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Review Article

Chimeric Antigen Receptor T-Cells (CAR T-Cells): An Engineered Targeted Therapy for Treatment of Cancer

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Abstract

We have undertaken this review to explore the various developments and insights of CAR-T cell therapy during 1989-2023 and its advantages in the treatment of cancer and immune modulation. It is a chimeric antigen receptor T-cell therapy, which is an innovative form of immunotherapy that harnesses the power of the immune system to fight cancer. At first, T cells are extracted from the patient's blood through a process called leukapheresis. Then the modification has been done in T cells by genetically engineered to express chimeric antigen receptors (CARs) on their surface. These receptors are designed to recognize specific proteins, or antigens, that are found on the surface of cancer cells. Many conventional therapies available in the market for the treatment of cancer and Immuno modulation but most of them having Adverse Drug Reaction (ADR). But CAR-T cells possess upper hand on these conventional Formulations. Once a sufficient number of CAR-T cells have been produced, they are infused back into the patient's bloodstream. Once reach inside the body, the CAR-T cells recognize and bind to the cancer cells that express the specific antigen targeted by the CAR. This triggers the destruction of the cancer cells by the immune system. CAR-T cell therapy has shown remarkable success in treating certain types of blood cancers, such as acute lymphoblastic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), and certain types of lymphoma. The content of this review will pave the way to work on CAR-T cell therapy.

Keywords: CAR-T, Immunotherapy, cancer, antigen, leukemia, lymphoma.

1.INTRODUCTION:

Chimeric antigen receptors (CARs) are receptor proteins that have been modified to allow T cells to target a particular antigen. They are also referred to as chimeric immune receptors, chimeric T cell receptors, or artificial T cell receptors in the field of biology. The receptors are chimeric, combining into a single receptor the ability to attach to antigen and activate T cells.

Production and injection of T cells with chimeric antigen receptor-

1. A patient's blood is used to separate T cells.
2. The T cells acquire a new gene that codes for a chimeric antigen receptor.
3. Target antigen-specific engineered T cells are currently available.
4. Tissue culture is used to grow engineered T cells.
5. The patient receives a second infusion of engineering t cell.[1]

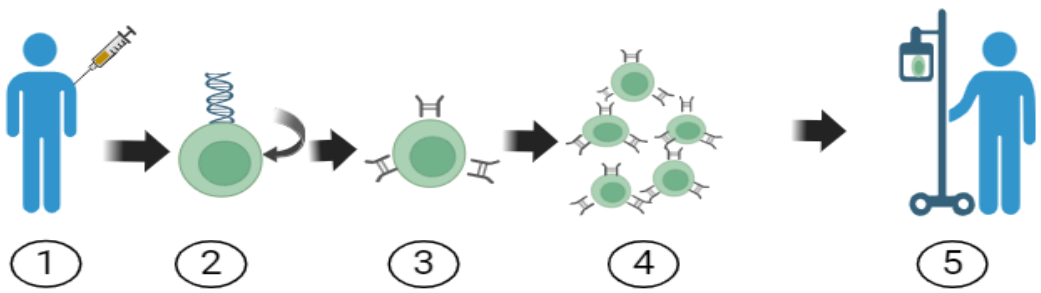

Figure 1: Production and infusion of T-cell

Table 1: History of CAR T-cell

Year	Achievement
1989	production of effector T cells that express the receptor for chimeric T cells[2,3]
1993	CAR-T cells from the first generation are not therapeutically effective.[4]
2002	The first CAR-T cells that are efficient against the prostate cancer antigen in the lab.
2003	Second-generation CARs: CD19-directed CAR-T cells have the ability to eradicate mice leukaemia cells.
2009	Relapsed or resistant leukaemia is treated using CD19 CAR.
2011	Patients with chronic lymphocytic leukaemia with CD19 CAR.[5]
2013	Paediatric acute lymphoblastic leukaemia using CD19 CAR-T cells. [6]
2013	Cancer immunotherapy was named the "Breakthrough of the Year" by Science magazine.
2014	Inducible caspase-9 suicide gene system as a "safety switch" to reduce on-target, off-tumour toxicities in third-generation CAR-T cells.[7]
2015	Fourth-generation CARs that generate different compounds being explored for ovarian cancer, such as armoured CARs or TRUCKs (CAR redirected T cells that deliver a transgenic product to the targeted tumour tissue).[8]
2015	The CAR-NK cell concept.[9]
2017	Clustered regularly interspaced short palindromic repeats (CRISPR) used to optimize CAR placement in T cells. [10]
2017	For children and young adults with relapsed or resistant acute lymphoblastic leukaemia, the FDA has approved CD19-CAR-T cells.
2017	FDA approves CD19-CAR-T cells for adult DLBCL patients with relapses or resistance.
2018	For relapsed or resistant acute lymphoblastic leukaemia in children and young adults as well as relapsed or resistant DLBCL in adults, the EMA has approved CD19-CAR-T cells.
2019	In both adults and children with acute lymphoblastic leukaemia, dual CD19/CD22 CAR-T cells are present. [11]
2023	CDSCO made NexCAR19, India's first approved CAR T-cell therapy.

CAR T-Cells show some side effects which should be taken cared of. Some include: Cytokine Release Syndrome (CRS) is a common adverse reaction following CAR T-cell treatment, causing minor symptoms like headaches and fevers, or serious ones like hypotension, capillary leak syndrome, and organ malfunction[12]. Neurological toxicity, also known as ICANS, is an immune effector causing neurological symptoms like delirium, seizures, and disorientation, often occurring alongside CRS. Hypogammaglobulinemia is Immunoglobulin levels may drop as a result of CAR T-cell treatment, raising the possibility of infections. Tumour Lysis Syndrome is a condition where cancer cells are rapidly killed, causing metabolic abnormalities like hyperphosphatemia, hypocalcaemia, hyperkalaemia, and hyperuricemia[13].CAR T-cell treatment, although rare, can occasionally lead to cardiac toxicity, causing symptoms like arrhythmias or reduced heart function[14].

