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CAR T-Cell therapy

Influence of the development of previous findings in nanoparticles and CRISPR technology and the applications and limitations regarding economic and ethical considerations on the use of CAR T-cell immunotherapy as a form of cancer treatment

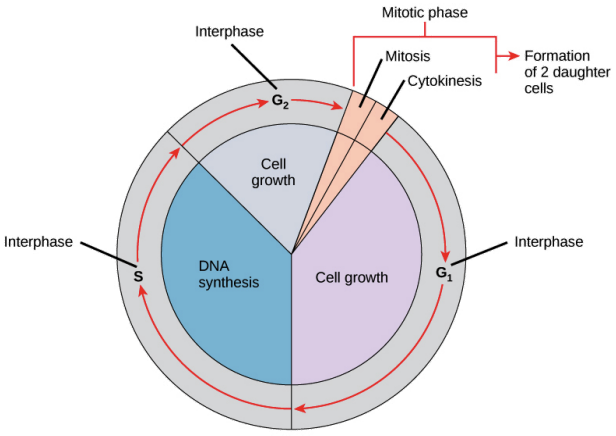
Introduction:

Cancer is a leading cause of death in Australia with up 50,000 deaths produced in 2019 (Cancer Council, 2020). Immunotherapy is the treatment of disease by activating or suppressing the immune system. This method has proven to be more effective than most current methods such as radiotherapy and chemotherapy. Specifically, chimeric antigen receptor (CAR) T-cell immunotherapy involves the use of modifying the patient's antibodies to target tumours and treat cancer (Dickinson, 2020). The development of artificial T-cells to target cancer cells using CRISPR gene editing technology has the ability to survive in the patient's body for up to 9 months.

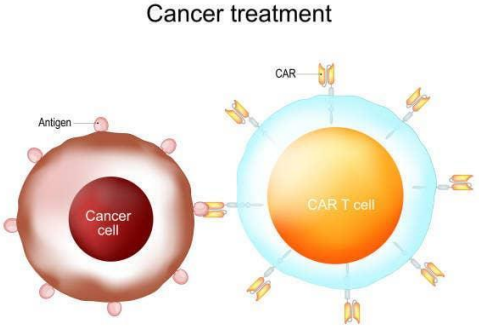
Development in the areas of biotechnology and nanotechnology have **influenced** the development of CAR T-cell therapy. Despite potential **applications** for patients with certain cancer related illnesses such as Acute Lymphoblastic Leukemia, **limitations** of this treatment include potential side effects of the therapy raising ethical concerns. Economic considerations also raise social consequences

