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Review Article

Car-T Cell Therapy: A Paradigm Shift in Cancer Treatment

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Abstract

Chimeric antigen receptor T-cell (CAR-T) therapy, a major application of precision and customized medicine, has emerged as a revolutionary advancement in cancer immunotherapy. CAR-T therapy genetically alters a patient's T cells to express synthetic receptors that accurately identify tumor-associated antigens in an MHC-independent manner, resulting in potent and targeted anticancer activity. This study provides an overview of the fundamental ideas of CAR-T cell therapy, including T-cell biology, CAR structure and generations, and the production process, which includes leukapheresis, genetic engineering, ex vivo expansion, conditioning chemotherapy, and patient injection. The mechanisms underlying CAR-T-mediated tumor destruction include antigen recognition, T-cell activation, cytotoxic effector pathways, cytokine production, and tumor lysis. We examine the most recent FDA-approved CAR-T treatments and their clinical applications. We also discuss novel applications in solid tumors and associated issues, such as immune-suppressive tumor microenvironment and antigen heterogeneity. The primary adverse effects, such as immune effector cell-associated neurotoxicity syndrome and cytokine release syndrome, are also discussed in the review along with current treatments. Finally, the drawbacks of CAR-T therapy, recent advances in technology, and the evolving CAR-T environment in India including domestic innovations are examined.

Keywords: Tumor; Cancer immunotherapy; Precision medicine; Cytokine release syndrom

1. INTRODUCTION:

1.1 Overview of cancer immunotherapy

Cancer is the second leading cause of death in the developed world. Most cancer patients are treated with chemotherapy, radiation, and/or surgery. It is often ineffective to prevent the disease from spreading through disseminated tumor cells, even though a combination of these fundamental medications can often effectively treat the underlying tumor. Therefore, eliminating disseminated tumor cells in the bloodstream and micro-metastases in distant organs is another promising approach in cancer immunotherapy. Immune checkpoints on T cells or tumor cells normally prevent autoimmunity, but in tumors, they inhibit T cell activity, reducing immune recognition and destruction of cancer cells. [38] In contrast to conventional treatments such as chemotherapy and radiotherapy, immunotherapy dynamically engages the immune system to attack cancer cells via multiple targets.[1]

1.2 Why T-cell therapy changed oncology

Although therapies like monoclonal antibodies and small-molecule inhibitors have improved treatment options, responses vary widely, and relapse with poor prognosis remains a major challenge. CAR T-cell therapy is revolutionizing cancer treatment by harnessing the power of a patient's own immune system. Adoptive therapy with gene-modified T cells represents a rapidly advancing cancer treatment, as CAR T cells can expand and persist after infusion to provide durable immunity, with proven efficacy in hematological cancers such as ALL, CLL, DLBCL, FL, and multiple myeloma.[2]

1.3 Discovery of CAR-T

Eshhar first described first-generation CARs in 1993, comprising an antibody-derived scFv linked to the CD3ζ signaling domain to activate T cells. To overcome limited efficacy, second-generation CARs incorporated an additional co-stimulatory domain, while third-generation CARs combined multiple co-stimulatory signals to enhance potency. Fourth-generation CAR-T cells, known as TRUCKs, further improved function by enabling inducible cytokine release upon antigen engagement. Fifth-generation or next-generation CAR-T cells include diverse strategies designed to enhance therapeutic safety and efficacy.[3] In 2017, the FDA approved Kymriah® (tisagenlecleucel), a CD19-directed CAR-T therapy, as the first cell-based gene therapy for treating relapsed/refractory ALL in pediatric and young adult patients, based on a unanimous advisory committee recommendation.[4]

1.4 Relevance to precision/targeted therapy

CAR-T cell therapy is a precision immunotherapy that targets tumor-specific antigens such as CD19 or BCMA

while sparing normal tissues. The effectiveness of this therapy is driven by its fundamental mechanism, which depends on the precise interaction between engineered T cells and specific surface antigens on diseased cells.[5]Advances in biomarker selection, genomic profiling, and gene editing continue to improve its safety, efficacy, and applicability to solid tumors.