2.STRUCTURE OF CAR T CELLS:

CARs are divided into three main domains:

1) The extracellular domain, or ecto-domain, is composed of a single peptide on the cell surface that is cleaved from the mature CAR cell and can be further subdivided into an antigen-recognition domain.[15]Aflexible linker divides the antigen-specific immune-globin segments that make up the antigen-recognition domain (scFV), which is primarily composed of heavy and variable light chain regions. A hinge connects the spacer (scFV) to the trans-membrane domain, which is in charge of transmitting receptor-binding signals.[16]

2) The hydrophobic alpha helix known as the transmembrane domain, which extends throughout the cell membrane, is crucial for receptor stability and surface expression.[17]

3) the endo-domain, an intracellular domain that, when stimulated, clusters and alters its conformation, making it possible for downstream signalling proteins to be recruited and phosphorylated.[18]

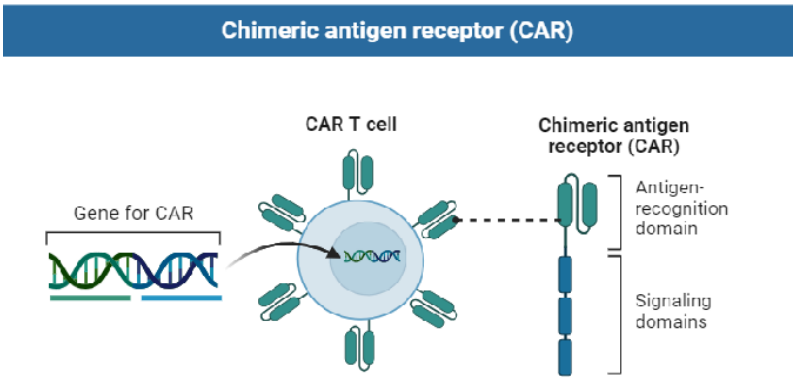

Figure 2: Structure of Chimeric antigen receptor (CAR)

3. EVOLUTION:

Five generations of CARs are distinguished by their intracellular domain:

The first has a single activation domain, a cytoplasmic domain primarily consisting of CD3 zeta (CD3ζ), and some studies use the gamma chain (γ) of the Fc receptors.2.) The second has CD3ζ plus one costimulatory domain, obtained from costimulatory molecules like 4-1BB or CD28 connected to an activator domain (CD3ζ/γ chain of Fc receptor), to improve the cytotoxic and cell proliferative abilities of CAR T cells.[19]Though it possesses several costimulatory domains with CD3ζ, including 4-1BB and CD28, CD134, and CD13 [20] 7.3.)The third generation of CARs, T cells redirected for universal cytokine-mediated killing (TRUCKs), aims to overcome TME immune suppression and support strong therapeutic outcomes by releasing transgenic cytokine-like interleukin 12 (IL-12) upon CAR signalling in tumour tissue. IL-12 induces IFN-γ, perforin, and granzymes in T-cells, preventing Treg proliferation.4.) IL-15 and IL-18 are also examined in the fourth generation [21-,24] .IL-15, a γ-chain family member, is crucial for T cell survival and growth. When large pancreatic and lung tumours are treated with IL-18 CAR T-cells, the immune cell landscape changes, with an increase in macrophages and NKs and a decrease in Tregs. This suggests that "IL-18 TRUCKs" can sensitize large tumour lesions for effective immune destruction [25].5.) Currently under investigation, the fifth generation of CARs is primarily based on the second generation. Nonetheless, it has the transcription factor STAT3/5 binding motif, a β-chain domain (IL-2Rβ truncated intracellular interleukin 2β chain receptor), and a truncated cytoplasmic receptor (IL-12). [26]

4. PRODUCTION

CAR T-cells are created by isolating T cells from human blood, either from the patient's own blood (autologous treatment) or a healthy donor (allogenic treatment). The process involves leukocyte apheresis, which separates PBMCs, and then being sent to a cell processing facility. T cells are stimulated by cytokine interleukin 2 (IL-2) and anti-CD3 antibodies. The enlarged T cells are purified and transduced with a modified CAR gene, such as integrated gamma-retrovirus (RV) or lentiviral vector. CRISPR/Cas9, a gene editing technique, is used to integrate the CAR gene into specific regions. Before the engineered CAR T-cells are introduced, the patient undergoes lymphodepletion chemotherapy, which increases cytokine production and reduces resource competition, promoting the proliferation of the altered CAR T-cells.[27-34]

5. CLINICAL PREPARATION OF CAR T CELLS:

Interest in CAR-T cell-based therapeutics has grown due to the success of CD19-targeted CAR-T cells in early phase clinical studies for hematologic malignancies. Current research focuses on targeting different cancer types using tumour-associated antigens like PSMA, mesothelin, GD2, HER2, and epidermal growth factor receptors. The production of CAR-T cells under cGMP is the central approach. The manufacturing process includes T-cell collection, processing, activation, genetic modification, large-scale expansion, and end-of-process formulation.

5.1 CAR T-Cell Source: CAR-T cells are produced through autologous treatment, involving peripheral blood mononuclear cells from patients through leukapheresis. Physicians determine the best collection time based on treatment plans. Different methods, such as Haemonetics Cell Saver 5+, COBE2991, and Fresenius Kabi LOVO, can be used to process collected apheresis products, eliminating platelet impurities and rough red blood cells. Terumo Elutra and Biosafe Sepax systems offer size-based cell fractionation for monocyte depletion and lymphocyte isolation.

