short- and long-term side effects of CAR-T therapy. Patients are advised to stay near their treatment centre for a few weeks and will often be admitted to hospital or require frequent assessment if they are not admitted.

Most short-term side effects can be managed with supportive therapies. However, other side effects can be more serious and potentially life-threatening and may require treatment in a hospital intensive care unit.

Severe side effects are often the result of the high activity of the immune system brought on by the CAR-T therapy. Immunosuppressive drugs, corticosteroids and other supportive therapies are used in symptom management, with the goal of curtailing the side effects without removing the CAR-T cells completely.

It is important patients and caregivers can identify symptoms quickly so they can be treated appropriately. The treatment centre will give you specific instructions about what to do and who to contact if a patient develops symptoms in the outpatient setting.

Cytokine Release Syndrome

As CAR-T cells are released and multiply in the patient's body, their immune system is highly activated and releases a massive number of inflammatory cytokines into the blood, causing cytokine release syndrome (CSR). CRS is the most common side effect of CAR-T therapy and can happen within the first week after infusion or later in some cases.

The duration and intensity of CSR can vary. Some patients only experience mild flu-like symptoms while others have high fevers, hypoxia (oxygen deficiency), low blood pressure and multi-organ dysfunction. A drug called tocilizumab and corticosteroids are often given to decrease the production of cytokines that contribute to CRS.

Neurotoxicity

(now termed IEC-associated neurotoxicity syndrome or ICANS)

IEC refers to Immune Effector Cells. The CAR-T cells can have an effect on the patient's brain, which can cause confusion, agitation and a lack of awareness. Patients may experience headaches, difficulties with written or spoken language, anxiety and occasional seizures.

Neurotoxicity can occur with or without cytokine release syndrome. It is reversible in most cases, but in rare cases, cerebral edema associated with neurotoxicity may develop, which is potentially fatal. Corticosteroids are commonly used to manage severe cases of ICANS.

Macrophage-Activation Syndrome

The severe inflammation of the immune system, which can cause multi-organ failure.

Febrile Neutropenia

An abnormal decrease in the number of certain white blood cells in the blood coupled with fever.

Anemia

A condition in which the number of red blood cells is below normal.

Thrombocytopenia

A decrease in the number of platelets in the blood.

B Cell Aplasia and Hypogammaglobulinemia

A decrease in the number of normal B cells, leading to decreased immunoglobulin (antibody) production and a higher risk of developing serious infections. Hypogammaglobulinemia can be managed by reconstituting the patient's immunoglobulin G (IgG) levels with intravenous (IV) or subcutaneous IgG, a blood product made from pooled plasma of healthy individuals.

Timeline: Ongoing