1.5 Basic Immunology Background

T lymphocytes are central to adaptive immunity, with cytotoxic T cells directly eliminating infected or malignant cells and helper T cells coordinating immune responses through cytokine secretion in collaboration with antibody-producing B cells. CAR T cells are T lymphocytes that have been genetically altered to produce artificial receptors, enabling their application in cancer immunotherapy.[6]T-cell activation is initiated by recognition of antigenic peptides presented by major histocompatibility complex (MHC) molecules encoded by highly polymorphic HLA genes, followed by co-stimulatory signaling through CD28–B7 interactions and cytokine-driven signals that promote proliferation, differentiation, and memory formation. CD19-targeted CAR T cells represent the leading model of engineered T cell therapies in cancer, highlighting the synergy between synthetic biology and T cell biology.[13]

2. CAR-T Cell Therapy

2.1 CAR Structure

Table 1: Structural Components of Chimeric Antigen Receptors (CARs)

CAR Component	Common Sources	Primary Function	Impact on CAR-T Activity
Extracellular antigen-recognition domain (scFv)	Monoclonal antibodies (e.g., anti-CD19)	Antigen binding and specificity	Determines antigen affinity and activation threshold
Hinge / Spacer region	IgG, CD8α, CD28	Provides flexibility and optimal antigen access	Influences synapse formation and targeting efficiency
Transmembrane domain [37]	CD3ζ, CD28, CD8α	Anchors CAR to T-cell membrane	Affects receptor stability and signaling strength
Intracellular signaling domain	CD3ζ ± CD28, 4-1BB	Initiates and sustains T-cell activation	Controls proliferation, persistence, cytokine production, and defines CAR generation

2.2 CAR Generations

Table 2: Evolution of Chimeric Antigen Receptor (CAR) Generations

CAR Generation	Key Intracellular Signaling Domains	Design Characteristics	Functional Outcome/ Limitations
First Generation	CD3ζ chain or Fc receptor γ-chain	scFv linked to CD3ζ or FcRγ without co-stimulatory domains	Provided activation signal only; insufficient T-cell proliferation, limited cytokine production, and poor persistence
Second Generation	CD3ζ + one co-stimulatory domain (CD28 or 4-1BB/CD137) [8]	Incorporation of a single co-stimulatory signaling domain in series with CD3ζ	Enhanced T-cell persistence, increased cytokine secretion, improved anti-tumor efficacy; demonstrated strong clinical responses in B-ALL and NHL
Third Generation	CD3ζ + two co-stimulatory domains (e.g., CD28–4-1BB or CD28–OX40)	Combination of multiple co-stimulatory domains to augment signaling strength	Greater cytokine production, enhanced T-cell proliferation, and improved anti-tumor potency compared to second-generation CARs
Fourth Generation (TRUCKs)	CD3ζ + co-stimulatory domain(s) + inducible cytokine genes (e.g., IL-2)	Engineered to secrete immunostimulatory cytokines upon CAR activation	Improved resistance to immunosuppressive tumor microenvironment; enhanced CAR-T expansion, survival, and function[7]
Fifth Generation	CD3ζ + co-stimulatory domain + cytokine receptor signaling motifs (e.g., truncated IL-2Rβ with STAT3/5 binding sites)	Integration of cytokine receptor signaling into CAR construct	Promotes sustained activation, memory T-cell formation, and enhanced immune system engagement

2.3 Key Steps in CAR-T Cell Therapy

The process begins with leukapheresis, during which whole blood is processed to isolate peripheral blood mononuclear cells by density gradient centrifugation, remove red blood cells, and subsequently enrich T cells.[9,23]The collected cells are cryopreserved and processed in a GMP facility for isolation, activation, and genetic modification. Prior to infusion, patients receive lymphodepleting chemotherapy, to eliminate competing immune cells and enhance supportive cytokines such as IL-7 and IL-15. [10,11] Common lymphodepletion regimens involve drugs such as cyclophosphamide, fludarabine, bendamustine, and azacytidine.[40] After intravenous infusion, CAR-T cells act as living drugs, becoming activated upon antigen recognition, expanding rapidly, releasing cytokines, and mediating tumor destruction, with a subset persisting as memory T cells to provide long-term disease control.