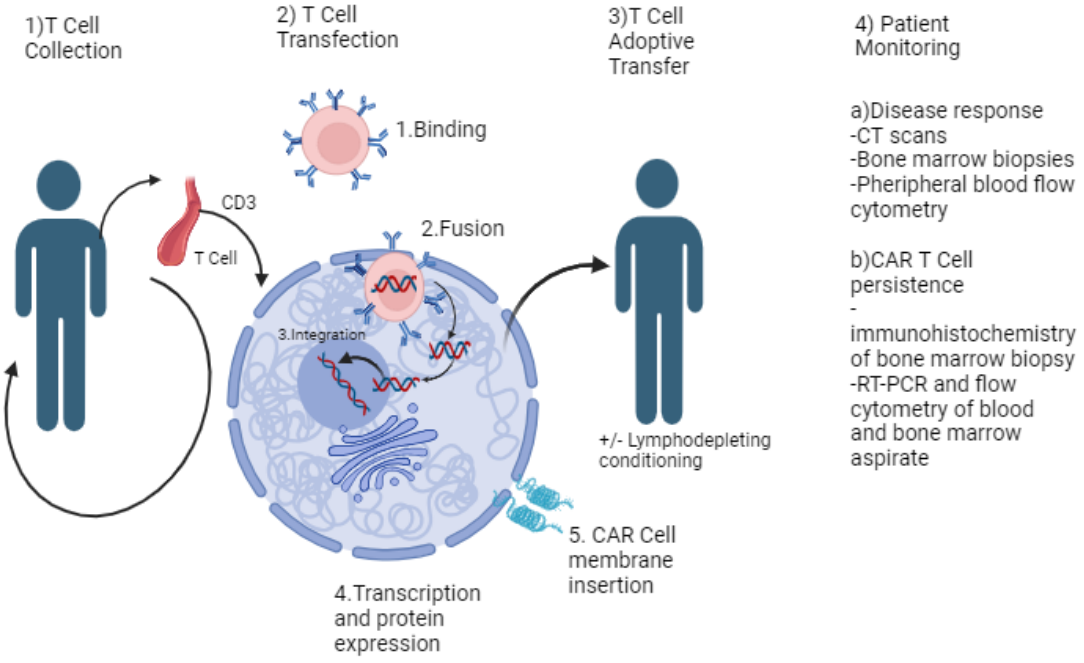

Figure 3: Production of CAR T-cell

Clinical trials often use CAR-T cells from the CD3+ population, but research shows specific T cell subsets like naïve, memory stem cells, and central memory may have functional advantages. Clinical-scale procedures for growth, transduction, and selection have been developed for these subsets. Identifying the best therapeutic benefit and minimizing toxicity is crucial for a reliable manufacturing process. Cryo-preserved T-cell source material can be used for later use or directly for subsequent treatments, with cryo-preserving providing more flexibility for downstream processes and product assessment.[35-37]

5.2 T-Cell Activation: T-cell growth in vivo requires specific and costimulatory signals from sources like CD28, 4-1BB, or OX40. Retroviral vector-mediated transduction of CAR cDNA also requires T-cell activation. Endogenous T-cell activators include dendritic cells (DCs), but their potency varies among patients, making them less reliable. Artificial antigen-presenting cells (AAPCs) are another cell-based T-cell activation strategy, induced by irradiated K562-derived AAPCs. However, generating and choosing GMP- grade HLA matched AAPC lines requires more work and resources. Biotech companies have produced clinical-grade T-cell activation reagents, such as Juno Stage Expamer technology, which significantly streamline the ex-vivo T-cell activation process.[38-4]

5.3 expamer Technology: Juno Therapeutics; Expamer is a recent advancement in T-cell activation reagent technology, using Streptamer technology to isolate lymphocytes specific to viruses. This soluble and dissociable reagent stimulates T cells to enable retroviral transduction and growth, inducing T cell receptor signalling. Despite functional assessment in vivo, Expamer is appealing for large-scale clinical manufacture due to ease of addition and removal from cell suspensions.[41-43]

5.4 Genetic Modification of T-Cell: Stable CAR expression is crucial for current CAR-T cell treatments. There are three main categories of stable gene expression vectors: γ-retroviral vectors, lentiviral vectors, and transposon/transposase systems. γ-retroviral vectors are used in 25% of clinical trials due to their extensive tropism, stable packaging cell lines, and high gene expression. Studies have shown the safety profile of retroviral vectors when used with adoptive T-cell treatment. Research suggests growing retroviral stable packaging producer cell lines in scalable bioreactors could produce sufficient cGMP quality vector stocks for phase 3 trials and beyond. Retroviral and lentiviral vectors require extensive biosafety testing due to their complexity. The transposon/transposase system, a recent plasmid-based expression technology, offers straightforward release testing, low cost, and easy manufacturing. However, random integration may pose a secondary oncogenic risk due to mutagenesis. Low T-cell toxicity has been observed in an ongoing anti-CD19 CAR-T cell experiment, but its effectiveness remains unestablished.[44-57]

5.5 Messenger RNA: Messenger RNA (mRNA) transfer allows transgenes to express themselves temporarily, unlike viral transduction or plasmid DNA transfection. This method eliminates genomic integration events, genotoxicity, and replication-competent retrovirus production. RNA transfection is used to transfer mRNA for TCR/CAR, chemokine receptors, and cytokines, allowing transgene expression for about one week. A recent study showed that "off the shelf" CAR-T cells can be produced from unrelated healthy donors using electroporation of transcription activator-like effector nucleases.[58-62]

