Iranian Journal of Blood & Cancer

Iran J Blood Cancer, 2026, 18(3), 90-101
https://ijbc.ir

Review

CAR T-Cell Therapy: From Conceptual Breakthrough to Clinical Transformation in Modern Oncology

Kamma Harsha Sri*[1], K Mounika[1], S. Sambasiva Raju[1], K. Shainisha [1], D. Pranathi[1], R. Sai Venkat[1], Ekambarapu Sree Charan[2], Sathish Kumar Konidala[3], Srinivasa Babu Puttagunta[4]

[1]*Department of Pharmaceutical Analysis, Vignan Pharmacy College, Vadlamudi, Guntur. AP, India.*
[2]*Department of Pharmaceutical Biotechnology, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, 576140, India.*
[3]*Department of Pharmaceutical Sciences, School of Biotechnology and Pharmaceutical Sciences, Vignan's Foundation for Science, Technology & Research, Vadlamudi, Guntur, 522213, Andhra Pradesh, India.*
[4]*Department of Pharmaceutics, Vignan Pharmacy College, Vadlamudi, Guntur. AP, India.*

Scan and read the article online

Citation Harsha Sri K, Mounika K, Sambasiva Raju S, Shainisha K, Pranathi D, Sai Venkat R, Sree Charan E, Kumar Konidala S, Babu Puttagunta S. CAR T-Cell Therapy: From Conceptual Breakthrough to Clinical Transformation in Modern Oncology. Iran J Blood Cancer. 2026 Sep 30;18(3): 90-101.

doi 0

Article info:

Received: 23 Jul 2026
Accepted: 17 Sep 2026
Published: 30 Sep 2026

Keywords:

Cytokine release syndrome (CRS)
Solid tumors
Blood-related cancers
Cancer immunotherapy
Chimeric antigen receptor (CAR) T-cell
Medical therapy
Allogeneic CAR T-cells

Abstract

Adoptive cellular immunotherapy has evolved into a remarkably potent precision medicine approach that has revolutionized cancer therapy, particularly for hematologic cancers, due to chimeric antigen receptor therapy, or CAR. The historical development, immunological concepts, CAR architecture, and manufacturing procedure that support the therapeutic potency of CAR T-cell are outlined in this paper. subsequently this study provides an overview of the history, immunological ideas, CAR architecture, and manufacturing techniques that enhance the efficacy of CAR T-cell, emphasizes significant toxicities like cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, as well as current management approaches, while highlighting the outstanding therapeutic results attained in lymphomas, B-cell acute lymphoblastic leukemia, and multiple myeloma. The paper also looks at therapeutic resistance mechanisms, obstacles to solid tumor efficacy, and new engineering solutions like logic-gated, multi-target, and armored CAR constructs. Lastly, new advances in combination therapy, earlier-line clinical applications, and "off-the-shelf" allogeneic CAR T-cells are being studied as potential methods to enhance accessibility, safety, durability, and broader therapeutic utility. All things considered, CAR T-cell therapy is a groundbreaking development in contemporary oncology that has the potential to fundamentally alter how cancer is treated in the future.

* Corresponding Author:
Kamma Harsha Sri
Affiliation: Department of Pharmaceutical Analysis, Vignan Pharmacy College, Valdamudi, Guntur. AP, India.
E-mail: **hk186909@gmail.com**

[Downloaded from ijbc.ir on 2026-11-24]

1. INTRODUCTION

1.1 Global Cancer Epidemiology (GLOBOCAN 2022 Statistics)

Oncology remains a predominant factor in global morbidity and mortality. GLOBOCAN 2022 forecasts indicate that globally, there were about 20 million new cases of cancer and 9.7 million cancer-related deaths [1]. Lung cancer (2.2 million), prostate cancer (1.5 million), breast cancer (2.3 million), and colorectal cancer (1.9 million) were the most commonly identified malignancies **(Figure 1)** [2]. The burden is unevenly distributed, with higher incidence rates in more developed regions but disproportionately higher mortality in less developed regions due to restricted availability to resources for early detection and treatment [3].

