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RESEARCH ARTICLE

THE EVOLUTION OF CAR T-CELL THERAPY: ETHICS AND EFFICIENCY

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Abstract

Engineering T cells with a chimeric antigen receptor (CAR) that reprograms their antigen selectivity and signalling has recently emerged as one of the most promising therapeutic approaches for treating cancers. The initial emergence and the evolution of this treatment has significantly contributed to its success. However, it is not known if the advancement of this technology is accompanied with any socio-economic or ethical concerns. This paper will first dive into the scientific evolution of CAR T-cell therapy as mode of cancer treatment. In addition, this paper will also describe the basic structure of the CAR and discuss how each of its domains affect the efficacy and safety of CAR-T therapies. It will also highlight the changing landscape of ethical concerns raised by CAR T-cell therapy. Overall, this paper analyzes how the advancement in CAR T-Cell therapy has or will impact public opinion and health.

Introduction:-

CAR (Chimeric Antigen Receptor) therapy involving T cells is a type of cancer immunotherapy that focuses on "supercharging a patient's T cells to recognise and attack cancer cells" (UChicagoMed).

As might be expected from the history of prior cell therapies, most specifically, Tumor-Infiltrating Lymphocyte (TIL) Therapy, the initial introduction of approved CAR-T cell therapies faces significant problems including long waiting lists, concerns over reimbursement and a small number of locations offering the treatments. Despite these initial challenges, hope in the field remains high with numerous companies racing to develop more advanced CAR-T cell therapies to improve the treatment of blood cancers and modify the approach to target solid tumours.

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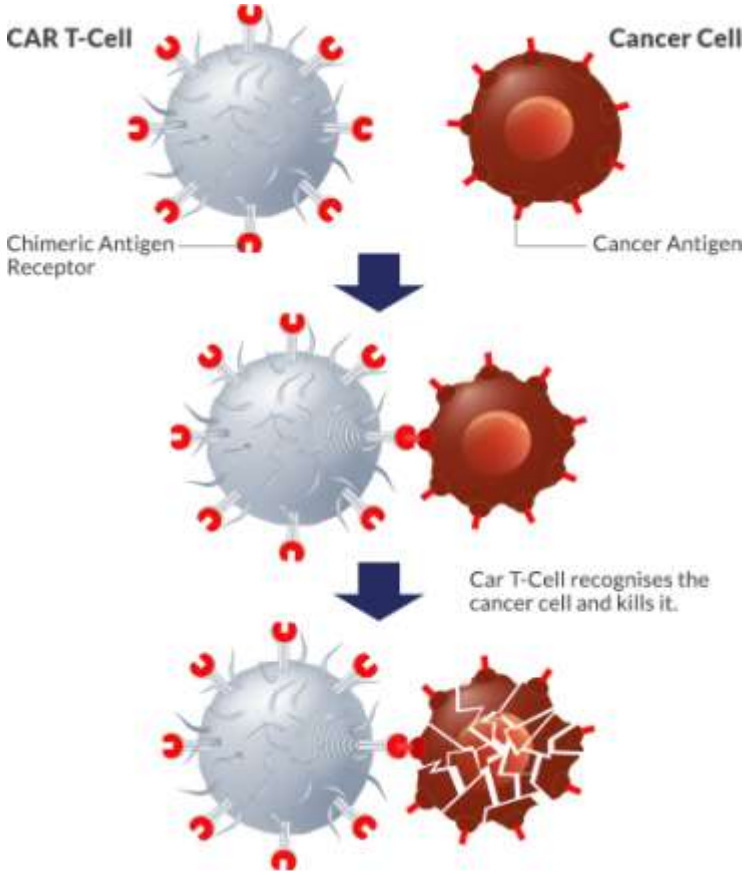

Figure 1:- Car T-Cells Attach To The Cancer Cells And Destroy Them.
"What is Cellular Therapy" (Center for Clinical Haemotology)

