ImmunoAnalysis, 2022, 2, 6
doi:10.34172/ia.2022.06
https://ia.tbzmed.ac.ir/

Review

Revealing Facts About CAR-T Cell Therapy

Daggupati Sai Padmanjali*, Boyina Revathi, Marri Jalaiah

Department of Pharmacology, QIS College of Pharmacy, Ongole-523272, Andhra Pradesh, India

ARTICLE INFO

Article History:
Received: November 22, 2022
Accepted: December 6, 2022
ePublished: December 24, 2022

Keywords:
CAR-T cell therapy, Cancer, Cytokine release syndrome, Immunotherapy, Tocilizumab

Abstract

Chimeric antigen receptor (CAR)-T cell therapy is a fast-emerging treatment for several types of cancers and has several applications beyond oncology. It is a new emerging treatment targeting for a broad range of cancers. The objective of this review is to provide the trending information on CAR-T cell therapies, basic principles involved in the CAR-T cell therapy, structure of CAR-T cell, and mainly various clinical applications in the field of oncology as well as beyond oncology, and major side effects of CAR-T cell therapy, methods to overcome the risk factors and to minimize the cost. Although, the cost of treatment is enormous, cost effectiveness can be done by understanding the demand informed by tertiary healthcare centers to manufacture units for decreasing the complexity of the procedure. But this therapy is associated with few-toxicities. Monitoring these toxicities and minimizing the severity is the main future prospective of CAR-T cell therapy. The next stage in developing CAR-T cell therapy for malignancies is to limit exposure to specific cells because future CAR-T cells can target different antigens. Due to the increasing number of potential targets for CAR-T cell therapy, this approach's tremendous success in treating cancer may also be used to the treatment of other diseases.

Introduction

Demographically today around 450-people are taking chimeric antigen receptor (CAR) T-cell therapy and next 5 years the number of patients taking the treatment may increase by two times. And in 10 years the patient count may reach up to 2000.The National Biopharma Mission–BIRAC of the centralized administration has authorized 19.15 crore for the crew to undertake the very first phase-1/2 clinical testing of CAR-T cells.[1]

CAR-T cells are genetically altered T-cells, to create synthetic T-cell receptors for use in immunotherapy. Indeed, CAR-T cells are the workhorse. T-cell adoptive transfer is enticing new region of oncology treatment. T-cells have undergone genetic modification to express a specific CAR that directs them to target an antigen present on the surface of cancerous tumors. After being injected into a patient, CAR-T cells fight cancer cells as a "living therapy." These are forms of cellular immunotherapy using allogenic or autologous T-cells that have been genetically modified to express T-cell receptors (TCARS) or CARs to be able to find new mechanisms to kill the tumor cells.[2]

The first clinical utility of CAR-T cells was in 1989-1993 by Zelig and Eshhar and Gideon gross. In 2011, immunologist Carl June and hematologist David Porter performed research at the University of Pennsylvania and Children's Hospital in Philadelphia on individuals with persistent lymphocytic leukemia and acute lymphoblastic leukemia (ALL) in 2011.[3] CARs were immunocompromised, scientifically upgraded and advanced during the next 30 years, and were classified as the first, second, third, and fourth generation, depending on their structure.[4] CAR-T cell therapy showed about 50%-90% recovery in the patients with B-cell cancer than other cancer therapies was proved with Phase-I/II evidence. Further, FDA has also approved the first anti CD19 CAR-T cell produced for the treatment of pediatric and adult patients for B-cell ALL.

The dual-targeted CAR-T cells were created using T-cells that can target several antigens. The dual targeted CAR or dual signaling CAR molecules or Tandem CAR (Tan CAR), both can trigger anticancer activity. CD20 and CD22 might be suggested to test for individuals aside to CD19 for the dual targeted CARs in B-cell malignancy. CD122 is an ideal option for dual targeted CAR. Better cancer treatment may result from CAR T-cell therapy that targets cancer stem cells specifically instead of tumor cells. Present novel targets are CD20, the cancer testis antigens. In preclinical investigations and early stage clinical trials, CAR-based and TCR-redirected cell treatments are being investigated for the treatment of B-cell maturation antigen. Both recurring and resistant B-cell malignancies have responded well to CAR-T cell treatment in cancer patients. But still there are many problems to be solved related to remission and the complications after therapy.[5]

*Corresponding Author: D. Sai Padmanjali, Email: revspharma@gmail.com

This review was done to outline the CAR-T cell therapy uses in cancer treatment, its uses beyond oncology and also future prospects to minimize the side effects and methods to overcome those side effects.