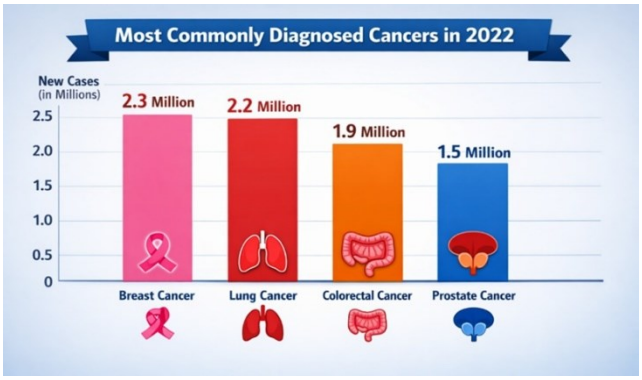

Figure 1. Most commonly diagnosed cancers in the year 2022.

Cancer is one of the major public health issues facing contemporary society. The World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) predict that factors such as aging populations, urbanization, poor lifestyle choices, tobacco use, obesity, environmental pollutants, infectious diseases, and genetic predisposition will increase the world's cancer burden. Breast cancer, lung cancer, colorectal cancer, prostate cancer, leukemia, lymphomas, melanoma, and multiple myeloma are among the most common cancers.

1.1.1 Chemotherapy goals

Chemotherapy is an essential part of cancer treatment, having several therapeutic objectives Controlling the unchecked growth of cancerous cells is one of its main goals. Chemotherapy also aids in stopping metastasis, which stops cancer from spreading to other organs. Another important goal is to minimize relapse by eliminating residual cancer cells that may remain after initial treatment. Over the years, advancements in chemotherapy have significantly improved survivability rates among cancer patients. Furthermore, in cases where a complete cure may not be achievable, palliative chemotherapy is employed to provide symptom relief, enhance quality of life, and reduce cancer-related complications.

1.2. Historical Evolution of Cancer Therapeutics

For decades, the therapeutic arsenal against cancer rested on three primary modalities **(Figure 2)**: surgery, radiation therapy, and systemic chemotherapy [4]. While surgery and radiation provide effective local control, metastatic disease requires systemic intervention [5].

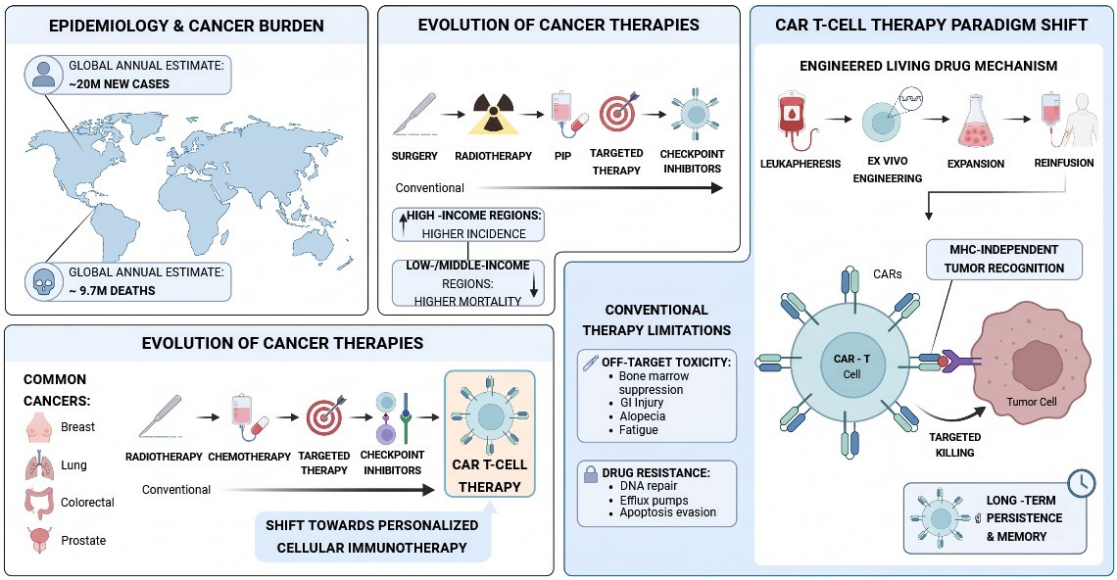

Figure 2. Evolution of cancer therapies.

