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Chimeric Antigen Receptors T Cells (CAR T) Therapy

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Abstract: ***Chimeric antigen receptors T cells (CAR T) therapy represents a revolutionary approach to cancer treatment. Utilizing the power of immune system to target and eliminate malignant cells. The studies included were reviewed from PubMed, cancer. net, cancer. gov, clinical trials. gov, web of science. Through genetic engineering, T cells are modified to express chimeric antigen receptors, enabling them to recognize and attack specific antigens present on cancer cells. The positive result of CAR - T therapy in treating hematologic malignancies, such as ALL acute lymphoblastic leukemia and non - Hodgkin lymphoma, has been remarkable. However, complications remain, including the management of CAR - T cell infusion - related effects such as cytokine release syndrome and neurotoxicity, as well as the growth of resistance mechanisms in some cases.***

Keywords: chimeric antigen receptor T cell, response, side effect, relapse, analysis

1. Introduction

Recent experiments done in clinical research have shown that immune - based therapies can completely cure tumor patients. Chimeric antigen receptor (CAR) - based T - cell adoptive immunotherapy has become popular as a replacement for individually targeted immunotherapy in the fight against cancer. CARs are antigen - targeting receptor that binds extracellular cancer - binding moieties to intracellular T - cell signaling domains. CAR - T recognizes cell surface antigens and carry out independent MHC - mediated expression, enabling the use of uniform receptor structure in all patients. Since CAR - engineered T cells targeting CD19 are most successfully used in B - cell lymphoma, researchers are developing different types of CAR T cells is used in clinical trials to treat the cancer. At present, four generation CARs are produced and tested while 5th generation is going through in clinical tests.

First - generation CAR - T developed in 1993. It contains scFv fused with CD3ζ/ FcϵRIγ and these engineered cells showed anti - tumormaneuverin murine models.

Second - generation CAR - Tare engineered to target and reprogram T lymphocytes to enhance their anti - cancer efficacy

Third - generation CAR - T integrate the second intracellular costimulatory domain of CAR to generate "third generation" (3G) CAR - T cells.

Fourth - generation of CAR – T cells were developed in 2015. These are known also as T cells redirected for antigen - unrestricted cytokine - initiated killing (TRUCKs). They are modified by the addition transgenic immune modifiers with the creation of inducible cytokines.

Fifth - generation of CAR - T cells which being currently under development. The CARs have a truncated IL - 2 receptor β - chain domain with a restatement factor like STAT3 and STAT5 Activation in Solid Cancers.

Problem Formulation:
The two main categories for the patients who have relapsed after CAR - T therapy are antigen - positive occurrences and anti - genetical negative initiation. Insufficient CAR - T therapy response results in antigen - positive relapse, which is caused by minimal impact on CAR - Ts cells. Relapse of antigen - negative nature is caused by antigen escape, which can be triggered by a mutation in the gene. For example, CD19 - negative relapses are observed in up to 20% of patients who have received CAR - T cells. In CD19 - negative relapse, CD19 cannot be detected on the cell surface.

- overcome antigen - positive relapses, studies assess the amalgamation of CAR - T with other cures, such as the evolution of AAPCs and the evolution of CARs with new models (novel design).
- Novel CAR models Another attempt to avert antigen - positive cells is the creation of CAR - T cells with a truncated IL - 2 receptor β - chain domain and transcription factor. They are considered fifth - generation CARs. This concept is currently being researched; However, it showed promising effects when tested in preclinical models.
- A procedure to prevent antigen - negative relapse is the combination of BiTEs with CAR - T cell therapy. One side of BiTE is designed to bind to CD3 and activate the T cells, while the other side is directed against a cancer antigen.
- Chances of survival of a patient with these problems are 30 - 50%.