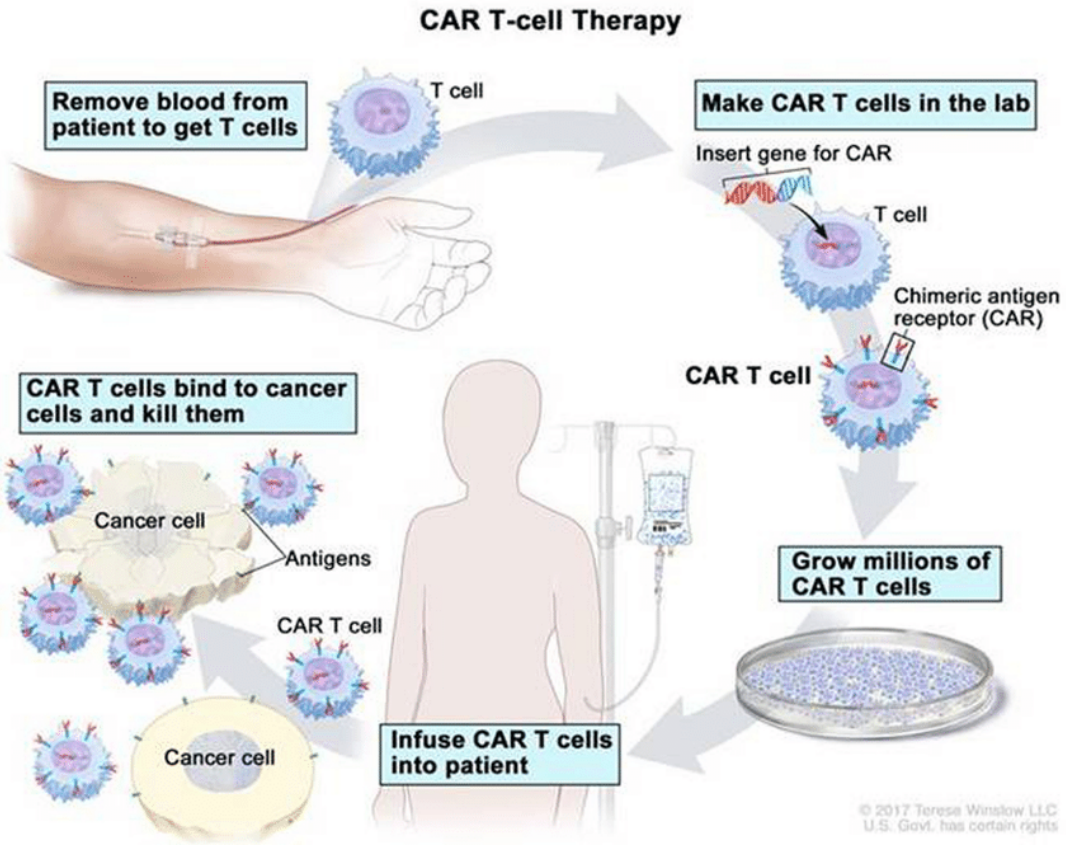
Background Biology

Cancer is caused by uncontrolled cell division through mitosis and hence the formation of tumours leading to the deterioration of body tissues. T-cells assist B-cells in creating antibodies to identify and fight infected cells. The immune system fights cancerous body cells through the use of T-cells which detect the Major Histocompatibility Complex (MHC) on these cancerous cells which are deactivated by binding to surface receptors (Janeway, 2015). However, mutations can occur in the MHC complex which will inhibit (the T-cells from eliciting a response against the cancer cells. In the cell cycle, cell division is regulated through checkpoints (Refer to figure 1). Mutations can occur which can cause uncontrolled cell division which leads to the formation of tumours. There are three mutagens which increase the rate of mutation including mutagenic chemicals, ionising radiation, and viral infections.



Chimeric Antigen Receptor (CAR) cell immunotherapy is a form of adaptive cell transfer (ACT) which involves the use of specially altered T cells. This is done through viral vectors which have been genetically engineered to inject the desired gene into the T-cell's DNA. CAR cells are then produced through altering the genetic sequence in T-cells which enables them to target tumour receptors. CAR T-cells deactivate these tumours without MHC restrictions. This is because, the CARs are genetically created to be structured with a complimentary shape to the tumour receptor (Refer to figure 2). In the process, a sample of the patient's T cells are collected in the blood and these T cells are modified to produce CARs on their surface (Refer to figure 3). These CAR T-cells are cultured and multiplied which increases the potency of immune response received by the patients. To further improve potency of the response, nanoparticle drug carriers can be used.