[Downloaded from ijbc.ir on 2026-11-24]

1.2.1 Chemotherapy: Mechanisms and Limitations

Chemotherapy employs a diverse arsenal of cytotoxic drugs designed to target rapidly dividing cells through distinct molecular mechanisms (Figure 3) [6]. Alkylating substances like cisplatin and cyclophosphamide, inflict DNA damage by forming covalent cross-links between DNA strands, thereby preventing replication and transcription [7]. Methotrexate and 5-fluorouracil are examples of antimetabolites that structurally resemble a natural purine or pyrimidine metabolites, thereby disrupting DNA and RNA synthesis by competitively inhibiting key enzymes [8]. DNA strand breaks and cell death result from topoisomerase inhibitors, such as etoposide and irinotecan, interfering with the function of topoisomerase enzymes, which are necessary for DNA unwinding and replication [9]. By either stabilizing or depolymerizing microtubules, mitotic inhibitors like paclitaxel and vincristine interfere with microtubule dynamics during cell division, stopping cells in mitosis [10]. Anthracyclines, such as daunorubicin and doxorubicin, produce reactive oxygen species, intercalate into DNA, and block topoisomerase II, collectively causing severe DNA damage and oxidative stress [11]. Despite their clinical efficacy, chemotherapeutic agents suffer from a fundamental limitation: nonspecific cytotoxicity [12]. Because these drugs target all rapidly dividing cells, they indiscriminately damage healthy tissues that proliferate, such the gastrointestinal tract, hair follicles, and bone marrow, leading to significant adverse effects, including immunosuppression, mucositis, and alopecia [6]. Furthermore, a number of adaptive mechanisms, including the over expression of efflux transporters like P-glycoprotein (which actively pumps drugs out of the cell), the activation of enhanced DNA repair pathways, and the avoidance of programmed cell death (apoptosis), are commonly used by cancer cells to develop multi drug resistance [13]. These resistance mechanisms collectively diminish therapeutic efficacy and contribute to disease relapse, highlighting the need for more focused and specific treatment approaches (**Figure 2**) [14].

