CAR-T Therapy

CAR-T Cell Therapy: A New Treatment for Aggressive Blood Cancers

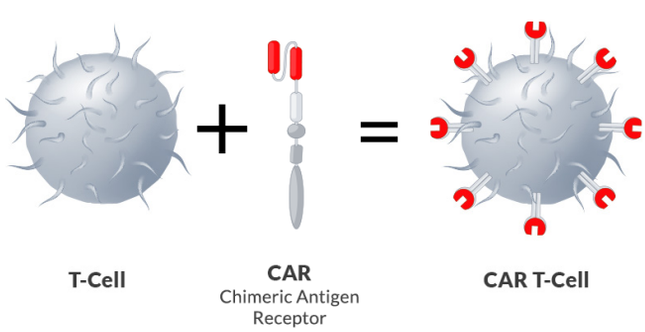
In recent years, a specific form of treatment known as CAR (Chimeric Antigen Receptor) T-cell therapy has gained attention worldwide for its use in the treatment of patients with aggressive forms of blood cancers. CAR T-cell therapy is an exciting new form of treatment that takes and modifies the immune cells of patients so that they can be more effective in killing cancer cells.

To date, CAR-T cell therapy has demonstrated significant benefit in the treatment of conditions such as B-cell acute lymphoblastic leukaemia, B-cell lymphomas and multiple myeloma. Several forms of CAR-T cell therapy have been licensed by the US FDA (Food and Drug Administration) for clinical use over the last few years.

WHAT IS CAR-T CELL THERAPY?

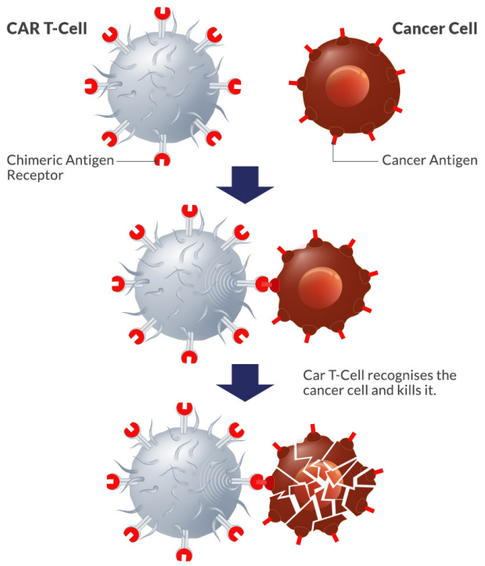
CAR stands for Chimeric Antigen Receptor, while T-cells are a form of white blood cells in our bodies which play an important role in the recognition and clearance of foreign bodies, including cancer cells. However, in patients with aggressive forms of cancer, the T-cells can sometimes be ineffective in clearing the cancer. This is due to the fact that they cannot effectively recognise the cancer cells, or they may not be able to infiltrate the areas where the tumour is.

CAR T-cell therapy is a way to get T-cells to fight cancer more efficiently by genetically modifying them in the laboratory. These



gene-modified CAR T-cells are able to express a protein on their cell surface which allows them to identify and destroy specific cancer cells with highly potent activity.

After CAR-T cells are infused into a patient, they act as a "living drug" against cancer cells. When they come in contact with targeted cancer cells, CAR-T cells rapidly multiply in numbers to become very potent cancer killer cells.



CAR T-Cell and Cancer

CELLS USED FOR CAR-T

The present generation of CAR T-cells use cells from patients themselves (autologous T-cells). This method can pose challenges as patients who require CAR-T usually have more aggressive disease and tend to be heavily pre-treated with different forms of chemotherapy. As a result, it is sometimes hard to obtain enough T-cells from a patient to manufacture the necessary CAR-T cell product.

In the near horizon, the next generation of CAR T-cells may be "off-the shelf" cellular therapy products made using pre-harvested cells from carefully selected donors, instead of using patient cells (allogeneic T-cells) .

ELIGIBLE PATIENTS FOR CAR-T CELL THERAPY

The initial development of CAR T-cell therapies focused largely on Acute Lymphoblastic Leukaemia (ALL), which is the most common form of cancer in children. In children with aggressive forms of ALL, relapsed ALL remains a leading cause of death from childhood cancer. However, in recent years, CAR T-cell therapy for children and adolescents with aggressive forms of B-ALL (Acute B-cell Lymphoblastic Leukaemia - a blood cancer that affects B-cells, which are white blood cells that grow in the bone marrow) has produced excellent results with initial response rates of 70-90%.

In summary, CAR-T cell therapy has presently been successfully used in the treatment of the following:

- Diffuse large B-cell lymphoma
- Follicular lymphoma
- Chronic lymphocytic leukaemia
- Multiple myeloma
- Acute B-cell lymphoblastic leukaemia

To date, the US FDA has approved more than 5 CAR-T cell therapies for the treatment of various blood cancers. The different agents utilise slightly different methods of genetic engineering to transform the patient's T cells into CAR-T cells.

In Singapore, there is only one approved commercial CAR-T cell product at present for patients with relapsed B-cell acute lymphoblastic leukaemia (under age of 25) or relapsed diffuse large B-cell lymphoma patients who have failed 2 prior lines of therapy.