In the last few years, we have seen significant advancements with CAR T-cell therapy towards tackling cancer. A major breakthrough that led to developments in CAR T-cell based therapy was the discovery of bone marrow transplantation in the 1950s. This was the first time living cells were used to control blood cancer through infusion which is the same mechanism as that of CAR T-cell therapy. However, it wasn't until the late 1980s, scientists first experimented with CAR T-cells. The first generation of CAR T-cells were developed in the late 1980s and these T cells were only able to send one dysregulation signal in the presence of tumour cells and these cells weren't very effective in terms of killing the tumour. However, in the 2010s, the second generation of CAR T-cells were developed which was able to send two types of signals, both dysregulation and recognition signals, which thus, increased its efficiency in killing tumours (Figure 1).

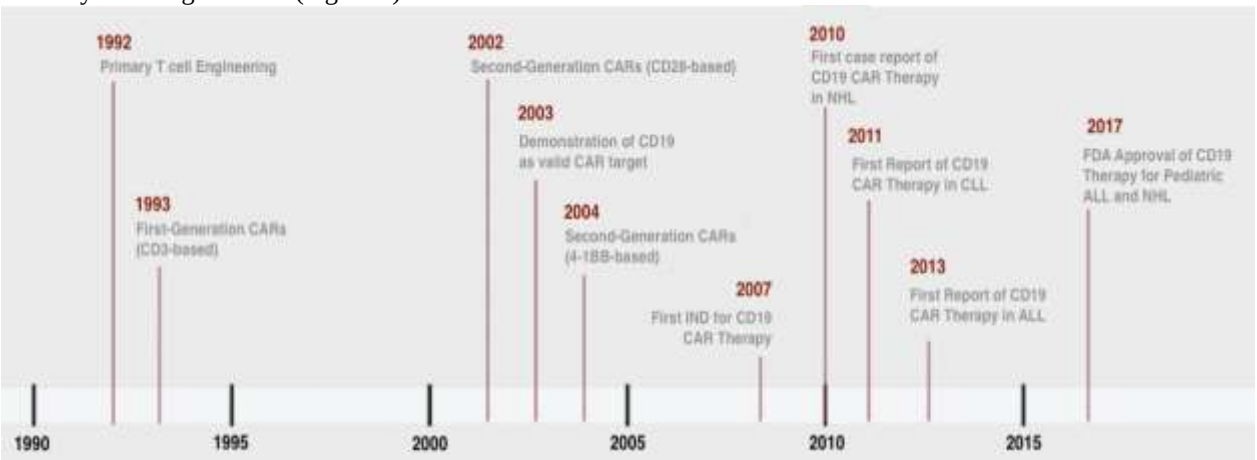

Figure 2:- Timeline Of Car T-Cell Therapy Developments Ferenandez, Clara Rodriguez. "How CAR-T Cell Therapy is Revolutionizing Oncology" (Labioetech.eu).

This increase in efficiency is specifically notable by how the US Food and Drug Administration approved the use of CAR T-cells for product use in 2017 (Figure 2)