Basic principles involved in CAR-T cell therapy

CARs are polypeptides that are fusions of a specific monoclonal antibody's signal peptide segment variable and a single or many T-cell binding site co – stimulatory sites. T-cells utilize T-cell receptors to identify and kill pathogenic microbes on their target cell surface. When a T-cell receptor identifies a specific protein on virus or bacteria, it transmits a signal to the T-cell to kill the intruder. When induced, additional receptors direct T-cells to expand and carry out various functions. Instead of noticing infectious agents, CAR is engineered to acknowledge a cancer cell antigen, and the internal domain alerts T-cells to kill the specific antigen, and they multiply until no more target is noticed. Similar to a lock and key, antigens and immune receptors interact. Similar to how a lock can only be opened with the right key, each foreign antigen has a distinct immune receptor that can attach to it. Cancer cells have antigens, but without the proper receptors, your immune cells won't be able to bind to the antigens and help to destroy the cancer cells.[6]

Structure of CAR-T cell

The four primary components of CAR-T cells, which are synthetic ligands to modify T-cell receptors, are as follows:

1. Ligand binding domain
2. Hinge or spacer region
3. A single or several intracellular signaling domains (Figure 1).

After being placed into viral vectors, these artificial domains are then transduced into T- cells, where they direct the immune system's reaction toward cancerous cells.[7]

Ligand-binding domain

The most widely utilized ligand binding sites in CAR structures are single chain variable fragments, while additional regions include nano bodies, ligands to complementary receptors, natural receptors against targets like natural killer group 2D and Tyrosine kinase receptor with ability to several ligands, and smaller peptides are also used.[8]

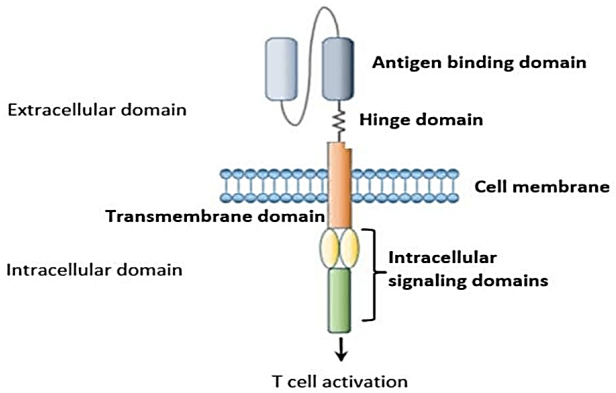

Figure 1. Structure of CAR-T cell.[7]

Hinge or spacer region

The spacer region links single chain variable fragment and transmembrane (TM) domain. CD8, CD28, IgG1, and IgG4 have recently been employed as hinges to connect CAR targeting domains to the TM domain. CARs' TM domain is made up of molecules like CD37, CD8a, CD4, CD28, and the inducible T-cell co-stimulator.[9] The CD28 heterogeneous complex formation of CARs is mediated by the CD28 Transmembrane protein. CAR T-cells with the anti-CD 19 domain are recognized therapies for cancers.

Intracellular signaling domain

The intracellular domains maintain the intracellular signaling required to activate the CAR-T cell's effector functions.[10]

The different generations of CAR- T cells

CARs are divided into three categories: (a) First-generation (no co-stimulatory domain), second-generation (one co-stimulatory domain), and third-generation (two or more co-stimulatory domains) (two co-stimulatory domains). (b) The co-stimulatory domains' order can potentially determine structural suitability for the transmembrane region and affect CAR conformation. The accessibility of membrane proximate kinases, which are important for signaling, may also be impacted. (c) Modulating the quantity of Immunoreceptor tyrosine- based activation motifs (ITAMs) on CD37 can change the way effector functions. Co-stimulatory domain signalling residue changes can also be employed to control effector actions[7] (Figure 2).

Production of CAR-T cells

To generate CAR-T cells, lymphocyte-rich Leukocytes from the patients are harvested, and the T-cells are genetically altered to eradicate malignant cells, followed by T-cell multiplication until millions of attacker cells are produced (Figure 3). After CAR-T cell production is finished, the cells are evaluated for authenticity, purity, stability, and effectiveness; thereby infused into patients to recognize and kill the cancerous cells. They are most often cryogenically preserved, deposited, and exported to the medical center where they are incorporated.[11] CAR-T cell therapy's effectiveness is dependent on having a good targeting antigen.[12] In addition to CAR-T cells manufacturing methods, the parameters affecting the function, *in vivo* stability, and anticancer effects of CAR-T cell stimulation effectors are T-cell subsets and their development stages.[13]

Mechanism of action

CAR-T cells triggered cytotoxic effects against specific tumor tissues. CAR-T cell treatments appear to promote