MANUFACTURE OF CAR-T CELLS

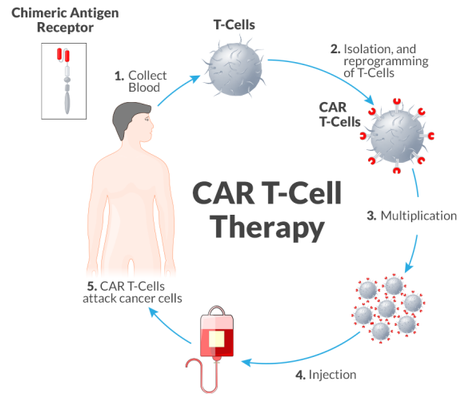
The present autologous CAR-T products use a process that requires collection from each individual patient and "bespoke" manufacturing for each individual patient product. CAR T-cell therapy production involves the following phases:

1. **Collection:** The T-cells are collected from the patient's blood. The procedure is known as apheresis or leukapheresis.

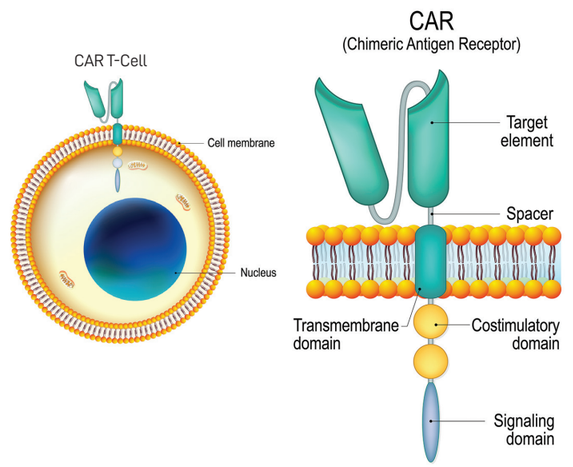
2. **Engineering:** The collected T-cells are sent to a laboratory to be genetically engineered into CAR T-cells.

3. **Multiplication:** The modified CAR T-cells are grown and multiplied in the laboratory. This process of multiplying the CAR T-cells can typically take 4-6 weeks. Once this phase is completed, the cells are frozen and sent back to the clinic to be used for the patient's treatment.

4. **Conditioning:** Before the new CAR T-cells are infused into the patient's body, the patient will have a brief course of chemotherapy. This will help to improve the chances of the body accepting the new CAR T-cells.



CAR T-Cell Therapy



Chimeric Antigen Receptor T-Cell

5. **Infusion:** Shortly after the chemotherapy, the modified CAR T-cells are infused into the patient through a process similar to a blood transfusion.

6. **Recovery:** After the CAR T-cell infusion, the patient may experience some side effects for the first 30 days after the infusion, and the recovery of the body's immune system may take several months.

POTENTIAL SIDE-EFFECTS OF CAR T-CELL THERAPY

Some common side effects of CAR T-cell therapy include:

1. Cytokine release syndrome (CRS)

- CRS occurs due to a sudden release in cytokines (chemicals) from the immune T-cells.
- In some cases, patients may develop flu-like symptoms such as fever, chills, headache, nausea, vomiting, loose stools, and muscle or joint pains.
- Up to 70-90% of patients can develop some form of CRS, but these symptoms are usually mild, and short-term - lasting about 5-7 days.

2. Neurological events

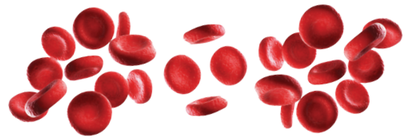
- Neurological events typically occur around 2-5 days after infusion.
- Patients may present with confusion, difficulty speaking, agitation, and in more severe forms - seizures, drowsiness, altered state of consciousness and encephalopathy (brain injury and malfunction).
- Patients will need to be monitored carefully for any neurological disturbances. Sometimes, they will need to be taken to intensive care for stabilisation in more severe grades of neurotoxicity.

Factors influencing the severity of these side-effects include the amount of active disease burden at time of CAR-T cell therapy, presence of underlying medical issues (such as prior neurological issues) as well as the type of CAR-T cell product infused.

FUTURE OF CELLULAR THERAPY FOR CANCER

Although the present generation of CAR-T therapy has produced impressive outcomes, setbacks such as relapse and resistance have been reported. The next generation of CAR-T cells for blood cancers may be more potent and may also come with lesser side effects. They are presently undergoing clinical trials.

To date, CAR-T cell therapy has demonstrated significant benefit in the treatment of conditions such as B-cell acute lymphoblastic leukaemia, B-cell lymphomas and multiple myeloma. Several forms of CAR-T cell therapy have been licensed by the US FDA (Food and Drug Administration) for clinical use over the last few years



CAR T-cells have also been presently applied in clinical trials for the treatment of solid tumours, including hepatocellular carcinoma, pancreatic cancer and mesotheliomas. While the data from the use of CAR-T therapy in these diseases remains preliminary, it is hoped that this exciting form of new cellular therapy will be used in many different types of cancers. PRIME

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