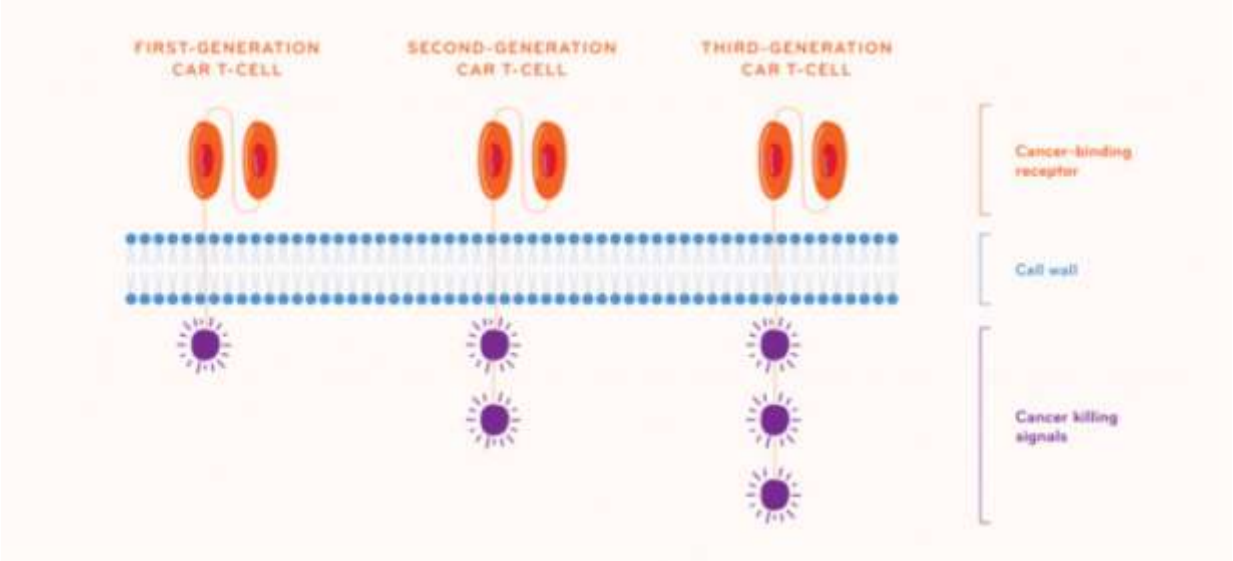

Figure 3:- Improving Car-T Cell Antigen Recognition Tian et al. "Gene modification strategies for next-generation CAR T cells against solid cancers" (Journal of Hemotology and Oncology).

Despite this, using second generation CAR T-cells in patients with B cell lymphomas, myeloma, and B-cell acute leukaemia, often led to relapse. Following this, third generation CAR T-cells were developed in 2018 that have 3 domains with three signals to kill the tumour, making it a lot more effective than the first 2 generations (Figure 3).

CAR T-cell therapies have become more efficient over time in their ability to recognize tumour cells ultimately leading to high successes due to changes in its biological module.

Discussion:-

Data analysis, ethical dilemma

CAR T cell Therapy has been significantly effective in the specific treatment of haematological malignancies. Several case studies, including those in patients with diverse types of cancer, have shown that due to the structure of CAR-T cells, specifically in regards to the ectodomain, transmembrane, domain, and endomain, this treatment is stronger and shows more promising results than current treatments for the same cancers.

Towards this, the University of Chicago conducted clinical trials in order to test the efficiency of the treatment and found that 70-90% of patients with acute lymphoblastic leukaemia went into remission after CAR T-cell treatment. In addition to this, they also found that 40-50% of patients with non-Hodgkin lymphoma had complete remission. Through this, they were able to conclude that CAR T-Cell therapy is indeed successful when treating refractory cancers.

Similarly, a trial conducted by the Medical Center of Haematology showed that 82% of patients with large B cell lymphoma responded positively to axicabtagene ciloleucel T cell therapy. This has been a significant improvement since the administration of the first CAR T drug (tisagenlecleucel) in B cell lymphoma patients which only yielded a positive response of 52%. Additionally, the Medical Center of Haematology also concluded that CAR T-cell treatments are considerably more effective in children and young adults (< 21 years old) alluding to the fact that external factors (ie, stress, sleep, active lifestyle etc.) could be having an impact on effectiveness of the treatment. This is further supported by how the journal, following positive results after the phase 2 trial, continued the study with 101 patients from the previous study with large B cell lymphoma. This part of the study led to disease progression or death in 61 of these patients. This was significantly concerning and contributed to a rise in ethical discussions into both the administration of CAR T-cell therapy and the clinical trials in which the drugs are tested.

