

Chimeric Antigen Receptor (CAR) T-Cell Therapy



OVERVIEW

Chimeric antigen receptor (CAR) T-cell therapy is a type of immunotherapy that uses a person's own immune system to try to destroy lymphoma cells.

The immune system normally protects us from infection and disease, including cancer. It is made up of a network of organs and specialist white blood cells called lymphocytes. There are three main types of lymphocytes that have different roles that include:

- **B lymphocytes (B-cells)** – make antibodies to fight infection
- **T lymphocytes (T-cells)** – help B-cells to make antibodies, to identify infected cells, fight infection & directly kill infected or cancer cells in the body
- **Natural killer (NK) cells** – also attack cancer cells and kill viruses

When lymphocytes gain certain genetic changes, they divide and grow uncontrollably resulting in lymphoma. This results in the immune system not being able to detect the abnormal cancerous cells or not being able to destroy them. Cancer cells can also develop ways to prevent the immune system from attacking them. For example, some cancer cells make special proteins on their surface that tell T-cells not to attack them.

Chemotherapy and radiation therapy have been the traditional ways to treat cancer. Immunotherapy is a type of treatment that improves the body's ability to detect and attack cancer cells by using the body's immune system. It is an active area of clinical research and there are proven immunotherapy treatments. These include monoclonal antibody therapy (rituximab or obinutuzumab), other targeted therapies (eg. pembrolizumab in Hodgkin lymphoma and primary mediastinal B-cell lymphoma), and most recently chimeric antigen receptor (CAR) T-cell therapy.

WHAT IS CAR T-CELL THERAPY?

CAR T-cell therapy is a new type of immunotherapy that uses a patient's own T-cells to recognise and attack cancer cells. CAR T-cell therapy uses specially altered T-cells to directly and precisely target certain cancers, including some subtypes of B-cell lymphoma. The reprogrammed T-cells strengthen the immune system to attack and kill the lymphoma cells.

A fraction of a patient's own T-cells are collected from the blood using a procedure called apheresis. These cells are genetically re-engineered in a special laboratory, so they now carry special structures called chimeric antigen receptors (CAR) on their surface. CARs are proteins that are designed to attach to a specific target on cancer cells. For the currently approved products, that protein is called CD19 which is found on the surface of normal and cancerous B-cells.

The manufactured CAR T-cells are then re-infused into the patient (like a blood transfusion). When they bind to their target receptor, they multiply rapidly, and kill the target cells which in this case is the B-cell lymphoma and normal B lymphocytes. They continue to multiply and attack the cancer cells until they are all gone. In some cases, it is thought that the CAR T-cells go on living in the body (called "persistence") and can continue to keep the lymphoma or leukaemia at bay. This is why many think of CAR T-cell therapy as a 'living drug'.

WHO IS ELIGIBLE FOR CAR T-CELL THERAPY?

CAR T-cell therapy is publicly funded in Australia for people who meet the strict eligibility criteria that will be followed by an expert medical panel. Patients who have been diagnosed with one of the listed B-cell diseases, who have relapsed after at least 2 prior therapies or are refractory (have not responded to chemotherapy) and are medically fit, may be eligible for CAR T-cell therapy. CAR T-cell therapy can have serious side effects and is not suitable for everyone.

The majority of patients usually go into remission after receiving current standard first-line therapy that usually includes chemotherapy and a monoclonal antibody. CAR T-cell therapy is very expensive and costs over \$500,000 per patient. The high cost is due to the specialist manufacturing process that is involved to create CAR T-cells. Only certain cancer centres will be specially trained to infuse CAR T-cell therapy and manage patient care.

The following lymphoma subtypes may be eligible:

- Diffuse large B-cell lymphoma
- Transformed follicular lymphoma
- Primary mediastinal B-cell lymphoma
- B-cell acute lymphoblastic lymphoma (B-ALL) for people younger than their 26th birthday.

CAR T-CELL THERAPY IN AUSTRALIA

In Australia, there have been two products that have had a positive recommendation from the Medical Services Advisory Committee (MSAC) and both will soon be publicly funded. These products include:

- Kymriah™ (tisagenlecleucel) a Novartis product – it is now publicly funded
- Yescarta™ (axicabtagene ciloleucel) a Gilead product – approved but NOT funded in Australia

At present these commercially available CAR T-cells are made in the USA, although a company located at Peter MacCallum Cancer Centre, in Melbourne, will soon be manufacturing Kymriah under contract. CAR T-cells will be then administered, and patient care managed at registered CAR T-cell cancer centres. The centres that are currently operating are located in Melbourne, Brisbane and Sydney. A centre will soon be located in Perth.

Until funding processes are finalised across Australia, Peter Mac, the Royal Brisbane & Women's Hospital (RBWH) and the Royal Prince Alfred Hospital (RPA) in Sydney, are the only locations that are providing commercial (non-clinical trial) CAR T-cell therapy to patients with lymphoma indications.