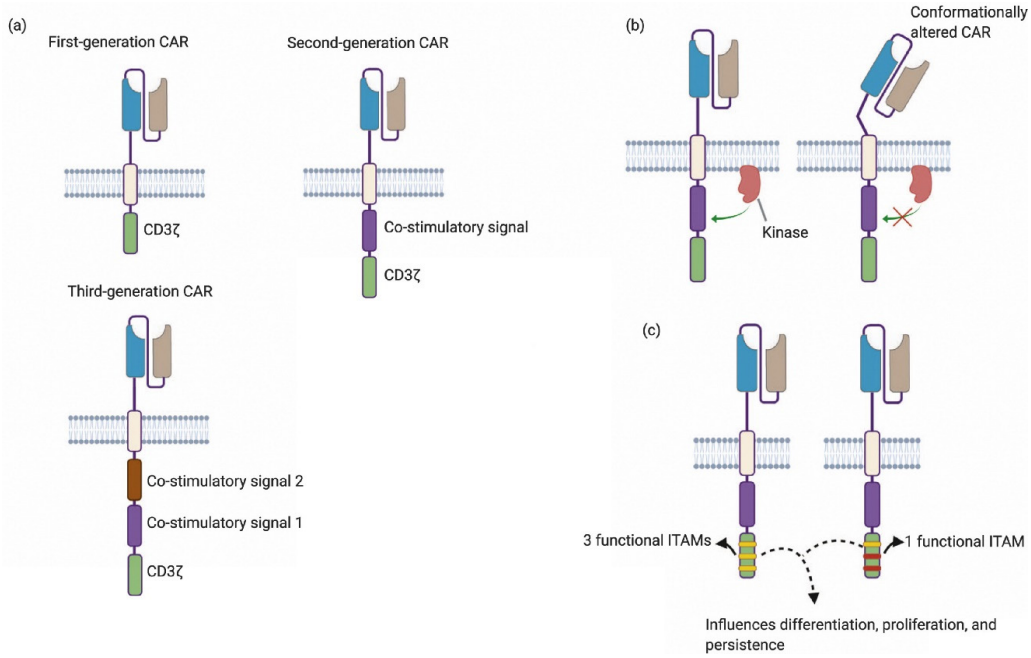

Figure 2. Different cenerations of CAR-T cells.[7] (Creative commons CC BY-NC-ND 4.0 license).

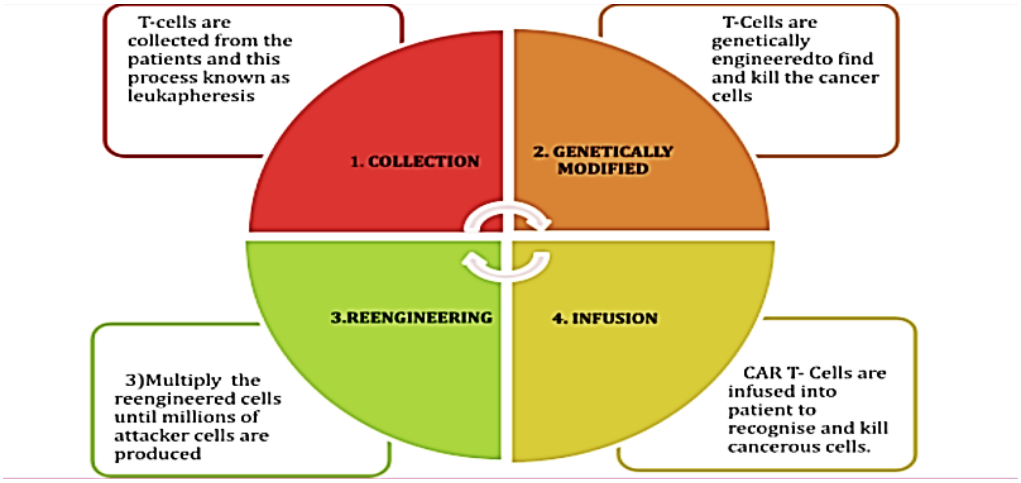

Figure 3. Production of CAR-T cells.

a T-cell response targeting antigen manifesting cell and cancer cells. The extracellular targeting element attaches to antigen, triggering the CAR-T cell. CAR-T cell then stimulate release towards cytokines along with various other soluble substances, which aid in the death of antigen specific receptors. CAR-T cells permit T cells to identify a specific cell adhesion via a signal peptide flexible segment recognition domain, resulting in Major Histocompatibility Complex-unrestricted tissue destruction. A novel immune response that is necessary for precise cytotoxic action is created when CAR-T Cells are activated.[14]

Clinical trials of CAR-T cell therapy in different diseases

B-cell malignancies, such as leukaemia, lymphoma, and myeloma, are the most prevalent diseases type in CAR-T trials. Tisagenlecleucel, a CD19-targeted autologous CAR-T cell therapy, was lately approved by the Food and Drug Administration (FDA) for therapy. B cell ALL that is refractory/relapsed (r/r). Thirty patients including those who received this product as young people and adults, 90% of them were cured completely (CR). In 27% of the patients, severe cytokine-release syndrome (CRS) was reported. This medicine has been tested in clinical trials for CD19 + B cell cancers such as chronic lymphocytic lymphoma, ALL, and lymphoma.