This study also led to the development of future studies analysing whether these deaths were caused due to patients already having terminal diseases or due to CAR T-cell therapy and unfortunately, this study, also conducted by the Medical Center of Haematology was inconclusive. Due to there being no causational evidence of whether or not CAR T-

cell therapy caused these deaths, it is dire for further research to be conducted before active usage of the same in clinical studies.

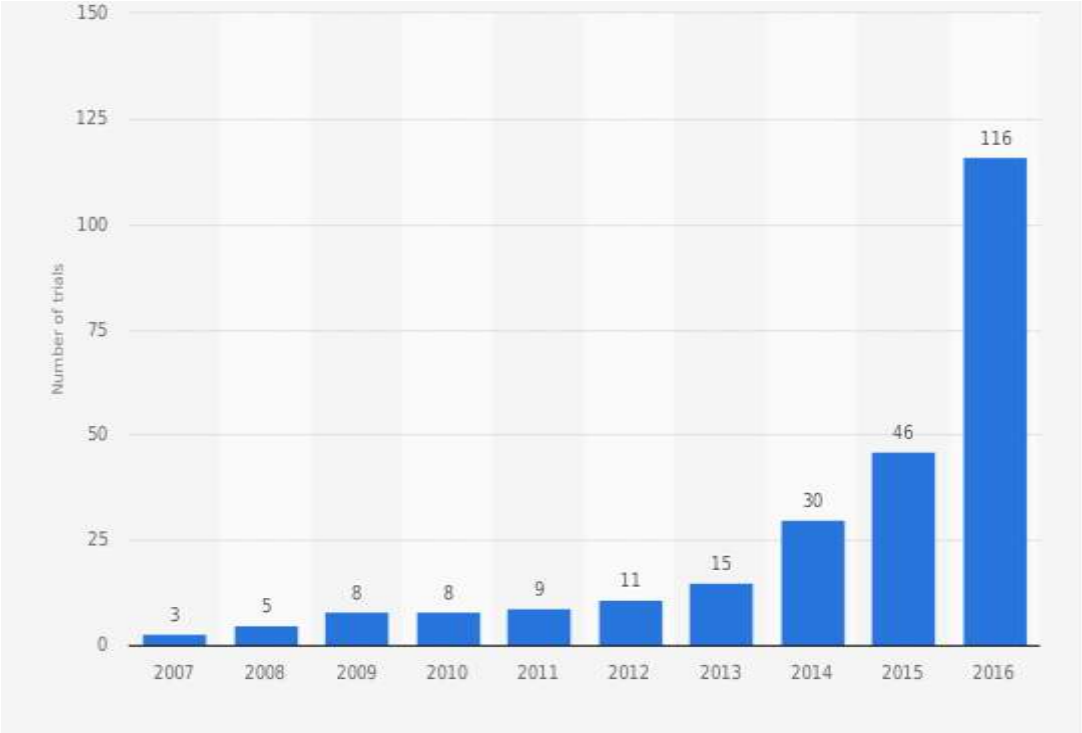

Figure 4:- Number Of Car Cell Therapy Trials Worldwide 2007-2016 Mikulic, Matej. (Statistica.com).

This raises the question of whether CAR T's efficiency outweighs its ethical concerns that will be further explored in this paper.

Literature Review:-

With advancements in immunotherapy technology and other similar medical advancements, CAR T-Cell therapy has had significant medical advantages in treating cancer. However, the literature around the third generation of CAR T-Cell therapy is generally limited due to how new this most recent version of CAR T-Cell immunotherapy is. Having received FDA approval only in the late 2010s, trials using CAR T-Cell therapy have only just begun (Subklewe et al.). While showing a large number of positives in treating cancer, the general public's opinion is still limited due to them often being uneducated or uninterested to learn more about this novel therapy due to a lack of need to learn more about CAR T-cell therapy and/or the lack of information in some cases. The therapy is often also misinterpreted as a "cure" for all types of cancer when in reality, like all other medical treatments, it still poses significant risks and has only been approved to be tested on blood cancers ("Study predicts who..").