Objectives:
The objectives of this research include:

1) Targeted Cancer Cell Elimination: Generating T cells capable of identifying and binding to antigens expressed on the surface of cancer cells, which permits the immune system's potential to specifically target and

destroy cancerous cells while minimizing harm to normal tissue.
2) Durable Remission: Achieving sustained remission in patients by ensuring that the CAR - T cells remain in the body and will continue to patrol and destroy cancer cells that may cause relapse.
3) Combination Therapies: Investigate and confirm the effectiveness of combining CAR - T cell therapy with other therapies, such as checkpoint inhibitors, to improve antitumor efficacy and overcome resistance mechanisms.
4) Innovative Design and Engineering: Development of next - generation CAR - T cells with advanced functions such as multi - antigen targeting and engineered cytokine production to improve their therapeutic potential and adaptability to different forms of tumor.

2. Methodology

Data is gathered and pre - processed from a diversity of sources, such as, PubMed, cancer. net, cancer. gov, clinical trials. gov, web of science. Since being discovered in the late 1980s, CAR T - cell therapies has developed significantly in an attempt to increase persistence, activity and efficacy. CAR – T cell therapy have changed through five generations in the last years.

Role of artificial intelligence and algorithms in helping cure cancer and helping with cancer detection. As we all know cancer cells are hard to locate and take a really long time to diagnose which is why the life expectancy of the patient to deteriorate. University of Washington came up with 'MERGE' that came up with an algorithm that detects to cancer type and create a drug according to needs of the patient which has been effective in curing AML.

Google has also created a machine learning model that helps us find the cancer in the body which used by many pathologists have said it being very effective in finding. They made it so what we see the microscopic camera also detects the footage and transfers it to a computer which then runs the calculations and detects the cancer cells in real - time. The knowledge that helps computer detect was helped by the pathologists by teaching the computer thousand's images what cancer cells look like.

There are various types of medicines that help us with the treatment being the 5 generations of CAR - T:
1) First - generation CAR – T developed in 1993. It contains cFv fused with CD3ζ/ FcєRIγ and these engineered cells showed anti - tumormaneuverin murine models.
2) Second - generation CAR - Tare engineered to target and reprogram T lymphocytes to enhance their anti - cancer efficacy
3) Third - generation CAR - T integrate the second intracellular costimulatory domain of CAR to generate "third generation" (3G) CAR - T cells.
4) Fourth - generation of CAR – T cells were developed in 2015. These are known also as T cells redirected for antigen - unrestricted cytokine - initiated killing (TRUCKs). They are modified by the addition transgenic immune modifiers with the production of inducible cytokines.
5) Fifth - generation of CAR - T cells which being currently under development. The CARs have a truncated IL - 2 receptor β - chain domain with a transcription factor such as STAT3 and STAT5 Activation in Solid Cancers.
6) Conventional (monovalent) CAR, beyond advanced CARs, AND/OR/NOT/IF - BETTER logic gate CAR, SUPER CAR system, Synthetic Notch (synNotch) receptor, reversed (rev) CAR, Avidity (avid) CAR, the synthetic T - cell receptor and antigen receptor (STAR): these are all different therapies which are represented as NOVEL CAR design.

3. Literature Survey

• Chen Yi - Ju, Abila Bams, et al. (2023)
Car - T what is next?
Authors said that in 2017 The FDA approved the first 2 CAR - T therapies. The approved indications were for the therapy of the patients of the age up to 25 years old and with ALL and relapsed or DLBCL. Since then, the researchers have been trying and improving the engineered cells with the progress of CAR - NK, CAR - M (NOVEL CARs). Detailing about the Efficacy Issues and relapse they discuss the strategies to controlthe side effects. While concluding they mentioned that CAR - T has significantly transformed the nursing of malignancies.

• Perica Karlo, Varela Juan Carlos, et al. (2015)
Adoptive T cell immunotherapy for cancer

Author tells us about how to engineers utilize the immune system to detect and destroy cancer cells which has been a goal of cancer immunotherapy. They tell us about how engineers use B cells to locate and cure tumor cells. Which they conclude with various ACT and challenges faced to make the medicine widely available.

• Park Jae H, Brentjens Renier J (2010)
Author tells about how Chemotherapy - resistant B - cell hematologic malignancies can be cured by HSCT. Also mentioning about genetically modified T cells and their adoptive transfer. Concluding with a diagram of all generations of CAR - T cell therapies.