Influence

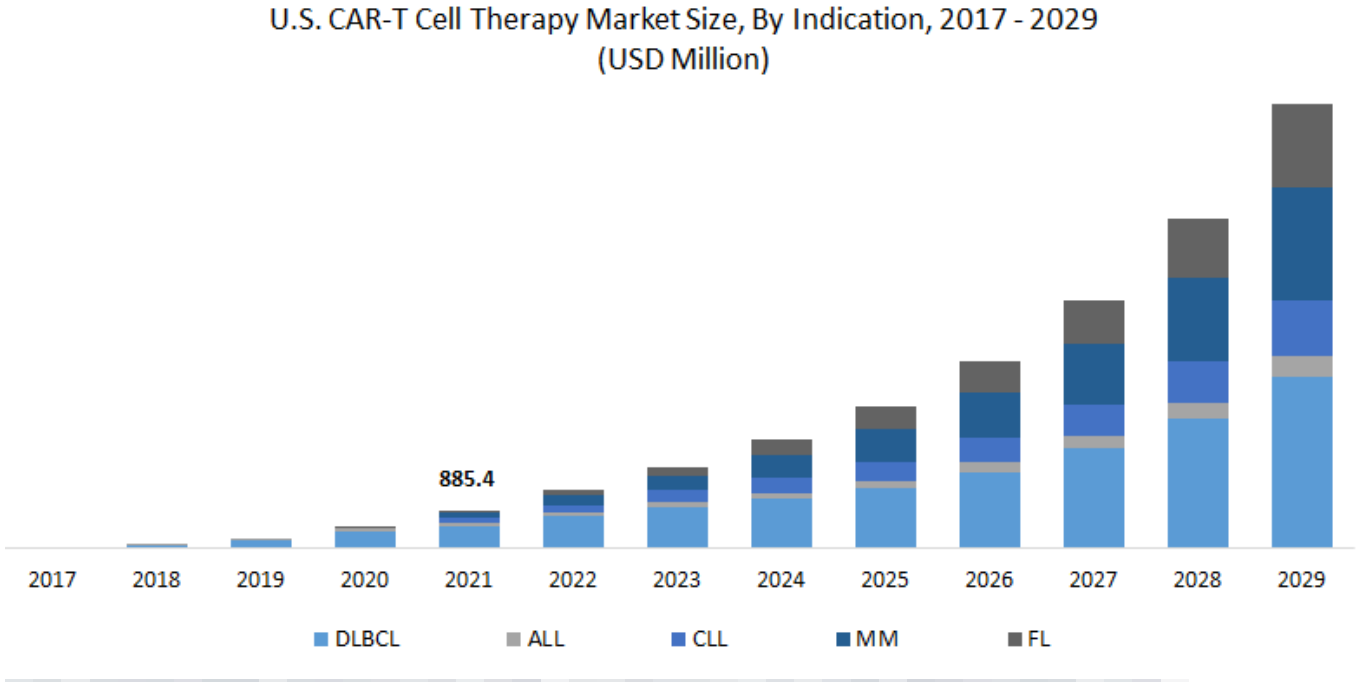
The development of nanoparticles has influenced the development of CAR T-cell therapy. In 2017, researchers were able to develop cancer-fighting immune cells in living animals using nanoparticles (National Cancer Institute, 2017). Nanoparticles are 'synthetic carriers which are injected into the bloodstream and deliver a desired gene' (Murthy, 2017) to T-cells to produce receptor proteins for tumour cells. Results showed that some nanoparticles did block some suppressor cells in mice. However, Dr Fry mentioned that 'you'd never know how many T cells you're going to end up with' in humans (Murthy, 2017) as 'CAR T-cells have toxicity.' Therefore, the full understanding of nanoparticles can benefit and influence the successful procedure of CAR T-cell immunotherapy.

Gene editing technologies such as CRISPR have influenced the development of CAR T-cell immunotherapy. In the past, CAR T-cells were created from other methods such as using viral vectors. However, this works via random integration of the target which potentially caused clonal expansion, oncogenic transformation, or transcriptional silencing. Other methods also include transcription activator-like effector nucleases and zinc finger nucleases. However, CRISPR/Cas9 allowed for the insertion of the CAR at precise regions on the genome. Therefore, CRISPR can improve the safety and efficacy as it is a more precise engineering tool. It can also be used to correct defects on autologous T-cells.

The body's immune response is regulated by Programmed Cell Death Protein 1 (PD-1 pathway). CRISPR can also be used to disrupt PD-1 which is a receptor that binds ligand PD-L1 and leads to inhibition of T-cell function as shown by a study in 2019 (Hu, Zi, Jin, & Li, 2019). To overcome the suppressive effect of PD-1 on

CAR T-cells, the adenine-base CRISPR technology was used to alter the PD-1 gene. This decreased the expression of the PD-1 protein which subsequently prolonged T-cell activity.