I believe that these misinterpretations are again a cause of the limited literature, limited access to this literature or a lack of understanding on the topic as well as the minimal clinical trials involving CAR T-Cell therapy (Figure 4). Additionally, I also think these misconceptions further shape the research conducted in this field, leading to biases. As well as this, with CAR T-Cell therapy still being a relatively new treatment in the medical industry and the medical industry still being a profit making sector, research is often influenced to portray the treatment's benefits as opposed to its risks in an effort to sway public opinion.

Despite its scientific and specifically medical prevalence, CAR T-Cell therapy, like other medical treatments, is increasingly becoming of interest to researchers and ethicists. CAR T-Cell therapy being an expensive and novel treatment, isn't as broadly available to cancer

patients as is traditional chemotherapy and other more traditional cancer treatments. This poses a significant ethical dilemma regarding the distribution and availability of the treatment. Furthermore, researchers are attempting to promote laboratory research into the same as opposed to clinical trials that have led to unfavourable impacts. Scientists focus on bringing the best treatment for people and policy makers, clinicians, and the FDA should ensure that the information and treatment reaches a broader audience. Again, due to the therapy being so new, literature looking into the ethical dilemma posed by the therapy is largely limited with little to no analysis into the same. This review will focus on the ethical and research based application of CAR T-Cell therapy with regard to cancer immunotherapy. It will outline the basis of CAR T-Cell in a scientific context, its prevalence in the healthcare sector along with its future implications, and legal advancements and barriers with its use. Finally, this review will also focus on the gaps with research and how this impairs our holistic understanding of CAR T-Cell therapy.

Information from patients and families of patients who have undergone CAR T-Cell therapy is significantly sparse. Due to this being a branch of experimental medicine, it is still in its research and trial phase which means that majority of the research into the same has had confidentiality policies and often unfavourable outcomes (Sterner and Rosalie, 2021). These notes draw parallels from how the newness of the therapy hinders its potential of becoming a revolutionary treatment in the near future. Additionally fatalities from CAR T-Cell therapy have added to some of the ethical concerns. The article also highlights how these fatalities limit patient opinions on their experience and also discourages their family members or friends from talking about the trauma. This is further supported by other similar articles (Lawrence, 2019). This article reports the mortality rate for CAR T-Cell therapy in leukaemia and lymphoma is at an astounding 15%. This is considered significantly high considering that the likelihood of these patients dying of treatment as opposed to the terminal illness itself should be close to nonexistent as these treatments are designed to increase their likelihood of survival. Additionally, more recent perspectives point out that CAR T- Cell therapy being so specific towards certain types of cancer and targeting only certain types of tumours further limits its scope which in turn limits the diversity of patients who have received the CAR T-Cell treatment (Safarzadeh et al., 2021).

In regards to CAR T-Cell therapy as a cancer immunotherapy, it is evident that gene editing is a type of therapy that targets cancer in a similar pattern as CAR T-Cell therapy. With cancers often caused by mutations, gene therapy targets a broader range of cancers while CAR T-