•Dejenie Tadesse Asmamaw, G/Medhin Markeshaw Tiruneh, et al. (2022)
Current updates on generations, approvals, and clinical trials of CAR T - cell therapy
Author tells about customized immunotherapy which is considered a self - perpetuating drug to cure tumor. They explain in detail about all the generations of car - t produced (5) and NOVEL car produced to treat cancer. Concluding they mentioned that current updates on CAR T cell therapy generations, approvals and clinical trials.

•Sterner Robert C. & Sterner Rosalie M. (2021)
CAR - T cell therapy: current limitations and potential strategies

Author mentions the limitation faced by CAR - T therapy and strategies to overcome those limitations. Mentioning those limitation author discusses about the cost and programs in process to provide these therapies to public and not in some rare clinical departments. As concluding author mentions that to evolve there should remain some limitations to find perfection.

4. Results and Discussions

1) Response Rates: Present data on overall response rates (ORR), complete response (CR) rates, and response rates (RR).
2) Overall Survival: 30% to 40% of patients are unresponsive or relapse, leading to a poor prognosis with a 2 - year overall survival (OS) of only 20% to 40%. The estimated OS is 59.4% in 12 months.
3) Interpretation of Efficacy Data: The ORR and OS of the patient varies
4) Mechanisms of Resistance and Relapse: Tumor cells can evade CAR - T cells by losing or reducing expression of the target antigen. This antigen loss may be due to genetic mutations, alternative splicing, or selective pressure exerted by CAR - T cells.
5) Limitations of the study: The studies are conducted with a small number of patients often due to rarity of the patients the graphs and results can vary.
6) Clinical and Practical Implications: The treatment isn't available in many hospitals/clinics and further the patients most likely don't agree to get tested on by a medicine with a 100% success rate.

5. Conclusions

CAR – T cells are a productive cure option for patients with hematologic malignancies. Long - term data show strong efficacy and generally low toxicity. CD19 - targeted CAR - T cell therapy has shown to induce highly durable remissions of B - cell lymphoma in chemotherapy - treated patients, recommending that this approach can induce therapy resorption. The existence of CAR - T cells in MM patients may increase the likelihood of allogeneic HSCT, which may lead to significant drug - free setting aside in B - ALL patients. Several promising areas of research may improve the duration of remission after this treatment. Overall, we live in an exciting time in CAR T cell development as responses improve and therapeutic indications expand.

6. Future Scope

1) **Target Antigen Selection:** Because of the excellent clinical results, more studies are being devoted to the evolution of such treatments. However, CD19 remains the most popular target antigen and Kymriah is the first anti - CD19 CAR approved in 2017. Certain targets, including CD20 (CD22 and BCMA), which have expression patterns similar to CD1, have been used with less success. The stability of CD19 expression is likely to be the main reason for the antitumor activity of anti - CD19 CAR in clinical applications. It is because of this factor.
2) **Efficacy, Safety, and Clinical Application Extensions:** CAR - T cell therapy has revolutionized the cure of several blood cancers that previously lacked adequate treatment options. However, CRS and neurotoxicity are potentially life - threatening serious side effects and significantly limit CAR - T cell therapy. Both remain unpredictable because precise cause - effect mechanisms are incomplete. It is believed that a more informative preclinical model must be developed to better recognize their toxicity.
3) **Treatment Costs:** Significant results of CAR - T cell therapy were considered a clinical success; however, on the commercial side, CAR - T therapy has been very limited. The expense of CAR - T cell therapy is a considerable barrier to patient access due to highly customized and time - consuming manufacturing process. For example, one infusion of Yescarta costs $373, 000 and Kymriah costs $475, 000, excluding hospitalization for side effects.
4) **Future Perspectives:** The evolution of new CAR - T cell models and other CAR cells such as CAR - NK and CAR - M have demonstrated their ability to target solid tumors. The unique properties of CAR - NK and CAR - M also make them potential and promising candidate for the evolution of ready - made CAR products. According to recent studies, CAR - based cell therapy should provide additional benefits to more cancer patients in the future.

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