67% of Australians mentioned that they were unable to work or had to limit their work hours due to be diagnosed with cancer which would impact the economy. Similar cases globally influenced research into more effective treatments that have a higher recovery rate. This will assist the patient in returning to work and having a normal lifestyle again. In 2020, the global CAR T-cell therapy market reached nearly $1037 million. It is expected to further grow in 2025 up to $3150 million (The Business Research Company, 2021). CAR T-cells have “good clinical value” that has huge “market potential (Refer to figure 4).” The model below demonstrates the increase in CAR T-Cell Therapy market in millions and the estimated point that it will be at in 2029 in which it will be a more standard intervention.



Applications and Limitations

An application of CAR T-cell therapy is in the treatment of Acute Lymphoblastic Leukemia (ALL). ALL is a type of cancer of the ‘blood and bone marrow that affects white blood cells (Leukemia Foundation, 2020).’ Dr. Kochenderfer claimed that the results regarding this illness ‘have been incredible successful’ and CAR T-cells ‘have become a frequently used therapy for several types of lymphoma.’ There was a recent trial of Axicabtagene Ciloucel which is a CAR T-cell therapy tested on patients with non-Hodgkin lymphoma. The Axicabtagene Ciloucel binds to the protein, CD19 which is found on most B-cell lymphoma cells which assists to kill cancer cells (National Cancer Institute, n.d.). This trial showed a 70% recovery rate. Other forms of treatment such as radiation therapy or chemotherapy cannot discriminate between healthy cells and cancerous cells. This can cause severe side effects whilst CAR T-cell immunotherapy uses a patient’s own immune system to fight cancer (Roberts, 2021). CAR T-cells have a unique specificity and therefore has a decreased chance of damaging body tissues. Overall, current applications of CAR T-cells are an indication of this immunotherapy becoming a standard intervention in society.

Limitations of CAR T-cell immunotherapy include economic considerations including the high costs inhibiting access to much of the general public. It costs over $500,000 per patient due to the high costs in manufacturing the CAR T-cells. However, due to the side effects faced, the costs could rise to approximately $1.5 million which poses disadvantages to the ‘less financially stable.’ These high costs and further deterioration of a patient’s condition could discourage the patient in receiving potentially beneficial

treatments. Subsidies should be provided by the government to make this therapy financially reasonable to enable a greater number of people in society to be benefitted from this immunotherapy.

Another limitation is the ethical considerations regarding the patient such as respecting patient autonomy and minimising the potential side effects from the therapy. T-cells provoke an immune response through the release of cytokines which are messenger molecules which signal the T-cells to perform its function. The increase in the number of CAR T-cells can lead to Cytokine Release Storm (CRS) which is observed within a few days to two weeks after CAR T-cell infusion (Portell, 2021). This is the process in which large numbers of cytokines are released into the bloodstream and can cause high fever, inflammation, severe fatigue, or nausea (National Cancer Institute, n.d.). In severe cases, this condition can lead to multiple organ failure. There are also concerns regarding the CAR's shape structure due to their affinity with antibodies. Their shape could cause them to bind to normal antigens on non-cancerous cells which can damage healthy tissue which could therefore cause the patient harm. Due to the therapy impacting the immune system, the body could be at a greater risk of infection. There could also be a shortage of white blood cells as well as low B-cell and antibody levels. If antibody levels are low, immunoglobulin replacement therapy may be needed (Dickinson, 2020).

Conclusion

The development of CAR T-cell immunotherapy is an efficient method in comparison to other methods of treatment in eliminating and treating cancerous tumours. There are both benefits and limitations regarding economic impacts. The introduction of a new form of cancer treatment and low recovery time will benefit the economy. However, limitations include the high costs of the treatment as well as ethical concerns in implementing this immunotherapy. This implies that greater research and testing needs to be undertaken before this method becomes a standard intervention in society.

Word Count: 1492

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