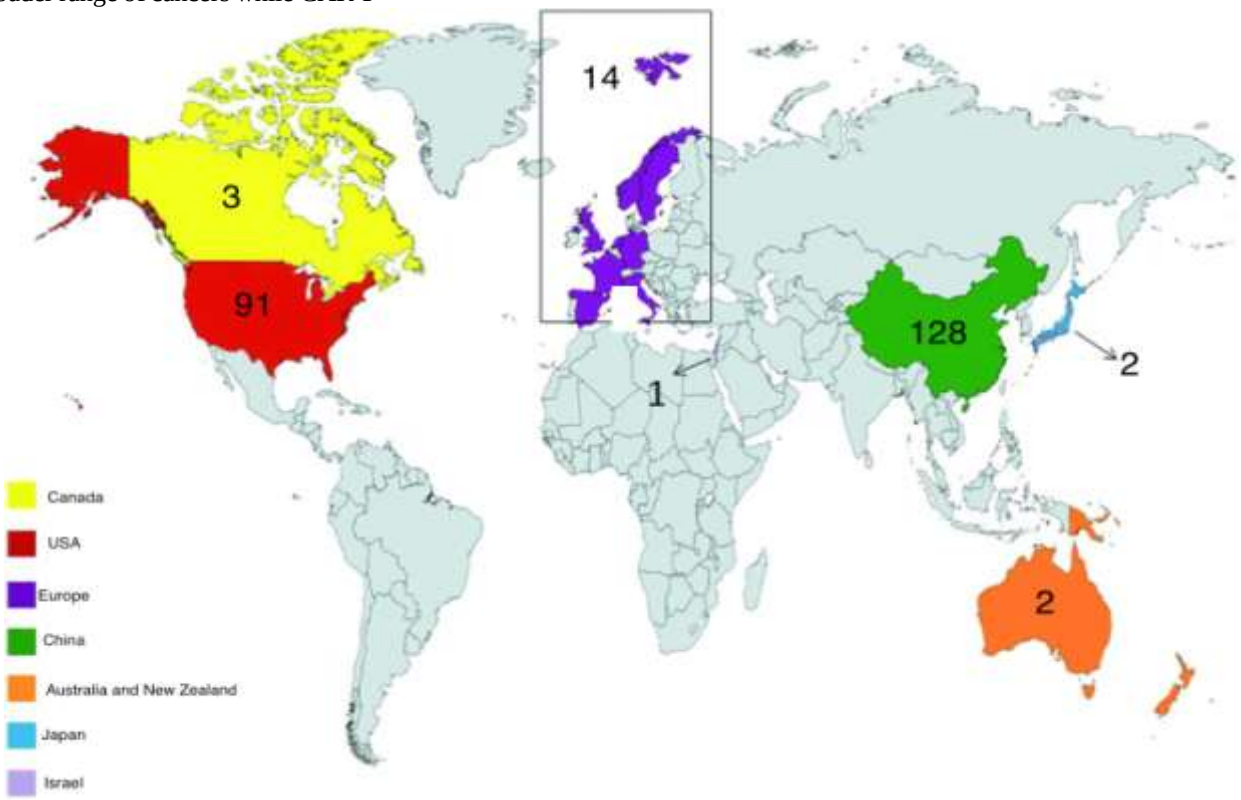

Figure 5:- Geographical Distribution Of Ongoing Chimeric Antigen Receptor (Car) T Cell Therapy Clinical Trials For Cancer Esmaeilzadeh et al. "Chimeric antigen receptor -T cell therapy: Applications and challenges in treatment of allergy and asthma" (Biomedicine and Pharmacotherapy Journal)

Cell therapy and the experimental research concerning the same is severely limited in terms of types of cancer. Several studies have been conducted into the therapy's efficacy with blood cancers such as multiple types of leukaemia and lymphoma with vital conclusions made from the same (Uchicago Med, 2019). In this study, the independent variable was the application of CAR T-Cell therapy, the control group was patients who hadn't received the therapy but had the same type of cancer as patients who had, and the dependent variable was patient response to the therapy. Similar studies have been conducted with minor changes (Huang et al., 2020). In this study, the independent variable was the drugs and the amount of these drugs involved with CAR T-Cell therapy, the control group was patients who had received a standard amount of one type of drug as part of their therapy, and the dependent variable was patient response to these varying drugs or varying amounts of drugs. Both these studies along with most others in the field were specifically targeting blood cancers showing how the literature on the treatment is significantly based on blood cancers which hinders scientific ability to reach a definite conclusion.