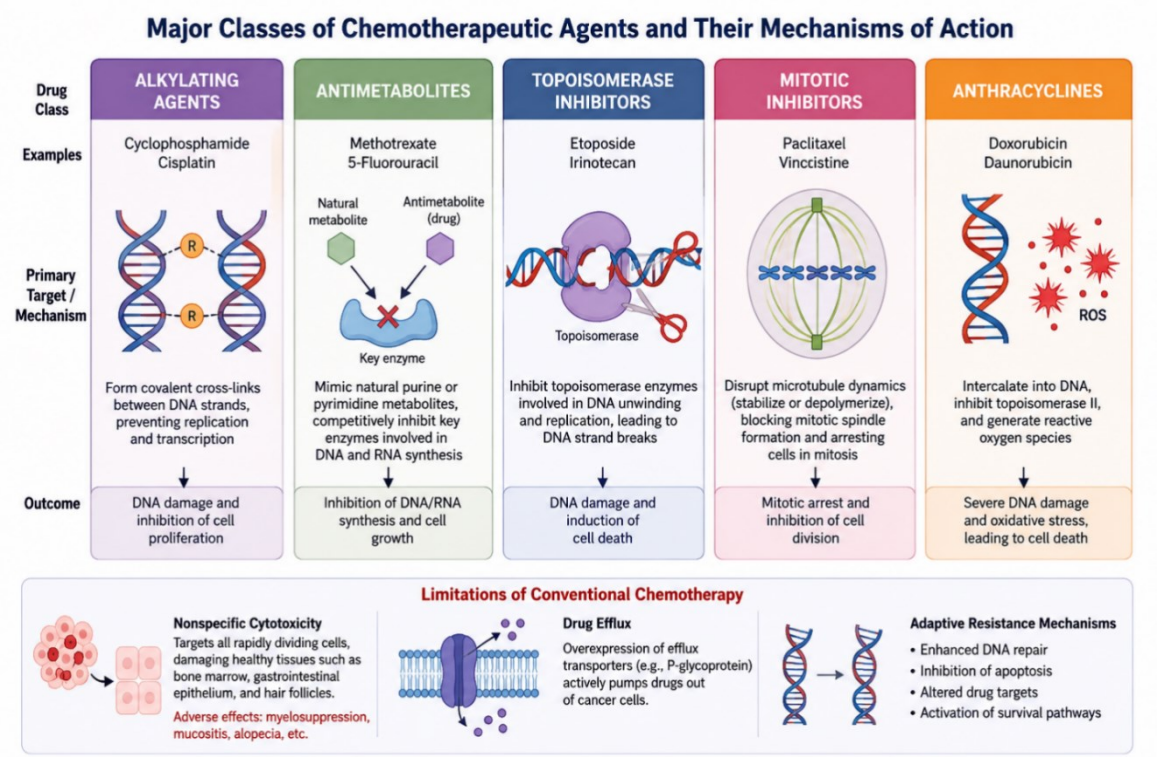

Figure 3. Mechanism of action of different chemotherapeutic agents and limitations.

1.2.2 Targeted Therapies and the Immunotherapy Revolution

Targeted interventions, small medicines, and monoclonal antibodies against certain molecular abnormalities (For example, trastuzumab for HER2 in breast cancer and imatinib for BCR-ABL in CML) were made possible by the knowledge of cancer biology [15]. While more specific than chemotherapy, these agents face challenges with resistance mutations and tumor heterogeneity [16].

The most profound evolution has been the emergence of immunotherapy, that use the immune system instead of directly targeting tumor cells [17] were made possible by the understanding of cancer biology. Immune checkpoint

[Downloaded from ijbc.ir on 2026-11-24]

inhibitors targeting PD-1, PD-L1, and CTLA-4 have emerged as important advances in cancer immunotherapy by helping the immune system regain its ability to recognize and attack tumor cells [18]. Another promising approach is adoptive cell therapy, particularly chimeric antigen receptor (CAR) T-cell therapy. In this strategy, a patient's own T cells are collected and genetically modified to recognize specific tumor-associated targets before being returned to the patient to exert an antitumor response. Because the treatment is generated from the patient's own immune cells and functions as a personalized therapeutic agent, CAR T-cell therapy is often described as a form of "living medicine" [19].

2. FOUNDATIONS OF CAR T-CELL THERAPY: FROM CONCEPT TO REALITY

2.1 Immunological Basis and Historical Development

Mitchison's groundbreaking work in the 1950s, which showed tumor-specific immunity through lymphocyte transfer in murine models, is the conceptual basis for adoptive cell transfer [20]. A fundamental and enduring challenge in cancer immunotherapy has been the need to break immunological tolerance to self-antigens, since tumor-associated antigens are frequently normal cellular proteins that are merely over expressed or aberrantly presented, rather than truly foreign neo antigens. Tumors can circumvent this restriction by down regulating major histocompatibility complex (MHC) molecules, which are necessary for conventional T-cell receptors (TCRs) to identify peptide antigens [21]. The antigen-binding domain of an antibody is combined with internal T-cell signaling domains to create chimeric antigen receptors (CARs), which are engineered fusion proteins that enable direct, MHC-independent recognition of surface antigens on cancerous cells [22]. Kuwana et al. reported the first synthetic immunoglobulin/TCR chimeric molecule in 1987, with subsequent functional validation provided by Gross, Waks, and Eshhar in 1989 [23]. Only the CD3ζ signaling region was present in the original first-generation CAR designs, which demonstrated poor *in vivo* durability and effectiveness [24]. The development of second-generation CARs, which linked the CD3ζ chain to co-stimulatory domains like CD28 or 4-1BB, was a major breakthrough in the field. The computed addition significantly increased T-cell longevity, proliferation, and antitumor efficacy, turning CAR T-cell immunotherapy from a theoretical idea into a practical treatment [25].

