Introduction

My final rotation of foundation year one was spent on a haematology ward. I clerked a patient with a background of a refractory B cell haematological malignancy who was admitted for chimeric antigen receptor (CAR) T cell therapy. I had read about this novel therapy online, but being involved in this case developed my appreciation of the complexities of the immune system and potential for personalised immunotherapy.

The anxious, but eager patient was admitted to a positive pressure room and received pre-conditioning chemotherapy. A few days later CAR-T cells were re-infused. The team conducted daily reviews, closely monitoring observations and handwriting. One afternoon I was bleeped to review due to hypotension and fevers, my body filled with adrenaline. I donned full personal protective equipment. On assessment, the patient appeared stable. I prescribed a fluid bolus and broad-spectrum antibiotics. However, the team was now on high alert for evidence of cytokine release syndrome (CRS). Persistent fevers prompted Tocilizumab treatment to control the CAR-T induced cytokine storm. Multiple weeks of ongoing monitoring ensued.

It was a privilege being involved in this case in my first year as a doctor. The immune system is a fascinating interconnected network designed to fight infections and abnormal cells. Despite constantly adapting, certain cancer cells evade detection, leading to proliferation. CAR-T therapy was approved by the National Health Service (NHS) in 2018 for management of multiple types of relapsed or refractory haematological malignancies (NHS England, 2018a). It uses genetically modified T cells and the body's own immune system to target cancerous cells (Haslauer et al., 2021).

CAR-T cell therapy (summarised in Figure 1)

The patient initially undergoes Leukapheresis to collect T cells. T cells are then genetically modified ex-vivo, replacing the endogenous T cell receptor with CAR. The CAR consists of multiple proteins designed to target specific antigens on cancer cells, most commonly CD19 (Haslauer et al., 2021). Pre-conditioning chemotherapy is administered before re-introducing CAR-T cells. Currently four types of CAR-T are NHS approved: Axicabtagene ciloleucel (Yescarta), Tisagenlecleucel (Kymriah), Brexucabtagene autoleucel (Tecartus), Lisocabtagene maraleucel (Breyanzi) (Blood cancer UK, 2025).

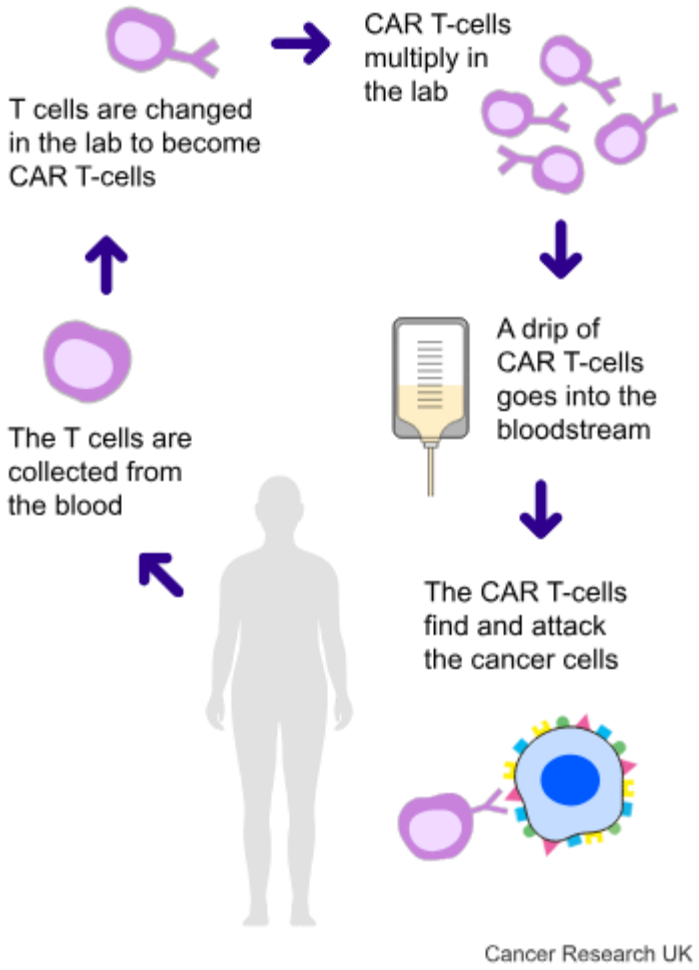

Figure 1: Summary of CAR-T cell therapy treatment (Cancer Research UK, 2024)

The impact this has had or will have on healthcare

CAR-T has provided new treatment for individuals, including children, with relapsed or refractory haematological malignancies including B cell acute lymphoblastic leukaemia (B-ALL), diffuse large B cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma, and mantle cell lymphoma (Velasco et al., 2023). One systematic review found 54% of patients with a haematological malignancy treated with CAR-T had a complete response, meaning absence of detectable cancer cells (Grigor et al., 2019).