Axicabtagene ciloleucel (KTE-C19) CD19-specific CAR-T cells have been shown to be safe for the treatment of aggressive neoplasms such as r/r diffuse large cell lymphoma. Myeloid leukemias target CD33 and CD123. In China, there are now three trials on CAR-T cells targeting CD33 and two trials targeting CD123 antigen. CAR-T clinical studies are being conducted on a variety of solid malignancies. In solid tumour trials, 20 distinct antigens are being targeted. The most targeted antigens were glypican-3, mesothelin, epidermal growth factor receptor, and epithelial cellular adhesion molecule.

In the resected tumour specimen, CAR-T cell infiltration was seen. According to this study, CAR-T cells

are safe and immunologically active, with the potential to detect cancer cells in the brain. Multiple antigens are being investigated as CAR-T cell targets in solid tumours. There is one clinical trial of autologous CAR-T19 cells treating patients suffering systemic lupus erythematosus, with a dosage of 1, 106 cells/kg. More trials for non-malignant conditions are expected.[15]

Clinical applications of CAR-T cell therapy in oncology

CAR-T cell therapies authorized by FDA, primarily used to treat blood cancers such as Hodgkin disease, cancer of B-lymphocytes, ALL, acute myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma and auto immune diseases. CAR-T cell researches showed significant promise in solid tumors like carcinoma, breast cancer, and sarcoma.[16]

Applications of CAR-T cell therapy beyond oncology

Allergy and asthma

When IgE binds to the suitable immunoglobulin receptor which is found on mast cells, eosinophiles and granulocytes, it triggers exocytosis and chemical mediator release. This results in immediate reactions and allergy manifestation.[17] Low levels of Tregs, decreased immunosuppressive activity, and excessive Th2-dominant responses to allergens are all linked with the pathogenesis of allergic asthma, which results in airway inflammation, hyper responsiveness, and reversible impairment.[18]

Infectious diseases

It was demonstrated that CAR-T cells identify the anti-hepatitis B surface antigen particles and hepatitis-B virus cells *in-vitro* and significantly decrease its viral DNA and hepatitis B antigen count *in-vivo*. In final stage for persistently effected people who are unresponsive to conventional treatments, chronic hepatitis C virus (HCV) infection is the therapeutic purpose for the transplantation of liver. HCV/E2 recognizing CAR-T cells are one of the virus particles that are formed on the top of infected cells and they serve as the main focus of the host's immune response.[19] Following organ transplantation, patients frequently experience the same issue brought on by invasive fungal infections. For example, aspergillosis altered the CAR structure with dectin-1 extracellular domain to recognize various carbohydrates produced on the fungal aspect.[20] The influenza virus A virus that caused H1N1 Flu and fowl plague was considered as a possible medical use of CAR-T cells. Studies conducted in laboratories revealed that the CD4 + CAR-T cells had the capacity to kill HIV-infected T-cells and HIV-infected macrophages and T-cells block viral replication.[21]

COVID-19

To treat COVID, which is caused by SARS CoV-2 virus, several scientists have become interested in using immune cells that have been CAR transduced to attack virus-infected cells.[22]

Cardiac fibrosis

A pathological condition known as fibrosis is characterized by extracellular matrix component deposition as well as fibroblast hyper activation and growth. There is currently no targeted medicine available to treat or prevent the onset of heart failure. The CAR-T cells are able to recognize fibroblast activation protein on heart fibroblasts in rodents with hypertension and fibrotic scarring, and target these cells to treat cardiac fibrosis. Application of CAR-T cell technology is highly awaited in many fields, such as the treatment of viral infections in those with primary immunological deficiencies[23] (Figure 4).