All referrals are discussed by medical experts at a national weekly CAR T-cell meeting. For more information speak to your haematologist or Lymphoma Australia.

THE CAR T-CELL PROCESS

CAR T-cells are made individually for each person. You may receive other treatments, such as chemotherapy (bridging therapy), to keep your lymphoma under control while the CAR T-cells are being made (3-6 weeks).

- **T-cell collection:** Blood is taken from the patient. The white blood cells, that include T-cells, are separated out and the rest of the blood is put back into the patient's bloodstream via apheresis (similar to collecting stem cells). The patient's T-cells are sent to the lab for manufacturing.
- **Manufacture of CAR T-cells:** The T-cells are modified or genetically engineered (changed) so they can find and kill cancer cells. The engineered T-cells are now called CAR T-cells. The patient's CAR T-cells are multiplied until there are millions of them and then are frozen. The CAR T-cells are then sent back to the patient's hospital. This process can take several weeks.
- **Chemotherapy:** The patient will receive chemotherapy (lymphodepletion), to reduce the number of normal T-cells in the body to make space for the CAR T-cells, so they can expand (multiply) once administered. Typically, this

chemotherapy is fludarabine and cyclophosphamide.

- **CAR T-cell infusion:** The patient's CAR T-cells are thawed and then put back into the patient's bloodstream, similar to receiving a blood transfusion or stem cells.
- **In the patient's body:** The CAR T-cells multiply rapidly in the patient's bloodstream. The CAR T-cell finds and kills the lymphoma cells. The CAR T-cells may remain in the bloodstream to attack if lymphoma returns.
- **Recovery:** The patient will be monitored carefully during and after the treatment. Patients who receive CAR T-cell therapy have a recovery period of approximately 2-3 months. During this period, patients will be evaluated for side effects and treatment response. During at least the first 30 days after discharge from hospital, patients need to remain close (within 20 min) to their treating hospital for regular follow up or urgent care if required.

POSSIBLE SIDE EFFECTS

All medicines and cancer treatments can cause side effects. CAR T-cell therapy is a new type of treatment, and as researchers understand the treatment better, so are the management of these side effects. CAR T-cell therapy can cause serious side effects and the treatment is only given in hospitals with the facilities and specialist staff to manage these side effects effectively.

Cytokine release syndrome (CRS) is a potentially serious side effect and is associated with CAR T-cell therapy. Cytokines (chemical messengers that help the T-cells carry out their functions) are produced when the CAR T-cells multiply in the body and kill the cancer cells. CRS symptoms can range from mild flu like symptoms through to more serious symptoms.

Some of the common side effects may affect a significant proportion of patients and can lead to prolonged hospitalisation. The frequency of these side effects may be linked to the product used, and to patient and disease-related factors. These include:

- Cytokine release syndrome
- Fever and chills
- Low blood pressure and low oxygen levels
- Nervous system problems including; brain problems (encephalopathy), headache, twitching or shaking (tremor) or dizziness
- Rapid heart rate (tachycardia) and changes in heart rhythm (arrhythmia)
- Fatigue (extreme tiredness)
- Cough
- Digestive symptoms; nausea, vomiting, reduced appetite, diarrhoea and constipation
- Febrile neutropenia (low neutrophils – immune system) and infections

See the Lymphoma Australia website www.lymphoma.org.au for

FACT SHEET

more information on CAR T-cell therapy and some of the side effects in more detail.

CLINICAL TRIALS

There are many clinical trials that are currently being conducted around the world for a number of different blood cancers and solid tumour cancers. It has been shown to be most successful in certain B-cell lymphomas. There are currently clinical trials for B-cell lymphoma across Australia available (from first-line treatment) for:

- Diffuse large B-cell lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- B-cell non-Hodgkin lymphoma
- Chronic lymphocytic leukaemia
- Allogeneic CAR T-cell therapy (donor cells)

For more information see 'Understanding Clinical Trials' fact sheet or see www.clinicaltrials.gov

FOR FURTHER INFORMATION

- Speak to your haematologist about whether you are eligible or appropriate to have CAR T-cell therapy. If so, your haematologist can arrange a referral.
- For any queries related to patient eligibility for CAR T-cell therapy or how patients can access this treatment, please email: CAR-T.enquiry@petermac.org
- You can contact the Lymphoma Nurse Support Line: **1800 953 081** or email: nurse@lymphoma.org.au for further information or advice.

SOME QUESTIONS TO ASK YOUR DOCTOR

- Am I eligible for CAR T-cell therapy?
- Are there CAR T-cell therapy clinical trials available in Australia that I may be eligible for?
- Are there any other treatments that are better for me?
- Are there any other clinical trials available for me?