Table 3: Steps in CAR-T Cell Therapy

Step	Description	Clinical Significance
Leukapheresis	Collection of autologous PBMCs and T cells	Determines CAR-T product quality[9]
Genetic modification	Introduction of CAR construct into T cells	Enables antigen-specific tumor recognition
Ex vivo expansion	Amplification of engineered T cells	Ensures adequate therapeutic dose
Conditioning chemotherapy	Lymphodepletion with fludarabine and cyclophosphamide	Enhances CAR-T expansion and persistence
CAR-T infusion	Intravenous administration of engineered cells	Initiates antitumor immune response
In vivo activity	Expansion, cytotoxicity, memory formation	Drives durable clinical responses

2.4 Mechanism of Action of CAR-T Cell Therapy

2.4.1 Antigen Recognition and cell activation

CAR-T cells recognize tumor-associated antigens such as CD19 or BCMA directly on cancer cells through antibody-derived single-chain variable fragments, enabling antigen detection independent of MHC molecules and allowing evasion of tumor immune escape mechanisms. Conventional CAR T-cell designs target a single antigen, despite solid tumors exhibiting diverse antigenic signatures. Incorporating combinatorial antigen recognition may offer improved specificity and therapeutic precision.[12] Antigen binding induces CAR clustering and formation of a stable immune synapse, which triggers potent T-cell activation, targeted cytotoxicity, and clonal expansion for sustained antitumor activity. Excessive stimulation may result in toxicities such as cytokine release syndrome. [6] Upon engagement, CAR-T cells release perforin, granzymes, and proinflammatory cytokines including TNF-α and IFN-γ, leading to tumor cell pyroptosis. Granzyme A and B activate gasdermin family proteins, forming membrane pores that cause cell swelling, rupture, and inflammatory tumor cell death. [14]

2.4.2 Cytotoxicity Pathways

Activated CAR-T cells eliminate tumor cells through multiple cytotoxic mechanisms:

Perforin–Granzyme Pathway:

CAR-T cells release perforin to form transmembrane pores in target cells, facilitating granzyme entry and apoptosis induction. Those granzymes then trigger caspase-driven apoptosis pathways, sparking programmed death in the cancer cell.[14]

Fas–Fas Ligand (Fas–FasL) Pathway:

CAR-T cells also pump out Fas ligand (FasL), which hooks onto Fas receptors on tumor cells and flips the switch for apoptosis via the extrinsic death receptor pathway.[14]

Cytokine Production

Cytokines are critical for the activation, expansion, and functional quality of T cells during CAR-T cell manufacturing. T cells are cultured in specialized media supplemented with cytokines such as IL-2, IL-7, IL-15, and IL-21, which shape the phenotype, composition, and overall quality of the infused cells. Currently, the most common CAR-T production strategies rely on IL-2 or IL-7, either alone or in combination with IL-15.[15] If too many cytokines flood the system, it can trigger serious side effects like cytokine release syndrome (CRS) which is why doctors keep a close eye on patients during treatment.[14]

Tumor Lysis

Rapid necrosis of a large number of tumor cells leads to the release of substantial intracellular contents and metabolites into the bloodstream. When the kidneys cannot adequately clear these substances, severe metabolic disturbances and clinical manifestations occur, a condition known as tumor lysis syndrome (TLS).[17] Patients with TLS exhibited hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and increased lactate dehydrogenase (LDH) levels. [16]

2.5 FDA-Approved CAR-T Therapies

Kymriah® (tisagenlecleucel), a CD19-directed CAR-T therapy, received FDA approval in 2017 as the first cell-based gene therapy for relapsed/refractory pediatric and young adult ALL.[4] Axicabtagene ciloleucel is a CD19-directed CAR-T therapy with a CD28 co-stimulatory domain, approved by the FDA in 2017 for adults with relapsed or refractory large B-cell lymphomas. Brexucabtagene autoleucel subsequently became the

third FDA-approved CAR-T therapy for certain leukemias and lymphomas. [41, 46] Despite approval, CAR-T therapies continue to be actively studied to expand indications and improve safety and efficacy. [18]