Off-the-shelf CAR T-cell therapies: CRISPR, natural killers, and mRNA: Scientists are exploring the origins of CAR T-cell treatments, using T cells from healthy donors instead of patients. The goal is to provide off-the-shelf CAR T-cell therapies that can be used immediately. FDA-approved therapies use a disarmed virus to transfer genetic material into T cells, but gene-editing technologies like CRISPR and TALON are being used to stimulate donated T cells. Natural killer (NK) cells are also being explored as an alternative form of immune cell. The therapeutic manufacturing process is also being re-examined, with research teams using mRNA-based strategies and nanotechnology to create CAR T cells inside the body.[63]

6.DEVELOPMENT OF CAR ENGINEERED T-CELL THERAPIES:

6.1. The Emergence of Chimeric T-Cell Receptor: The concept of a chimeric T cell receptor was first documented in 1987 by Dr. Yoshikazu Kurosawa and his colleagues at the Institute for Comprehensive Medical Science. They demonstrated that anti-phosphorylcholine chimeric receptors in murine T-cell lymphomaEL4 cells caused a calcium influx, indicating that the receptor could activate T cells in response to antigens. In 1989, Israeli immunologist Dr. Zelig Eshhar and his colleagues reported that T cells can recognize antigens in a non-major histocompatibility complex (MHC)-restricted manner using a similar strategy. The resulting chimeric T-cell receptor (cTCR) was made up of the constant sections of alpha and beta TCR chains fused with the variable heavy and light chains of the anti-2,4,6-trinitrophenyl (TNP) antibody Sp6. Functional cTCRs were expressed on the cell surface and able to bind to TNP antigen upon co-transfection into murine MD.45 cyto-toxic T lymphocyte hybridoma cells, resulting in T cell activation and the generation of interleukin-2 (IL-2) and the destruction of target cells. [64-69]

6.2. The First Generation CAR: In mouse models, the modified T cells containing the first-generation CAR, which had scFv fused to CD3ζ or FcϵRIγ, demonstrated anti-cancer activity. For example, in athymic BALB/c mice, the growth of subcutaneous tumours was reduced by a scFvR including anti-ERBB2/HER2 scFv and a murine CD3β signalling endo-domain. In a different investigation, syngeneic C57BL/6 mice, athymic nude mice, and murine tumour-infiltrating T cells expressing a scFvR called MOv-γ—a combination of anti-α-folate receptor (FR) scFv and the Fc receptor γ chain—exhibited anticancer efficacy in vitro. It is significant to remember that following the infusion of the gene-modified T cells in these in vivo studies, mice got systemic high-dose IL-2 therapy [70-72].Two human clinical trials of CAR T cell therapy were conducted in ovarian cancer patients and metastatic renal cell carcinoma patients. Despite promising anticancer results in vitro and in mice, no patient showed a decrease in tumour amount and most patients' genetically modified T cells rapidly decreased to undetectable levels. In another study, modified T cells expressing CE7R(huCD3ζ) were durable in vivo for up to six weeks in children with recurrent neuroblastoma. However, drug-selection genes were produced by modified T cells, potentially reducing their ability to persist in vivo. Patients with neuroblastoma showed some durability and antitumor activity from first-generation GD2-specific CAR T cells. Efforts to improve first-generation CAR design have been prompted by their inefficiency in treating cancer in humans [73-77]

6.3. The Second Generation-CAR: Two signals are normally needed for T cell activation: the first is produced when the TCR engages with peptide-loaded major histo-compatibility complex (pMHC), and the second is produced by costimulatory receptors like CD28[78]. Therefore, it was suggested that adding a costimulatory endo-domain to T cells that have been modified could improve the cells' ability to proliferate and remain in place. A chimeric receptor that combines the CD3ζ and CD28 endo-domains was created by Dr. Michel Sadelain's lab at Memorial Sloan Kettering Cancer Centre (MSKCC). This receptor produces both activation and co-stimulatory signals, and it improves antigen-dependent proliferation, interleukin-2 production, and in vitro cancer cell death. Moreover, compared to T cells expressing chimeric receptors containing only the CD3ζ endo-domain, T cells expressing chimeric receptors containing both the CD3ζ and CD28 endo-domains demonstrated noticeably greater growth and durability in human patients. These findings unequivocally showed how crucial it is for the chimeric receptor to contain a

costimulatory endo-domain like CD28 [79-81] .Another important development in the field is the inclusion of the 4-1BB/CD137 signal transduction domain in the CAR design, which was pioneered by Dr Dario Campana at St Jude Children's Research Hospital. The longevity and anticancer activity of CAR-engineered T cells in mice were markedly enhanced by the addition of 4-1BB costimulatory endo-domain. Furthermore, while employing the elongation factor-1α promoter (EF-1α) in lentiviral vector, T cells have expressed chimeric receptors more steadily and permanently than when using promoters from ubiquitin, phosphoglycerate kinase (PGK), and cytomegalovirus (CMV). A noteworthy advancement in the field of CAR T cell therapy was reached when a second-generation CAR construct incorporating both a costimulatory endo-domain (like CD28 or 4-1BB) and the CD3ζ signalling endo-domain demonstrated remarkable success in human clinical trials. The comparison between the second-generation CAR that recognises tumour-associated antigen and the standard TCR that recognises peptide-major histocompatibility complex (pMHC). It also demonstrates the extraction of the single-chain variable fragment (scFv) domain from a monoclonal antibody.[82-84]

6.4.The Clinical Success of CAR-T Cell Therapy: A patient at NCI and MSKCC showed promise with second-generation CAR T cell therapy for advanced follicular lymphoma and relapsed B-cell ALL and CLL. The treatment involved expressing a CD19-specific CAR using a retroviral vector called MSGV. The patient experienced selective B-lineage cell elimination and partial remission of the lymphoma after two doses of CAR T cells and eight doses of IL-2. Autologous CD19-targeted CAR T cells were assessed for safety and durability in the MSKCC Phase 1 study. Individuals treated without prior conditioning did not show objective disease responses [85,86].