2.2. CAR Structure and Signaling

The chimeric antigen receptor (CAR) of later generations is an engineered fusion protein composed of distinctive modular elements that collectively facilitate robust and accurate tumor targeting and T-cell activation [26]. The architecture starts with an extracellular domain made up of a single-chain variable fragment (scFv) that is derived from a monoclonal antibody's variable heavy (VH) and variable light (VL) chains [27]. These chains are joined by a flexible peptide linker, allowing the scFv to form a persistent antigen-binding site that may recognize specific tumor surface antigens without being restricted by MHC [28]. Connected to this targeting domain is a hinge or spacer region, usually formed from immunoglobulin domains like IgG or CD8α, which offer the best steric access to the target antigen and structural flexibility. Throughout this timeframe, a transmembrane domain typically derived from CD8α or CD28 firmly affixes the receptor to the T-cell membrane [29]. The intracellular component of the CAR contains a co-stimulatory domain, typically CD28 or 4-1BB (CD137), including CD3ζ chain, which transmits the primary T-cell activation signal through its immune receptor tyrosine-based activation motifs (ITAMs) [30]. The selection of co-stimulatory domain influences the functional characteristics of CAR T cells: 4-1BB enhances long-term survival and promotes a memory-like phenotype, while CD28 facilitates rapid expansion and robust cytokine secretion [31]. To improve signaling and stamina, third-generation CARs expand upon this foundation by incorporating supplementary co-stimulatory domains (like CD28-4-1BB or CD28-OX40) [32]. In addition to these, contemporary "armored" CAR designs integrate supplementary attributes such as constitutive or inducible cytokine release (e.g., IL-12, IL-15) to modify the tumor microenvironment or genetically encoded safety mechanisms (e.g., inducible caspase-9) that enhance safety and efficacy by allowing controlled CAR T cell removal in cases of severe toxicity [33].

3.THE MANUFACTURING PROCESS OF CAR T-CELLS

3.1. Stepwise Production Pipeline

CAR T cell production is a complicated, customized procedure that needs approximately 3 to 5 weeks from leukapheresis to infusion [34]. The initial stage in the formation of CAR T cells is leukapheresis. A single intravenous line is used to draw blood from the patient, which is then run through an apheresis machine to extract white blood cells, including essential T lymphocytes, and then reintroducing the remaining blood components into the patient's circulation [35]. This process, which typically spans several hours and may need to be repeated to collect an adequate number of cells, carries potential complications such as hypocalcemia, manifesting as numbness or muscle spasms due to citrate anticoagulation; this is readily managed with calcium supplementation [36]. Although the leukapheresis result is a heterogeneous collection of cells that includes both T cells and inhibitory myeloid populations, which may prevent future CAR T-cell proliferation, effective T-cell isolation is essential to manufacturing success [37]. After being isolated,

[Downloaded from ijbc.ir on 2026-11-24]

paramagnetic beads coated with anti-CD3 and anti-CD28 antibodies are usually used to activate the T cells, which mimic physiological co-stimulation and initiate proliferation [38]. After being activated, the T cells undergo genetic change through transduction using viral vectors that carry the designed CAR transgene, most frequently lentiviral or cytomegalovirus [39]. When compared to gamma retroviral systems, lentiviral vectors are frequently chosen because of their greater transduction efficiency and possibly safer integration profile [40]. After successful transduction, cytokines including IL-2, IL-7, and IL-15 are used to support the ex vivo expansion of the modified CAR T cells in bioreactors over a period of days to weeks, until a therapeutic dose numbering in the hundreds of millions to billions of cells is achieved [41]. The final manufacturing steps (shown in **Figure 4**) involve harvesting these expanded cells, formulating them into an infusion-ready product, cryopreserving them for stability, and transporting them under strict chain-of-custody protocols back to the clinical site for patient administration [42].