Side effects of CAR-T cell therapy

There are numerous problems to be resolved, both in terms of the main disease's remission and side effects from the therapy. Despite the fact that patients treated with CAR-T cell therapy for relapsed or refractory B-cell malignancies have proved to have a generally satisfactory prognosis.[2] Though CAR-T cell therapy has generated

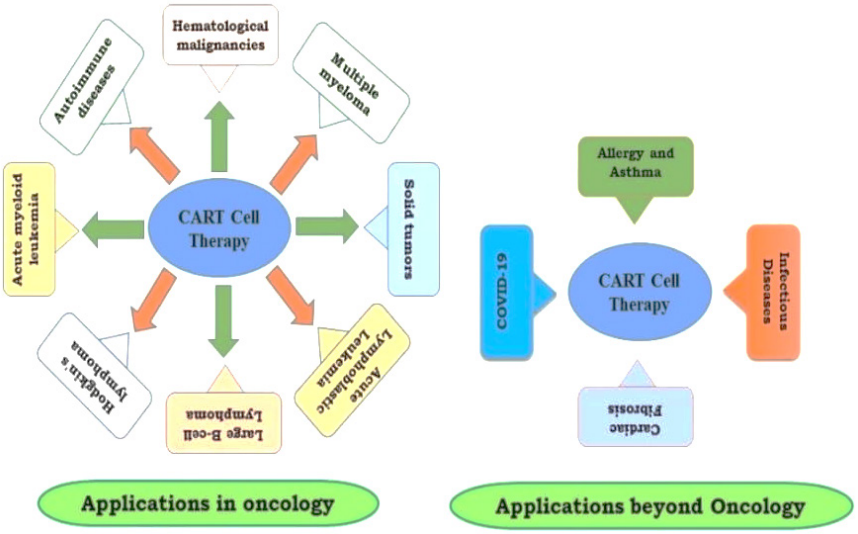

Figure 4. Applications of CAR-T cell therapy in cancer therapy and beyond oncology.

phenomenal diagnostic and therapeutic responses for certain subgroups of B-cell cancers, numerous barriers restrict their clinical benefit. Such barriers usually involve the life-threatening toxic side effects, moderate anti-tumor function, antigen escape, restrained trafficking, and restricted tumor invasion. B-lymphocytes that express CD19 are attacked and killed by anti-CD19 CAR-T cells, causing major effects such as CRS, macrophage activation syndrome,[24] neurotoxicity[25] and B-cell aplasia.[26]

Because CAR-T cell therapy is indeed a distinct and unique medication, these must be created specifically for each patient, which is a time-consuming and critical process that also demands logistics. Customized techniques need testing equipment rather than a manufacturing facility, resulting in production problems and limited scalability. These variables push up the cost of producing CAR-T cells, resulting in incredibly expensive therapeutic costs.[27] The restricted target domains accessible, as well as susceptibility in the tumor environment, are the main drawbacks of CAR-T cells.[28]

Methods to overcome the side effects of CAR-T cell therapy

Most CAR-T cell therapy adverse effects will resolve on their own or can be treated appropriately.[29] Tocilizumab is often used as a first-line treatment for chronic CRS, while research into its influence on CAR-T cell proliferation and functionality is continuing. Steroids and supportive therapy (including anti-epileptic therapy) are used to alleviate neuron toxicity.[30] Tocilizumab (Actemra) suppresses the interleukin-6 receptor, relieving inflammation by impairing T-cell functionality.

The ability to distinguish between cancerous and healthy cells has been achieved by researchers through the development of smart CAR constructs. The innovative method based on "masked CARs," increases the utility of the CAR-T cells via management of malignancies. It have not definite tumor-associated antigens, consists of a selectively Probody-based active CAR design with an antigen noticing region.[31] The implementation of an antigen-specific iCAR is another technique for reducing the adverse effects of "on-target off-tumor toxicities" or bystander healthy tissue destruction.[32] The T cell excitation response and co-stimulatory transmissions are physically isolated from one another in a trans-signaling CAR strategy using CAR-T cells with logic gates, which adopt a "double or nothing" technique. These CAR-T cells, also known as logic-gated CAR-T cells, can only target malignant cells that simultaneously express both antigens detected by the two distinct CARs' antigen recognition domains. Universal CAR, which is a new concept helps in reducing the cost and also makes the production process simple and effective. Remote-controlled CARs are a new technique in which an inducible gene–regulatory mechanism helps in the expression of CARs when the drug is administered (Table 1).[33]

Discussion

CAR-T cell therapy is indeed a novel effective cancer therapy.[34] Immunotherapy is currently thought of as the fifth pillar of cancer treatment, including surgeries, chemotherapeutic, radiation oncology, and combination therapies.[35] CAR autologous T-cells have been used to make T-cells, which provide new significant barriers in developing therapeutically efficient remedies.[7] This is a relatively new field of transfusion medicine that includes rejuvenating lymphocytes with anticancer. FDA has approved CAR-T cell therapy for patients suffering from ALL, multiple myeloma and brain tumors.[36] The common goal of immunotherapy is of specifically targeting and eradicating neoplastic cells.[37,38] Adoptive cell transplantation is a proven immunotherapy technique for the management of advanced cancers.[28]