7. CAR T-CELL THERAPY:

Chimeric antigen receptor (CAR) T-cell treatment is used in immunotherapy for certain blood cancers. This treatment alters T-cells by inserting a new gene, increasing their ability to identify and eliminate malignant cells. CAR T-cell therapy can sometimes cure blood cancer and prolong patient survival [87].

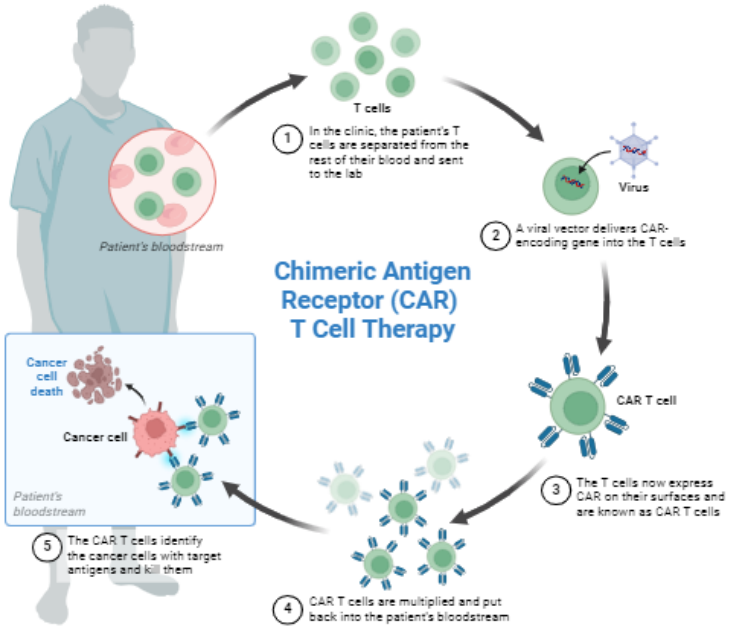

Figure 4: Diagrammatic representation of CAR T-cell Therapy

7.1 How Does It Works: Formation of tumours include the mechanism: Viral genetic information disrupts the sequence of cellular oncogenes by integrating into the cellular genome. Viral gene products interact with tumour suppressor gene products, leading to a transformation process. Viral proteins can also interact with basic regulatory proteins of the cell cycle, affecting transcription and expression of certain genes. They promote cell proliferation and have an anti-apoptotic effect. Some viruses contribute to this transformation by increasing telomerase activity in cells, which plays a crucial role in chromosome stability during the cell cycle. Telomerase activity is present in prenatal development, isolated groups, and individuals lives. Recent studies have found an association between increased telomerase activity and infection with viruses like HPV 16, herpesvirus HHV8, and EB virus.

T-cells are white blood cells in the immune system that track antigens on the surface of intruder cells, including cancer. They system for aberrant cells, activating when a receptor identifies one. CAR T-cells are modified T-cells that identify a specific antigen on the surface of cancerous cells. Scientists introduce a synthetic gene for a chimeric antigen receptor, stimulating the T-cells to proliferate and develop until an adequate number of cells exist to efficiently target malignant cells.

7.2 Who Can Have CAR T-Cell Therapy: The FDA has approved CAR- T cell therapy for various types of B-cell cancers, including acute lymphoblastic leukaemia, Large-cell diffuse B-cell lymphoma (DLBCL), primary mediastinal lymphoma, follicle lymphoma, high-grade B cell lymphoma, activating B-cell lymphoma without specific indication, mantle cell lymphoma, and follicular lymphoma tumours.

7.3 Therapy process: CAR T cell treatment is a complex procedure requiring skilled professionals. It involves collecting T-cells from an arm vein, engineering them in a lab using synthetic CAR, and infusion into the patient arm. To increase treatment efficacy, chemotherapy may be advised before the infusion. The procedure can occur at a hospital or outpatient infusion facility. It typically takes a few weeks to complete.[88]

8. FDA APPROVED CAR T-CELLS THERAPIES

The US Food and Drug Administration (FDA) has authorized CAR T-cell therapy for the treatment of multiple myeloma and certain types of leukaemia and lymphomas. Usually, CAR T-cell therapy is employed following the failure of conventional forms of treatment. Currently authorized CAR T-cell treatment include the following: [89]

Table no.2: FDA approved CAR T-cell therapies

GENERIC NAME	BRAND NAME	TARGET ANTIGEN	TARGETED DISEASE	PATIENT POPULATION
Tisagenlecleucel	Kymriah	CD19	B-cell acute lymphoblastic leukaemia (ALL) B-cell non-Hodgkin lymphoma(NHL)	Children and young adults with refractory or relapsed B-cell ALL Adults with refractory or relapsed B-cell NHL
Axicabtagene ciloleucel	Yescarta	CD19	B-cell non-Hodgkin lymphoma(NHL) Follicular lymphoma	Adults with refractory or relapsed B-cell NHL Adults with refractory or relapsed follicular lymphoma
Brexucabtagene autoleucel	Tecartus	CD19	Mantle cell lymphoma(MCL) B-cell acute lymphoblastic leukaemia (ALL)	Adults with refractory or relapsed MCL Adults with refractory or relapsed B-cell ALL
Lisocabtagene maraleucel	Breyanzi	CD19	B-cell non-Hodgkin lymphoma(NHL)	Adults with refractory or relapsed B-cell NHL
Idecabtagene vicleucel	Abecma	BCMA	Multiple myeloma	Adults with refractory or relapsed multiple myeloma
Ciltacabtegene autoleucel	carvykti	BCMA	Multiple myeloma	Adults with refractory or relapsed multiple myeloma