While analysing the legal context of CAR T-Cell therapy, it is vital to take account of the geographical context. Specifically, only 7 countries today have employed the use of CAR T-Cell therapy whether it be for research or medical purposes (Figure 5). This raises questions on why its use is so limited when it has been proven to be a beneficial cancer treatment. These questions can be answered by looking at the legality of the treatment. Due to there being laws on experimental medicine and its use, there are stringent limitations on the same which further leads to a gap in literature regarding its legal implications (Cooper, 2000). This limitation on literature regarding legal implications is detrimental to the interest in use of CAR T-Cell therapy and the public's understanding of the same.

CAR T-Cell therapy is often used as an indicator of advancements in cancer treatments for the future. Furthermore, scientific models and theorems to support the same are largely prevalent and often looked at to further understand its futuristic implications and goals. Now, the idea of the treatment growing at a larger scale in the future is supported by efforts to make the treatment more efficient and accessible to best ensure this (Lee and Chan, 2019). A significant amount of literature into the same allows pharmaceutical companies as well to better modify the procedure as well as make it more widely available.

While the prevalence and basis of CAR T-Cell Therapy has been determined and a clear cause and effect relationship has been established with its efficiency in treating cancer, due to a significant lack of research, its ability to target a multitude of cancers is yet to be concluded. Its futuristic employment is something that seems viable and is supported by numerous works of literature and studies. Research should still continue at the medical level with further publication and increased transparency to the public in order to gain traction and educate others about the treatment. Based on research findings, clinical trials would help confirm the futuristic debate of the butterfly effect as well as its positive contributions to medicine.

Limitations

Taking into account the ethical considerations and the efficiency of CAR T-Cell Therapy, the treatment also has significant limitations.

After analysing data from studies conducted by several medical journals, we can come to the conclusion that CAR T-Cell therapy is not as effective in adults as it is in children. Specifically, the treatment might not be suitable for adults in any case. This can be attributed to the fact that adults have a constantly changing epitope expression which modifies the antigen used in CAR T-Cell treatments. Changes in epitope expression is significantly more common in adults than in children due to the fact that changes in body's pH are what contribute to the same and with a stagnant cell growth in adults than in growing children, this is a lot more prevalent. This is largely vital because it shows the importance of further research regarding age in terms of the therapy considering that there are several external factors that yet have to be accounted for.

Additionally, while plenty of research has been conducted into analysing the role of CAR T cell therapy in treating cancers, this research is significantly limited to blood cancers such as leukemias, lymphomas, and neuroblastoma and limited research into breast cancer. Because of this, the treatment is inconclusive for cancers holistically and thus, it is impossible to approach a definite inference.

Conclusion:-

CAR-T cells have been designed to increase their ability to kill tumours, extend their persistence in vivo, increase their ability to infiltrate solid tumour tissues, and increase their ability to modulate the immune microenvironment.

The evolution of these strategies as treatments for haematological malignancies should include a consideration of the characteristics of different types of disease. The problem is not only based on methods to improve the initial efficacy but also involves needed improvements in CAR-T cell persistence and helping patients regain an immune response to the tumour.

On the other hand, CAR-T cells for solid tumours require increased trafficking and infiltration abilities and enhanced resistance. The specific target is not easy to determine and towards this, all possible antigens may be necessary to combine RNA-based CAR-T cells to best help patients. In terms of the ethical discussion, the interpretation of clinical trials may be limited by the enrolment of small numbers of subjects, therefore, ensuring the safety and efficacy of each variety of CAR-T cells requires clinical trials with a larger scope and long-term follow-up. In addition, a cure for cancerous malignancies will never be achieved by relying on only just one therapy (which in this case is CAR T), therefore, combined treatments and disease monitoring methods should be developed in parallel (PubMed). Last but not least, the cost of CAR-T cell therapy should be reduced by technological advances and the development of universal CAR-T cell.

Overall, I personally believe that while CAR-T cell therapy does pose significant ethical concerns, its effectiveness in targeting certain types of cancer should be prioritised over this ethical dilemma. Given this, I do think the aforementioned steps are necessary to be taken prior to the widespread use of CAR-T cell therapy in an attempt to minimise ethical risks and make the treatment as justifiable as possible.

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