Table 4: FDA-Approved CAR-T Therapies

CAR-T Therapy	Target Antigen	Indication	ORR (%)	CR (%)
Tisagenlecleucel	CD19	B-ALL, DLBCL	80–85	60–70
Axicabtagene ciloleucel	CD19 [36]	LBCL	80–85	50–60
Brexucabtagene autoleucel	CD19	MCL, B-ALL	85–90	60–65
Lisocabtagene maraleucel	CD19	LBCL	70–75	50–55
Idecabtagene vicleucel	BCMA	Multiple myeloma	70–75	30–35
Ciltacabtagene autoleucel	BCMA	Multiple myeloma	95–98	65–80

2.6 Applications of CAR-T Cell Therapy in Solid Tumors

Although CAR T-cell therapy has transformed the treatment of hematological malignancies, it faces distinct challenges in solid tumors, limiting its efficacy. Recent clinical trials have shown promising outcomes in brain, gastric, liver, sarcoma, neuroblastoma, pleural, and CLDN6-positive tumors.[19]

2.7 Difficulties in Treating Solid Tumors with CAR-T Cells

Unlike blood cancers, CAR T-cell therapy encounters unique and complex obstacles in solid tumors including tumor microenvironment–mediated immunosuppression, limited trafficking and tumor infiltration, antigen heterogeneity and escape, on-target off-tumor toxicity, and CAR-T cell exhaustion with limited persistence etc.

The tumor microenvironment (TME) is highly immunosuppressive, driven by cytokines and chemokines that recruit Tregs, MDSCs, and TAMs. Tregs inhibit cytotoxic T-cell function through suppressive cytokines, IL-2 depletion, CTLA-4–mediated APC inhibition, and blockade of T-cell activation. [47] This hostile environment limits CAR-T cell trafficking and metabolism, promoting T-cell exhaustion and reducing therapeutic efficacy.[20] Heterogeneous antigen expression in solid tumors enables antigen-negative escape and relapse through antigen loss or downregulation. Multi-antigen targeting may improve efficacy and reduce escape. [21] [50] Solid tumors present major physical barriers to CAR T-cell infiltration, including a dense, fibrotic tumor microenvironment driven by TGF-β–activated cancer-associated fibroblasts that promote extracellular matrix deposition and suppress T-cell motility and chemokine receptor expression. Abnormal tumor vasculature further limits T-cell extravasation by inducing hypoxia, recruiting immunosuppressive cells, upregulating inhibitory checkpoints, and downregulating adhesion molecules such as VCAM-1 and ICAM-1, collectively leading to T-cell exclusion and reduced CAR T-cell efficacy.[20]

2.8. Manufacturing and Delivery Challenges

Despite initial success, many patients relapse after CAR T cell therapy due to primary or secondary resistance driven by CAR T cell dysfunction, tumor intrinsic factors, and an immunosuppressive tumor microenvironment. Antigen heterogeneity, poor trafficking, and T cell exhaustion further limit durable responses.[30] Compared with traditional mixed-expression CAR T cell infusions, bispecific CAR T cells reduce treatment costs and enhance manufacturing efficiency.

Making CAR-T cells from a patient's own blood takes time and costs a fortune. CAR T-cell production comprises multiple controlled steps with quality testing at every stage. A major limitation to access is the prolonged manufacturing and release timeline, which often spans 2–4 weeks. Access is further constrained by limited manufacturing capacity at pharmaceutical facilities, and the centralized production process requires shipment and cryopreservation, extending the clinically relevant "vein-to-vein" time from leukapheresis to CAR T-cell infusion.[24]

3. TREATMENT-RELATED TOXICITIES OF CAR-T CELL THERAPY

3.1Cytokine Release Syndrome (CRS)