CAR-T cell treatment works by genetically modifying T-cells to prevent cancer and causing them to generate CARs on their surface and instructing CAR-T cells to exclusively stabilize cancer cells. The safety and efficacy of CAR-T cells for conditions other than CD19 positive B-cell malignancies are currently being investigated in larger research.[39] Beyond oncology, there are several applications of CAR-T cell therapy as we discussed earlier. Because of the rapid advancement of modern biotechnology, researchers can now put their ambitious ideas to the test by adopting unique and even revolutionary clinical strategies for the treatment of serious diseases.[40]

In this review, we first discuss the introduction to CAR-T cell therapy, basic principles involved in CAR-T cell therapy, structure of CAR-T cell, production and mechanism of action of CAR-T cells. Finally, we address the clinical applications of CAR-T cell therapy in oncology and beyond that of oncology along with the side effects of the therapy and methods to overcome.

Conclusion

This review looked into CAR-T cell therapy, which will fall becoming more of a scientific and clinical interest. It is

Table 1. FDA approved CAR-T cell Therapies and the related complications

Brand name	Antigen targeted	Treatment	Number of populations tested	Complications
Tecartus	CD19	B-cell ALL mantle cell lymphoma	Adult people over 50	Neurotoxicity[27]
Abecma	BCMA	Multiple myeloma	127	Tumorlysis syndrome[16,27]
Breyanzi	CD19	B-Cell non-Hodgkin lymphoma	Recently introduced	B-cell aplasia[27]
Kymriah	CD19	B-cell ALL, B-cell non-Hodgkin lymphoma	5300	Cytokine release syndrome[27,28]
Yescarta	CD19	Follicular lymphoma, B-cell non-Hodgkin lymphoma	5300	Graft versus host disease[27,33]

now established that CAR-T cell therapy offered multiple treatment options for cancer which extended beyond oncology. For better effectiveness, durability, infiltration, and anti-apoptosis capability, CAR-T cell clinical impacts, similarly the CAR-T cells model, which includes the ectodomain, transmembrane domain, and endodomain, product engineering, and T-cell sources, are researched and carefully analysed. Many currently incurable diseases may one day be treated due to the advancement of innovative CAR-T cell treatments. Ongoing research within this area ultimately provides the way for future progress in the clinical uses of these therapies.

Acknowledgements

I am extremely grateful to my guides Dr.B.Revathi and M.Jalaiah for their constant support and guidance.

Author Contributions

Conceptualization: Daggupati Sai Padmanjali, Marri Jalaiah.
Data curation: Daggupati Sai Padmanjali, Boyina Revathi.
Formal Analysis: Daggupati Sai Padmanjali, Boyina Revathi.
Investigation: Boyina Revathi.
Methodology: Daggupati Sai Padmanjali, Boyina Revathi, Marri Jalaiah.
Project administration: Boyina Revathi.
Resources: Daggupati Sai Padmanjali, Marri Jalaiah.
Supervision: Boyina Revathi.
Validation: Boyina Revathi, Marri Jalaiah.
Visualization: Daggupati Sai Padmanjali, Marri Jalaiah.
Writing – original draft: Daggupati Sai Padmanjali, Boyina Revathi.
Writing – review & editing: Daggupati Sai Padmanjali, Boyina Revathi.

Funding Sources

This review did not receive any specific grant from any funding agencies in the public, commercial or not-for-profit sectors.

Ethics Issues

Not applicable.