9. DIFFERENT TYPES OF CANCER ON WHICH CAR T-CELL THERAPY ACTS:

Since the U.S. Food and Drug Administration (FDA) initially authorised CAR T-cell therapy in 2017, the treatment has become accessible. Six iterations of CAR T-cell therapy have been authorised by the FDA thus far to treat various forms of blood cancer, including:

- ***Leukaemia acute lymphoblastic***-Acute lymphoblastic leukaemia (ALL) occurs when white blood cells from lymphoid progenitors aggregate in the bone marrow. T-cells and B-cells, two subtypes of lymphoid cells, are involved in ALL. B-cells are often linked to ALL and work to keep the body free of pathogens and illnesses by eliminating diseased cells.

- ***Multiple myeloma-*** Multiple myeloma is a blood cancer that originates from the bone marrow's plasma cells, which produce antibody proteins to aid the body's immune system in fighting infections. As the cancer spreads, an overabundance of aberrant plasma cells forms, causing tumours to develop throughout the bone marrow, affecting the formation of healthy red blood cells and weakening the body's defences against infection. This type of cancer is usually uncontrollable and develops into multiple tumours, often not being detected until it has spread.

- ***Hodgkin lymphoma-*** Non-Hodgkin lymphoma is a cancer that develops in the lymph system, which transports immune cells and filters wastes and poisons. It affects areas other than lymph nodes, such as the stomach, Waldeyer ring, central nervous system, lung, bone, and skin. The disease can also affect the spleen. B cells and T cells are affected by lymphoma, which helps produce antibodies against pathogens. CAR T-cell therapy targets specific cancer cell types, allowing treatment for follicular lymphoma, high-grade B-cell lymphoma, and mediastinal large B-cell lymphoma.[90]

10. PROCEDURE DETAILS:

10.1 What happens before CAR T-cell therapy?

Prior to receiving CAR T-cell therapy, patients usually follow these procedures:

1. **Consultation and Evaluation:** Patients consult with a haematologist or oncologist to talk about possible courses of treatment, such as CAR T-cell therapy. To decide if CAR T-cell therapy is appropriate, the medical team considers the patient's past medical history, present health, and response to prior therapies.

2. **Pre-Treatment Testing:** A battery of tests is administered to patients in order to evaluate their general health and eligibility for CAR T-cell treatment. This might involve heart evaluations, imaging studies, and blood testing.

3. **T Cell Collection:** Leukapheresis is the procedure used to obtain the patient's immune cells (T cells), should they be found to be candidates for CAR T-cell treatment. Leukapheresis involves drawing blood from the patient, then using machine to separate the white blood cells—including T cells—out of the blood. After that, a lab receives these T cells to be genetically altered.

4. **Genetic Modification:** In a lab setting, the patient's T cells undergo genetic modification to produce chimeric antigen receptors (CARs) on their surface. The T cells are now able to identify and attack cancer cells because to this alteration.

5. **Preparatory Treatment:** Patients frequently go through a conditioning programme prior to getting the modified T cells. Chemotherapy or other therapies to get the body ready for the CAR T cell injection may be part of this. The conditioning regimen assists in reducing the number of immune cells already in place and improves the conditions for the proliferation and assault of cancer cells by the modified T cells.

6. **CAR T-cell Infusion:** Following their preparation, the altered T cells are reinfused into the patient's circulation. Usually, this infusion happens in a hospital environment so that the patient may be thoroughly watched for any negative responses.

7. **Monitoring and Follow-Up:** CAR T-cell therapy patients undergo regular monitoring and assessments to ensure effectiveness and avoid adverse effects. A multidisciplinary team, including nurses, supportive care providers, haematologists, and oncologists, supports their safety and wellbeing throughout the treatment.

10.2 What happens during CAR T-cell therapy?

Several crucial processes take place throughout the CAR T-cell treatment procedure:

1. **Preparation and Conditioning:** Patients frequently go through a conditioning programme prior to receiving a CAR T cell injection. Chemotherapy or other therapies to get the body ready for the injection of T cells that have been changed may be part of this. The conditioning regimen aids in fostering an environment that is more conducive to the proliferation and assault of cancer cells by the modified T cells.

2. **CAR T-cell Infusion:** The keystone of the process is the CAR T-cell infusion. The patient receives the altered T cells intravenously. These cells are designed to express chimeric antigen receptors (CARs) on their surface. Typically, the infusion happens in a hospital environment so that the patient may be continuously watched for any negative responses.

3. **Monitoring:** Patients are constantly watched for any adverse responses or acute side effects following the infusion. Vital signs are monitored often, and the patient's health is continuously watched for indications of neurotoxicity or cytokine release syndrome (CRS), two possible side effects of CAR T-cell treatment.

4. **Hospitalization:** Depending on their unique response and any potential consequences, patients usually stay in the hospital for a while after receiving a CAR T-cell infusion. This duration might range from a few days to a few weeks. They get expert attention and supervision throughout this period to handle any negative effects and guarantee their safety.

5. **Supportive treatment:** Patients get supportive treatment to manage side effects and maximise their comfort and well-being during the surgery and hospital stay. This might involve supportive therapy to address certain issues like CRS or neurotoxicity, as well as drugs to reduce symptoms like fever, nausea, and discomfort.

6. **Follow-Up:** Patients undergo CAR T-cell therapy, a complex procedure requiring careful monitoring and supportive care to optimize outcomes. The treatment is tailored to each patient's individual needs, aiming to achieve a durable, effective anti-cancer response while minimizing risks and complications.