It has also been shown to have a positive impact on patients' quality of life. More specifically, one study found quality of life in children and young adults with B-ALL improved post CAR-T treatment (Laetsch et al., 2019). Quality of life was found to be higher in the short-term post CAR-T cell therapy when compared to stem cell transplant therapy (Sidana et al., 2019).

Early studies have shown promise for CAR-T therapy targeting solid tumours (Del Bufalo et al., 2023). However, these tumours express multiple tumour specific markers compared to haematological malignancies, making it more challenging to target the CAR-T which can lead to severe toxicities (Marofi et al., 2021). More research is required to develop CAR-T for these indications.

Barriers to use in frontline health care and their possible solutions

One major barrier to CAR-T cell therapy is its potentially life-threatening side effect. There are three major recognised side effects:

1. CRS occurs when the body reacts to the CAR-T with a 'cytokine storm', presenting as fever, hypotension and hypoxia. CRS is initially managed with supportive therapy. In more severe grades Tocilizumab can be used, a monoclonal antibody against IL-6 receptors. Corticosteroids can also be used but may reduce CAR-T cell efficacy (Zhang et al., 2023).
2. Immune-Effector-Cell-Associated Neurotoxicity Syndrome (ICANS) presents with neurological symptoms including dysgraphia, confusion, word-finding difficulties and tremors. The exact mechanism is not fully understood, but likely involves systemic cytokine activation (Holtzman et al., 2020). Its management initially is similar to CRS with supportive care. Corticosteroids are indicated in more severe cases (Velasco et al., 2023).
3. Tumour lysis syndrome is a well-recognised syndrome often occurring following chemotherapy administration and is also a recognised side effect of CAR-T. Tumour cell death leads to electrolyte efflux, causing renal dysfunction. Its effects can be mitigated with hydration and prophylactic medication (Zhang et al., 2023).

To reduce risks associated with toxicities, CAR-T must be administered in an appropriate hospital. One multicentre observational cohort study found 27% of patients required intensive care unit admission (ICU) following CAR-T therapy (Azouley et al., 2021). Only specialist centres can administer it to ensure an appropriate level of support is available for patients (NHS England, 2018b). Early recognition of side effects is important for timely management. This can be achieved using grading tools. For example, the 'ASTCT CRS Consensus Grading' for CRS grades severity by assessing fever, hypotension and hypoxia. Similarly, the 'ICE' tool for ICANS uses a ten-point score assessing orientation, naming, following commands, writing and attention (Lee et al., 2019).

Another major barrier to CAR-T cell therapy is its cost, estimated at around £280,000 per patient (NICE 2023; NICE 2024). The NHS is struggling to provide effective and timely care for the UK population with the current budget which could pose a barrier for CAR-T cell treatments. This has been overcome with use of the Cancer Drugs Fund. This reimburses CAR-T costs in specific patient populations until further research is conducted to recommend use in routine NHS care (Jørgensen et al., 2020). Additionally, administration of outpatient versus inpatient CAR-T was found to reduce costs of implementation (Hansen et al., 2023). However, unplanned hospital admissions were higher in the outpatient group. Further research into the safety and feasibility of outpatient CAR-T is required.

Conclusion

CAR-T cell therapy has provided an additional treatment option to patients with refractory or relapsing haematological cancers. There are multiple barriers to CAR-T therapy in the NHS including significant side effects and the costs of treatment. However, with early recognition of side effects and appropriate funding, CAR-T therapy has been shown to have a positive impact on individuals' lives. I strongly believe CAR-T therapy has opened the door for development of targeted and patient specific treatment for multiple different conditions and malignancies in the coming years.

The patient under our care recovered well over many weeks and was discharged. It was a privilege to have played a small part in this patient's journey.

Word count (excluding references and bibliography): 999

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