Cytokine release syndrome (CRS), often termed a cytokine storm, is a systemic inflammatory reaction induced by infections or drug therapies. CRS symptoms include fever, fatigue, muscle/joint pain, nausea, rapid breathing, low blood pressure, rashes, headache, seizures, hallucinations, and coordination loss.[39] With the expansion of CAR T-cell therapy, CRS has become the most frequently observed toxicity, with particularly high incidence reported in CD19- and BCMA-directed CAR T-cell trials.[17] Tocilizumab, an FDA-approved IL-6 receptor–blocking monoclonal antibody, is the mainstay treatment for moderate to severe CRS, as it rapidly controls inflammation without compromising CAR-T cell expansion or antitumor efficacy, significantly improving the safety of CAR-T therapy. [25],[48]

3.2 Immune Effector Cell Neurotoxicity Syndrome (ICANS)

Immune effector cell–associated neurotoxicity syndrome (ICANS) is a potentially life-threatening neurological complication frequently observed in CAR-T cell therapy. Clinically, ICANS may manifest as confusion, headache, attention and language difficulties, focal neurological deficits, encephalopathy, seizures, transient coma, or, in

severe cases, cerebral edema.[26] Engagement of CAR-T cells with tumor cells triggers the release of large amounts of pro-inflammatory cytokines from both CAR-T cells and host immune cells, leading to endothelial activation, increased vascular permeability, and blood–brain barrier dysfunction. [27, 42]

3.3 On target off tumor toxicity

As CAR-T clinical trials have rapidly expanded, a range of treatment-related toxicities has emerged, significantly limiting broader clinical application. On-target off-tumor toxicity arises when CAR-T cells recognize antigens such as CD19 or HER2 that are shared by tumor cells and normal tissues, even at low expression levels. Among these, on-target, off-tumor toxicity remains one of the most critical adverse effects associated with CAR-T therapy.[28] Even though the targeting is super specific to that antigen, the problem is it's not exclusive to tumors leading to unwanted damage in normal cells.

4. RISKS ASSOCIATED WITH CAR-T CELL THERAPY

Patients receiving CAR T cell therapy often have substantial immunosuppression even before infusion, with prior infections, underlying malignancy such as B cell acute lymphoblastic leukemia, and extensive previous treatments increasing the risk of infection. In the early post infusion period, severe neutropenia along with cytokine release syndrome and immune effector cell associated neurotoxicity syndrome, as well as their immunosuppressive management, are major contributors to bacterial infections. In the later phase, depletion of normal B lineage and plasma cells leads to hypogammaglobulinemia and impaired cellular immunity, particularly with BCMA targeted therapy, resulting in prolonged susceptibility to infections.[29]

5. NOVEL APPROACHES AND FUTURE DIRECTIONS OF CAR-T THERAPY

CAR-T therapy has revolutionized the treatment of hematological malignancies but faces challenges including antigen escape, limited persistence, toxicity, high cost, and poor efficacy in solid tumors. To overcome these limitations, several next-generation strategies are being developed:

5.1 CAR-NK Cells

CAR-NK cells blend the precision targeting of CARs with natural killer (NK) cells' built-in cancer-killing skills. Unlike CAR-Ts, they skip MHC restrictions, dial down risks of cytokine release syndrome (CRS) and neurotoxicity for a safer profile, and can be mass-produced as universal "off-the-shelf" products ready to go fast and potentially cheaper. Early trials are showing solid promise against blood cancers. [31]

5.2 Allogeneic “Off-the-Shelf” CAR-T Cells

Custom autologous CAR-T therapy made from each patient's own cells is pricey and takes weeks. Allogeneic CAR-T cells, sourced from healthy donors, can be batch-made ahead, frozen, and shipped out fast, skipping those delays.[32]

5.3 Dual-Target CAR-T Cells

Dual-target CAR-T cells are designed to hit two antigens at once like CD19 and CD22, or BCMA and TACI to cut down on relapse from cancer cells ditching a single target. This double-barreled approach wipes out tumors more thoroughly, boosts lasting responses, and is showing real promise in tough, relapsed B-cell cancers. [33, 45]