10.3 What happen after CAR T-cell therapy?

Following CAR T-cell treatment, patients move into an important phase of care that involves follow-up surveillance. This is what usually occurs:

1. **Acute Monitoring:** After receiving a CAR T-cell infusion, patients are promptly watched for any negative responses or acute side effects. Based on the patient's condition and reaction to therapy, this monitoring typically takes place in a hospital environment for a few days to a few weeks.

2. **Management of adverse Effects:** Cytokine release syndrome (CRS) and neurotoxicity are two adverse effects that patients may encounter as a result of CAR T-cell treatment. Medical professionals give the proper care, which may include drugs to reduce fever, inflammation, and other symptoms. In order to minimise side effects and maximise comfort and well-being, patients get supportive care.

3. **Hospital Discharge:** Patients may be allowed to leave the hospital if their side effects have been managed and they are considered stable. Close observation is still necessary, though, and patients usually need to make follow-up consultations with their doctors on a regular basis.

4. **Long-Term Follow-Up:** Patients receive long-term follow-up to track how well CAR T-cell treatment is working and to look for any problems or late-onset adverse effects. In order to monitor the course of the disease and general health, this follow-up may involve routine blood tests, imaging scans, and clinical assessments.

5. **Supportive Care:** To address any residual side effects and enhance their quality of life, patients get continuous supportive care. In addition to supportive therapies including physical therapy, dietary support, and mental support, this may involve prescription drugs to treat persistent symptoms.

6. **Survivorship Care Planning:** Medical professionals create a survivorship care plan specific to each patient as they go from current treatment to survivorship. The purpose of this plan is to address any potential side effects of therapy and to promote long-term wellbeing by including suggestions for supportive care, health maintenance, and continuing monitoring.

7. **Education and Resources:** Post-CAR T-cell treatment, patients receive resources for side effects management, maintaining a healthy lifestyle, seeking help, and managing psychological and emotional aspects. Continuous monitoring, supportive care, and survivorship planning are essential for optimal outcomes, requiring close coordination between patients, carers, and healthcare professionals.[91]

11. CLINICAL APPLICATIONS OF CAR T-CELLS

Chimeric antigen receptor T-cell therapy (CAR T-cell therapy) is an immunotherapy method that uses the patient's immune system to target and eliminate cancer cells. It requires genetic modification to express chimeric antigen receptors on cancer cells' surface. CAR T-cell therapy has shown remarkable results in treating certain cancers, particularly those with haematological malignancies. The following are some important clinical uses:

11.1 Acute lymphoblastic leukaemia (ALL): CAR-T cells are used in treating haematological malignancies like Acute lymphoblastic leukaemia (ALL), which is characterized by rapid proliferation of naïve cells in the bone marrow. They have shown efficacy in treating ALL, especially when engineered T cells target CD19, a highly expressed biomarker of the B-cell lineage. However, T-cell malignancy of ALL showed limited efficacy when engineered CAR T-cells targeted CD19. Anti-CD4 CAR-T cells show promising results against T-cell lymphoma models. Clinical trials have shown promising results with multitargeted CAR-T cell therapy.[92-95]

11.2 Chronic Lymphocytic Leukaemia (CLL): Chronic lymphocytic leukaemia (CLL) is a condition characterized by excessive mature lymphocytes in the blood, bone marrow, and lymphoid tissue. The use of CD19 as a target for CLL treatment has shown promising results in patients with complete remission and minimal residual disease. Pharmacokinetics play a crucial role in enhancing the outcomes and safety of CAR-T cell treatments. A recent study showed that higher doses effectively induce complete remission without excessive toxicities. However, antigen-negative relapse poses a threat to CAR T-cell therapy's success. Current data suggests that ibrutinib administration and partial reversing of exhausted

CAR T-cells in CLL patients are promising. Genetic modification and bispecific CAR targeting antigens on tumour cell surfaces could also improve treatment efficacy.[96-102]

11.3 Non-Hodgkin Lymphoma (NHL): Non-Hodgkin's lymphoma (NHL) is a group of neoplasms with varying degrees of malignancy. These malignancies are less predictable and have a higher risk of spreading to extranodal sites. Anti-CD19 CAR-T cells have shown success in treating chemo-resistant lymphomas, while CD22 has shown promising results in patients with diffuse large B-cell lymphoma. In 2017, the FDA approved YESCARTA, a CD19 directed second-generation CAR-T cell product for NHL treatment.[103-108]

11.4 Multiple Myeloma: Multiple myeloma (MM) is a B-cell malignancy involving long-lived plasma cells that produce specific immunoglobulins. Disease management has been compromised due to the lack of an ideal target. Syndecan 1 (CD138) was used as a target for MM treatment, but it caused "on-target-off-tumour" toxicity. BCMA, a highly expressed B-cell maturation antigen, is considered a better target in CAR-T cell therapy. A phase 1 clinical trial showed preliminary results, with one patient achieving complete remission for over three months. BCMA CAR T-cells have shown minor cytotoxicity and an objective response rate (ORR) of 20%. Bispecific CAR T-cell (LCAR-B38M) targets VHH1 and VHH2 epitopes of BCMA, with an ORR of 88% and a 68% CR. In 2021, the FDA approved ABECMA (idecabtagene vicleucel) for MM, a second-generation CAR-T cell product directed against the BCMA tumour antigen.[109,110]

11.5 Solid Tumours: CAR-T cell therapies targeting specific antigens have shown poor results in solid tumours, despite the unmet clinical need for these therapies. The biological complexity of this field and the lack of evidence supporting any single CAR-T cell product against specific solid tumours have contributed to these unsatisfactory results. Common factors contributing to these unsatisfactory results include difficulty accessing target cells in poorly vascularized tumour masses, exposure to a hostile tumour microenvironment, and a scarcity of appropriate single-antigen targets. Improvements in CAR-T cell design have the potential to infiltrate and counteract immunosuppressive milieu, and experiments are underway to promote tumour-associated antigen expression via radiation or epigenetic treatment [111]. The most practical and successful use for CAR-T cells in solid tumours is to deepen or sustain chemotherapy, radiation, or surgically induced remission in diseases with a high risk of recurrence. Replicating techniques used in blood cancers is unlikely to yield clinical benefits, and finding the right single-antigen target for third-generation CAR-T cells will require more complicated, new techniques. Addressing these concerns could provide fascinating outcomes for solid malignancies, representing a significant unmet need and a potentially profitable market for investors.