3.2 Critical Quality Attributes

Clinical efficacy and patient outcomes are significantly influenced by the final CAR T-cell infusion product's composition and functional features [43]. Beyond the mere quantity of cells, specific qualitative attributes including the ratio of CD4+ to CD8+ T-cell subsets, the predominance of certain memory phenotypes, the absence of exhaustion markers, and the functional versatility of the cells collectively shape the therapeutic potential of the product [44]. A definedCD4+:CD8+ ratio, such as a balanced 1:1 formulation, may enhance overall potency by promoting synergistic helper and cytotoxic functions. T-cell subsets with enhanced stem cell memory (TSCM) and central memory (TCM), which are linked to strong expansion capacity, improved long-term persistence, and persistent anticancer activity in vivo, is equally significant [45]. Conversely, the presence of T cells expressing high levels of markers of fatigue, including TIM-3, LAG-3, and PD-1, correlates with impaired engraftment, limited proliferative capacity, and reduced tumor control. Therefore, products with minimal expression of these inhibitory receptors are generally predictive of better clinical responses [46]. In addition, polyfunctional potential—the ability of CAR T cells to release many cytokines, including TNF-α, IL-2, and IFN-γ—in response to antigen encounter—serves as a biomarker of strong cellular fitness and effector capability, further differentiating products with high therapeutic promise from those that are likely to show reduced activity [47]. When taken as a whole, these characteristics highlight the significance of advanced manufacturing and quality control techniques targeted at creating CAR T-cell products that are optimized not only in quantity but also in cellular composition and functional readiness [48].

4. CLINICAL APPLICATIONS

4.1 Therapy of pediatric B-cell acute lymphoblastic leukemia (ALL)

Individuals with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL) typically face a bleak prognosis, even though initial therapies yield cure rates exceeding 80% [49]. The FDA granted complete approval for the inaugural CAR T-cell therapy, tisagenlecleucel (tisa-cel, Kymriah®), in 2017, predicated on the pioneering ELIANA trials. This study revealed an 81% complete remission rate in pediatric and young adult patients with refractory or relapsed B-ALL [50]. A substantial number of these patients maintain long-lasting remissions, according to long-term follow-up data, indicating possible curative outcomes [51]. As the treatment framework evolves, CAR T-cell therapy is presently under examination as a secondary intervention for high-risk B-ALL patients exhibiting poor responses to initial chemotherapy. According to Dr. Terry Fry from Children's Hospital Colorado, this method may save responsive patients more than two years of potentially harmful chemotherapy.

4.2. B-Cell Lymphomas

4.2.1 DLBCL (Diffuse large B-cell lymphoma)

The use of CAR T-cell therapy for malignant lymphomas has produced groundbreaking outcomes. In patients with refractory large B-cell lymphoma, the ZUMA-1 trial of axicabtagene ciloleucel (axi-cel, Yescarta) showed an objective response rate of 83%, with 58% achieving complete responses at a median follow-up of 15.4 months [54]. Most notably, long-term analysis revealed that over 30% of treated patients remained alive and free of disease at five years, an unprecedented achievement in this heavily pre-treated population [55].

4.2.2 Follicular Lymphoma

94% of responses were received overall, and 80% of responses were completed. The ZUMA-5 study showed that axi-cel was very effective in treating indolent lymphomas, including relapsed/refractory follicular lymphoma [56]. This success underscores a dramatic shift in prognosis. According to Dr. James Kochenderfer of the National Cancer Institute, patients with advanced lymphomas who were once considered "virtually untreatable" can now achieve profound and meaningful remissions through CAR T-cell therapy [57].

4.2.3 Other Lymphoma Subtypes

Other B-cell cancers can now be treated with CAR T-cells. Lisocabtagene maraleucel (liso-cel, Breyanzi) has been approved to treat a variety of B-cell malignancies, including

[Downloaded from ijbc.ir on 2026-11-24]