5.4 CRISPR-Edited CAR-T Cells

CRISPR/Cas9 gene editing lets scientists make pinpoint changes to CAR-T cells, boosting their power and safety. It can knock out PD-1 to stop T-cell burnout, add co-stimulatory genes for better staying power, or build in kill switches for on-demand shutdown. This tech speeds up custom tweaks for personalized treatment and helps beat resistance hurdles.[22]

5.5 Safety Switches and Suicide Genes

To tackle dangerous or surprise toxicities, CAR-T cells now come with built-in safety switches like inducible caspase-9 or truncated EGFR. Suicide genes encode enzymes that convert non toxic prodrugs into cytotoxic agents. Delivery of virus encoded suicide genes into solid tumors kills infected cells and neighboring tumor cells through diffusion of toxic metabolites. Similarly, engineering tumor homing cells, including mesenchymal stem cells, neural stem cells, and immune cells such as T cells, NK cells, and CAR T cells, to express suicide genes enables targeted tumor cell destruction.[34]

6. REGULATORY AND ETHICAL CONSIDERATIONS:

Developing and rolling out CAR-T cell therapies demands rock-solid regulatory compliance and ethical guidelines to safeguard patients, guarantee top-notch product quality, and ensure fair access for all.

6.1 Clinical Trial Design

CAR-T therapy trials need smart design to weigh safety, effectiveness, and long-term results, especially with risks like cytokine release syndrome (CRS), ICANS, and off-tumor effects. They typically use phase I/II setups with gradual dose ramps, staggered groups, and round-the-clock monitoring. Key measures include overall response rate (ORR), complete remission (CR), how long responses last, toxicity patterns, and survival stats. Patient picks are strict usually relapsed/refractory blood cancers with trackable tumors to keep risks low.

6.2 Good Manufacturing Practice (GMP) Compliance

CAR-T cell production involves genetic tweaking, viral vectors, and growing cells in bulk, all under strict Good Manufacturing Practice (GMP) rules to guarantee consistency, sterility, and safety. Facilities must nail quality checks, validate every step, and track everything from blood draw to infusion. GMP is non-negotiable for approvals from watchdogs like the FDA, EMA, and India's CDSCO. [35] In Europe, CAR-T therapies are classified as ATMPs/GTMPs, with trial requirements varying by country. In the U.S., they are regulated under the Public Health Service Act, requiring standard clinical trials. FDA

and EMA provide general guidance, but none are CAR-T specific. [44]

6.3 Ethical Concerns

CAR-T cell therapy raises important ethical concerns related to gene editing, patient access, and vulnerable populations. While technologies such as CRISPR enable precise genetic modification of T cells, the risk of unintended off-target effects and unknown long-term consequences requires careful oversight. Ethical challenges also arise from patient selection, as the high cost and limited availability of CAR-T therapy raise issues of equitable access and prioritization, underscoring the need for transparent criteria and robust informed consent. Additionally, the expanding use of CAR-T therapy in pediatric leukemia demands heightened ethical safeguards, including thorough risk–benefit assessment and parental consent.

6.4 Regulatory Pathways

CAR T cell therapies are regulated as advanced therapy medicinal products or cell based biologics depending on the region. In the United States, the FDA approves CAR T products through the Biologics License Application pathway and issues guidance covering clinical trials, manufacturing, and post marketing surveillance. In Europe, the European Medicines Agency evaluates CAR T therapies under the advanced therapy medicinal product framework using a centralized review process. In India, the Central Drugs Standard Control Organization regulates CAR T cells as new biological entities, requiring clinical trial authorization, compliance with good manufacturing practices, and approval from institutional ethics committees.

7. PHARMACOECONOMICS AND HEALTHCARE IMPACT

CAR-T cell therapy represents a major advance in oncology but is associated with **s**ubstantial financial implications that influence healthcare decision-making.