11.6 HIV- Infection: CAR T-cell therapy, while effective in treating some cancers, is still experimental and faces challenges in treating HIV infection. However, studies are exploring its potential as an HIV/AIDS therapeutic strategy.

- **Targeting HIV Reservoirs:** CAR T lymphocytes are used to target and eradicate HIV-positive cells, particularly those serving as viral reservoirs, which allow the virus to survive despite antiretroviral treatment. These reservoirs, mostly composed of infected CD4+ T cells, can be reduced by CAR T cells.
- **HIV Entry Inhibition:** CAR T cells can be engineered to prevent HIV entry into host cells by expressing CD4-mimetic receptors or other molecules, disrupting the virus-host cell connection and blocking viral entry, thus preventing HIV infection and replication.
- **Boosting Immune Reactions:** Modifying CAR T cells can enhance body defence against HIV-positive cells by targeting viral antigens or co-stimulatory molecules. Engineered CAR T cells can lower HIV reservoir and manage viral replication by enhancing the immune response.

CAR T-cell therapy is a promising and rapidly developing cancer treatment method, providing hope to patients with limited treatment options. Current studies aim to expand cancer types and improve safety and effectiveness of this treatment.[112,113]

12. CAR T-CELLS: FUTURE PERSPECTIVES

CD19-expressing blood cancers are most suitable for CAR-T cell therapy due to their high tumour expression, easy access, and tolerability of B cell aplasia. However, only 5% of new cancer diagnoses are CD19-targetable by licensed products. Innovative strategies to improve tumour killing efficacy, CAR-T cell persistence, and activity control are being pursued to bring CAR-T cell therapies to other diseases.

The future of CAR T-cell therapy is promising, with ongoing research and development aimed at overcoming current challenges and enhancing its therapeutic potential. Some potential prospects for CAR T-cell treatment include:

12.1 Advancements in Target Identification: Researchers are discovering new tumour-specific antigens for CAR T-cell therapy, expanding the target repertoire to treat a wider range of malignancies and reducing antigen escape.

12.2 Next-Generation CAR Designs: Future CAR designs may enhance T-cell persistence, invasion, and specificity by developing dual-targeted and switchable CARs that target multiple antigens simultaneously[114].

12.3 Allogeneic CAR T-cells: Off-the-shelf universal CAR T-cells from healthy donors may address manufacturing issues in patient-specific treatment, while strategies to reduce graft versus-host disease risk and improve allogeneic CAR T-cell durability are being developed.

12.4 Gene Editing Technologies: Advances in gene editing technologies likeCRISPR-Cas9 show promise for enhancing the functionality and safety of CART cells by disrupting fatigue-related genes or boosting T-cell activity[115].

12.5 Combination Treatments: CAR T-cell therapy is being combined with other therapeutic options like checkpoint inhibitors, targeted treatments, and chemotherapy to prevent resistance, enhance antitumor immunity, and enhance

treatment outcomes.

12.6 Expanded Applications Beyond Oncology: CAR T-cell therapy, primarily used in cancer treatment, is gaining interest for potential applications in autoimmune, infectious, and transplantation diseases, despite challenges and promising therapeutic innovation.

12.7 Personalized Medicine Approaches: Advances in biomarker identification and patient classification may enable more personalized CAR T-cell treatment, focusing on specific patient features like tumour genetics, immunology, and microenvironmental variables.

12.8 Improved Manufacturing and Accessibility: The CAR T-cell treatment manufacturing process is being improved through automation, closed-system production platforms, and alternative cell sources to reduce costs, enhances calability, and enhance patient access.

CAR T-cell therapy's future is marked by continuous innovation, with potential to transform cancer treatment and expand its use to other diseases.

Collaboration between academics, industry, and regulatory authorities is needed [115-118].

DISCUSSION AND CONCLUSION

CAR T-cell therapy (Chimeric Antigen Receptor T-cell therapy) is a form of immunotherapy that involves modifying a patient's T cells to attack cancer cells. Here are some advantages includes that the therapy has shown remarkable efficacy, particularly in hematologic malignancies like certain types of leukaemia and lymphoma. It provides long-lasting remissions, potentially resulting to cure different types of cancer. The disadvantages include that CRS is a potentially life-threatening adverse effect of CAR T-cell treatment produced by cytokine production in response to T cell activation. It can cause fever, hypotension, and organ malfunction, some people may develop neurotoxicity, which can cause disorientation, seizures, or other neurological symptoms. This adverse effect is frequently connected with CRS.CD19-expressing blood malignancies are most suited for CAR-T cell treatment due to their high tumour expression, ease of access, and tolerance of B cell aplasia. Only 5% of new cancer diagnoses may be treated with approved drugs that target CD19. Innovative ways for improving tumour killing effectiveness, CAR-T cell persistence, and activity control are being developed in order to introduce CAR-T cell therapy to various disorders. The future of CAR T-cell therapy is bright, with continuing research and development targeted at overcoming present obstacles and increasing therapeutic potential.

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