Conflict of Interest

No conflict of interest

References

1. Belleudi V, Trotta F, Fortinguerra F, Poggi FR, Olimpieri O, Santelli E, et al. Real world data to identify target population for new CAR-T therapies. Pharmacoepidemiol Drug Saf. 2021;30(1):78-85. doi: 10.1002/pds.5165.
2. Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15(1):47-62. doi: 10.1038/nrclinonc.2017.148.
3. Wachowiak J, Bettoni C, Lange A, Malicki J, Kaczmarek-Kanold M, Głuszak B, et al. Can busulfan replace fractionated total body irradiation as conditioning regimen for allogeneic bone marrow transplantation in children with acute lymphoblastic leukemia. Acta Haematol Pol. 1995;26(4):377-84.
4. Styczyński J. Infections following CAR-T cells therapy: current state-of-the-art review and recommendations. Acta Haematol Pol. 2020;51(1):11-6. doi: 10.2478/ahp-2020-0004.
5. Wang Z, Wu Z, Liu Y, Han W. New development in CAR-T cell therapy. J Hematol Oncol. 2017;10(1):53. doi: 10.1186/s13045-017-0423-1.
6. Met Ö, Jensen KM, Chamberlain CA, Donia M, Svane IM. Principles of adoptive T cell therapy in cancer. Semin Immunopathol. 2019;41(1):49-58. doi: 10.1007/s00281-018-0703-z.
7. Jayaraman J, Mellody MP, Hou AJ, Desai RP, Fung AW, Pham AHT, et al. CAR-T design: elements and their synergistic function. EBioMedicine. 2020;58:102931. doi: 10.1016/j.ebiom.2020.102931 .
8. Larson RC, Maus MV. Recent advances and discoveries in the mechanisms and functions of CAR T cells. Nat Rev Cancer. 2021;21(3):145-61. doi: 10.1038/s41568-020-00323-z.
9. Safarzadeh Kozani P, Safarzadeh Kozani P, Rahbarizadeh F, Khoshtinat Nikkhoi S. Strategies for dodging the obstacles in CAR T cell therapy. Front Oncol. 2021;11:627549. doi: 10.3389/fonc.2021.627549.
10. Riddell SR, Sommermeyer D, Berger C, Liu LS, Balakrishnan A, Salter A, et al. Adoptive therapy with chimeric antigen receptor-modified T cells of defined subset composition. Cancer J. 2014;20(2):141-4. doi: 10.1097/ppo.0000000000000036.
11. Pagel JM, West HJ. Chimeric antigen receptor (CAR) T-cell therapy. JAMA Oncol. 2017;3(11):1595. doi: 10.1001/jamaoncol.2017.2989.
12. Mao R, Hussein MS, He Y. Chimeric antigen receptor engineered T cells and their application in the immunotherapy of solid tumours. Expert Rev Mol Med. 2022;24:e7. doi: 10.1017/erm.2021.32.
13. Lee YH, Kim CH. Evolution of chimeric antigen receptor (CAR) T cell therapy: current status and future perspectives. Arch Pharm Res. 2019;42(7):607-16. doi: 10.1007/s12272-019-01136-x.
14. Benmebarek MR, Karches CH, Cadilha BL, Lesch S, Endres S, Kobold S. Killing mechanisms of chimeric antigen receptor (CAR) T cells. Int J Mol Sci. 2019;20(6):1283. doi: 10.3390/ijms20061283.
15. Liu B, Song Y, Liu D. Clinical trials of CAR-T cells in China. J Hematol Oncol. 2017;10(1):166. doi: 10.1186/s13045-017-0535-7.
16. Zhao Z, Chen Y, Francisco NM, Zhang Y, Wu M. The application of CAR-T cell therapy in hematological malignancies: advantages and challenges. Acta Pharm Sin B. 2018;8(4):539-51. doi: 10.1016/j.apsb.2018.03.001.
17. Ward DE, Fay BL, Adejuwon A, Han H, Ma Z. Chimeric antigen receptors based on low affinity mutants of FcεRI re-direct T cell specificity to cells expressing membrane IgE. Front Immunol. 2018;9:2231. doi: 10.3389/fimmu.2018.02231.
18. Skuljec J, Chmielewski M, Happle C, Habener A, Busse M, Abken H, et al. Chimeric antigen receptor-redirected regulatory T Cells suppress experimental allergic airway inflammation, a model of asthma. Front Immunol. 2017;8:1125. doi: 10.3389/fimmu.2017.01125.
19. Sautto GA, Wisskirchen K, Clementi N, Castelli M, Diotti RA, Graf J, et al. Chimeric antigen receptor (CAR)-engineered T cells redirected against hepatitis C virus (HCV) E2 glycoprotein. Gut. 2016;65(3):512-23. doi: 10.1136/gutjnl-2014-308316.
20. Kumaresan PR, Manuri PR, Albert ND, Maiti S, Singh H, Mi T, et al. Bioengineering T cells to target carbohydrate to treat opportunistic fungal infection. Proc Natl Acad Sci U S A. 2014;111(29):10660-5. doi: 10.1073/pnas.1312789111.
21. Sahu GK, Sango K, Selliah N, Ma Q, Skowron G, Junghans RP. Anti-HIV designer T cells progressively eradicate a latently infected cell line by sequentially inducing HIV reactivation then killing the newly gp120-positive cells. Virology. 2013;446(1-2):268-75. doi: 10.1016/j.virol.2013.08.002.
22. Golchin A. Cell-based therapy for severe COVID-19 patients: clinical trials and cost-utility. Stem Cell Rev Rep. 2021;17(1):56-62. doi: 10.1007/s12015-020-10046-1.
23. Keller MD, Bollard CM. Virus-specific T-cell therapies for patients with primary immune deficiency. Blood. 2020;135(9):620-8. doi: 10.1182/blood.2019000924.
24. Graham C, Hewitson R, Pagliuca A, Benjamin R. Cancer immunotherapy with CAR-T cells - behold the future.