7.1 Cost Comparison vs. Bone Marrow Transplant (BMT)

Allogeneic bone marrow transplants (BMT) have long been a go-to cure for blood cancers, but CAR-T therapy brings a custom-tailored, precision punch with better shot at responses in tough relapsed or refractory cases. CAR-T usually costs more upfront than BMT because of the intricate manufacturing, patient-specific prep, and expert delivery running ₹3–4 crore globally versus lower BMT prices that vary by center and donor match. [49]

7.2 Major Cost Drivers

The high cost of CAR-T cell therapy is primarily driven by several interrelated factors. These include the use of viral vectors and gene-editing reagents, which are costly and require good manufacturing practice (GMP)–grade production standards. In addition, the complex manufacturing process involves specialized infrastructure and highly trained personnel for leukapheresis, genetic modification of T cells, ex vivo expansion, quality control, and sterility testing. Substantial expenses also arise from hospitalization and intensive supportive care, as patients frequently require close monitoring or intensive care unit admission to manage severe toxicities such as cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), and infections. Furthermore, long-term post-infusion monitoring contributes to overall costs, including ongoing management of complications such as B-cell aplasia, immunodeficiency, and related infectious risks.

7.3 Health Technology Assessment (HTA)

Health Technology Assessment (HTA) weighs CAR-T therapy on cost-effectiveness, patient benefits, and its ripple effects on healthcare systems.It looks at metrics like quality-adjusted life years (QALYs), long-term survival gains, and fewer follow-up treatments needed.

CAR-T packs a clinical punch, but HTA reports flag its steep price tag and heavy infrastructure demands as roadblocks to broad rollout especially in low- and middle-income countries.

7.4 Reimbursement Challenges

Reimbursement for CAR T cell therapy varies worldwide and faces several challenges. Pricing is not standardized due to individualized manufacturing, and uncertainty about long term outcomes affects insurer coverage. Performance based reimbursement models, which pay only for patients achieving sustained responses, are increasingly considered. Access is also limited in low income regions because of financial and infrastructure constraints.

8. INDIAN SCENARIO AND FUTURE OF CAR-T THERAPY

India's push into CAR-T therapy has really picked up steam lately, spotlighting affordable precision cancer care. Top institutions like IIT-Bombay, Immuno ACT, Tata Memorial Hospital, and CSIR-IGIB are leading the charge, building both patient-specific and off-the-shelf CAR-T options, fine-tuning production, and running early human trials.Despite progress, many Indian cancer patients lack access to care. Only four companies—Immuneel, ImmunoACT, Aurigene, and Intas are developing CAR-T programs. [43]

A huge win came in 2023 with NexCAR19 approval India's first homegrown CAR-T therapy. This CD19-targeting treatment, made from a patient's own cells, tackles relapsed or stubborn B-cell cancers like acute lymphoblastic leukemia (ALL) and some non-Hodgkin lymphomas. It cuts reliance on pricey imports that most patients can't touch.

Early data shows NexCAR19 matching global standards in results and side effects, with solid response rates and handleable toxicities all thanks to teamwork between Indian labs, biotechs, and hospitals proving the country's chops in cell therapy.

Cost-cutting is underway via smarter GMP vector making, streamlined processes, and local sourcing, potentially dropping prices to ₹35–60 lakh versus ₹3–4 crore for foreign versions. Still, scaling faces bumps: few GMP facilities, training gaps, heavy monitoring needs,

regulatory mazes, and reaching rural folks through smart partnerships.

CONCLUSION

CAR-T cell therapy is a game-changer in cancer treatment, perfectly capturing the promise of precision and personalized medicine. It reprograms a patient's own immune cells to hunt down and destroy tumor-specific markers, delivering stunning results especially against tough, relapsed blood cancers.

Breakthroughs like smarter CAR designs, added co-stimulatory boosts, streamlined manufacturing, and cutting-edge gene editing have ramped up its power, staying power, and safety. Still, hurdles persist: cancer dodging targets, serious side effects, sky-high costs, tricky production, and spotty access in developing regions. Exciting fixes on the horizon like ready-made "off-the-shelf" allogeneic CAR-Ts, CAR-NK cells, dual- or armored CARs, and emergency kill switches could solve these. With more research, smarter regulations, and global pushes for affordability and infrastructure, CAR-T is poised to become safer, cheaper, and ready for prime time across all cancers.

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Nikita Game (Author 3) validated the scientific content, performed plagiarism checking, and completed the final formatting of the manuscript according to journal guidelines

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