Clin Med (Lond). 2018;18(4):324-8. doi: 10.7861/clinmedicine.18-4-324.
25. Schubert ML, Schmitt M, Wang L, Ramos CA, Jordan K, Müller-Tidow C, et al. Side-effect management of chimeric antigen receptor (CAR) T-cell therapy. Ann Oncol. 2021;32(1):34-48. doi: 10.1016/j.annonc.2020.10.478.
26. Safarzadeh Kozani P, Safarzadeh Kozani P, Rahbarizadeh F. Optimizing the clinical impact of CAR-T cell therapy in B-cell acute lymphoblastic leukemia: looking back while moving forward. Front Immunol. 2021;12:765097. doi: 10.3389/fimmu.2021.765097.
27. Zheng PP, Kros JM, Li J. Approved CAR T cell therapies: ice bucket challenges on glaring safety risks and long-term impacts. Drug Discov Today. 2018;23(6):1175-82. doi: 10.1016/j.drudis.2018.02.012.
28. Feins S, Kong W, Williams EF, Milone MC, Fraietta JA. An introduction to chimeric antigen receptor (CAR) T-cell immunotherapy for human cancer. Am J Hematol. 2019;94(S1):S3-S9. doi: 10.1002/ajh.25418 .
29. Bonifant CL, Jackson HJ, Brentjens RJ, Curran KJ. Toxicity and management in CAR T-cell therapy. Mol Ther Oncolytics. 2016;3:16011. doi: 10.1038/mto.2016.11.
30. Gill S, Maus MV, Porter DL. Chimeric antigen receptor T cell therapy: 25years in the making. Blood Rev. 2016;30(3):157-67. doi: 10.1016/j.blre.2015.10.003.
31. Han X, Bryson PD, Zhao Y, Cinay GE, Li S, Guo Y, et al. Masked chimeric antigen receptor for tumor-specific activation. Mol Ther. 2017;25(1):274-84. doi: 10.1016/j.ymthe.2016.10.011.
32. Fedorov VD, Themeli M, Sadelain M. PD-1- and CTLA-4-based inhibitory chimeric antigen receptors (iCARs) divert off-target immunotherapy responses. Sci Transl Med. 2013;5(215):215ra172. doi: 10.1126/scitranslmed.3006597.
33. Hanada K, Restifo NP. Double or nothing on cancer immunotherapy. Nat Biotechnol. 2013;31(1):33-4. doi: 10.1038/nbt.2471.
34. Stroncek D, Panch SR, Jin P, Highfill SL. CAR T-cell: cell processing laboratory considerations. In: Lee DW, Shah NN, eds. Chimeric Antigen Receptor T-Cell Therapies for Cancer. Elsevier; 2020. p. 17-28. doi: 10.1016/b978-0-323-66181-2.00003-2.
35. Singh AK, McGuirk JP. CAR T cells: continuation in a revolution of immunotherapy. Lancet Oncol. 2020;21(3):e168-e78. doi: 10.1016/s1470-2045(19)30823-x.
36. Wang Z, Wu Z, Liu Y, Han W. New development in CAR-T cell therapy. J Hematol Oncol. 2017;10(1):53. doi: 10.1186/s13045-017-0423-1.
37. Figueroa JA, Reidy A, Mirandola L, Trotter K, Suvorava N, Figueroa A, et al. Chimeric antigen receptor engineering: a right step in the evolution of adoptive cellular immunotherapy. Int Rev Immunol. 2015;34(2):154-87. doi: 10.3109/08830185.2015.1018419.
38. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. Science. 2018;359(6382):1361-5. doi: 10.1126/science.aar6711.
39. DeRenzo C, Krenciute G, Gottschalk S. The landscape of CAR T cells beyond acute lymphoblastic leukemia for pediatric solid tumors. Am Soc Clin Oncol Educ Book. 2018;38:830-7. doi: 10.1200/edbk_200773.
40. Zmievskaya E, Valiullina A, Ganeeva I, Petukhov A, Rizvanov A, Bulatov E. Application of CAR-T cell therapy beyond oncology: autoimmune diseases and viral infections. Biomedicines. 2021;9(1):59. doi: 10.3390/biomedicines9010059.