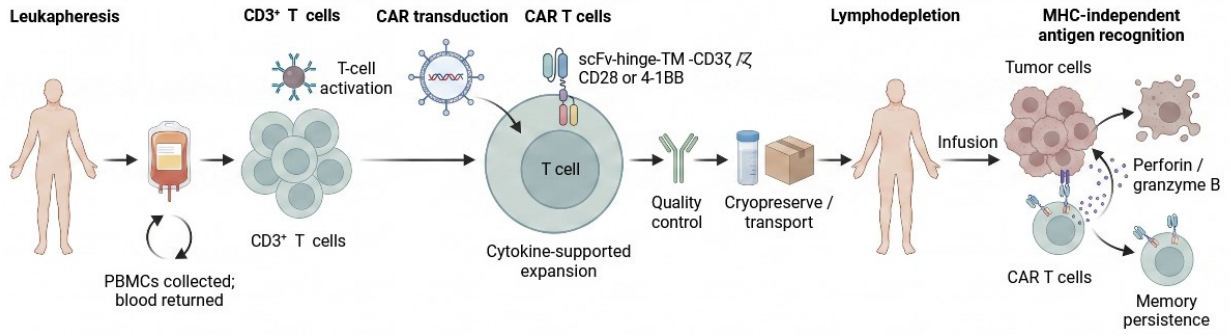

Figure 4. The steps involved in producing CAR T cells.

diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, and chronic lymphocytic leukemia [59]. Mantle cell lymphoma can be treated with brexucabtagene autoleucel (brexu-cel, Tecartus).

4.3 Multiple Myeloma

The emergence of B-cell maturation antigen (BCMA)-targeted CAR T-cell therapies has revolutionized the treatment of highly pre-treated multiple myeloma, a plasma cell malignancy known for its persistence [60]. Decabtagene vicleucel (ide-cel, Abecma) demonstrated an overall response rate of 73% in patients who had undergone at least three previous lines of treatment, including immunomodulatory drugs, proteasome inhibitors, and anti-CD38 antibodies [61]. Ciltacabtagene autoleucel (cilta-cel, Carvykti) showed even more remarkable outcomes, with 83% of patients achieving a full response or better and a 98% overall response rate in the CARTITUDE-1 trial [62]. For a patient population with traditionally few options, these results offer profound and long-lasting remissions, marking a paradigm change [63].

5. TOXICITIES AND MANAGEMENT STRATEGIES

CAR T-cell therapy's exceptional effectiveness is complemented with a distinct range of toxicities that require vigilant monitoring and specialized management. Understanding and mitigating these adverse events are crucial for the safe administration of this powerful treatment [64].

5.1 Cytokine Release Syndrome (CRS)

CRS, a systemic inflammatory response that causes the abrupt release of cytokines like IL-6, IFN-γ, and IL-10, is brought on by the excessive activation and proliferation of CAR T cells. Its severity varies from mild fever (Grade 1) to capillary leak, multi-organ failure, and potentially lethal hypotension (Grade 3–4) [65]. The mainstay of treatment for moderate to severe CRS is tocilizumab, an IL-6 receptor antagonist. Corticosteroids are used to broadly inhibit the immune response in situations that are resistant or severe [66]. Concurrently, aggressive supportive care including intravenous fluids, vasopressors, and supplemental oxygen is essential to stabilize patients during the acute phase [67].

Table 1. FDA-Approved CAR T-Cells.

Brand Name	Common Name	Indications
Kymriah	tisagenlecleucel	Therapy of B-ALL, DLBCL, and Follicular lymphoma
Yescarta	axicabtagene ciloleucel	Therapy of Follicular lymphoma and Large B-cell lymphoma
Tecartus	brexucabtagene autoleucel	Therapy of Mantle cell lymphoma, and Adult B-cell ALL
Breyanzi	lisocabtagene maraleucel	Therapy of Follicular lymphoma, Large B-cell lymphoma, Mantle cell lymphoma, CLL
Abecma	idecabtagene vicleucel	Therapy of Multiple myeloma
Carvykti	ciltacabtagene autoleucel	Therapy of Multiple myeloma
Aucatzyl	obecabtagene autoleucel	Therapy of Adult B-cell ALL

5.2 ICANS (Immune Effector Cell-Associated Neurotoxicity Syndrome)

A unique neuropsychiatric toxicity, ICANS (shown in **Figure 5**) frequently occurs concurrently with or after CRS [68].

[Downloaded from ijbc.ir on 2026-11-24]

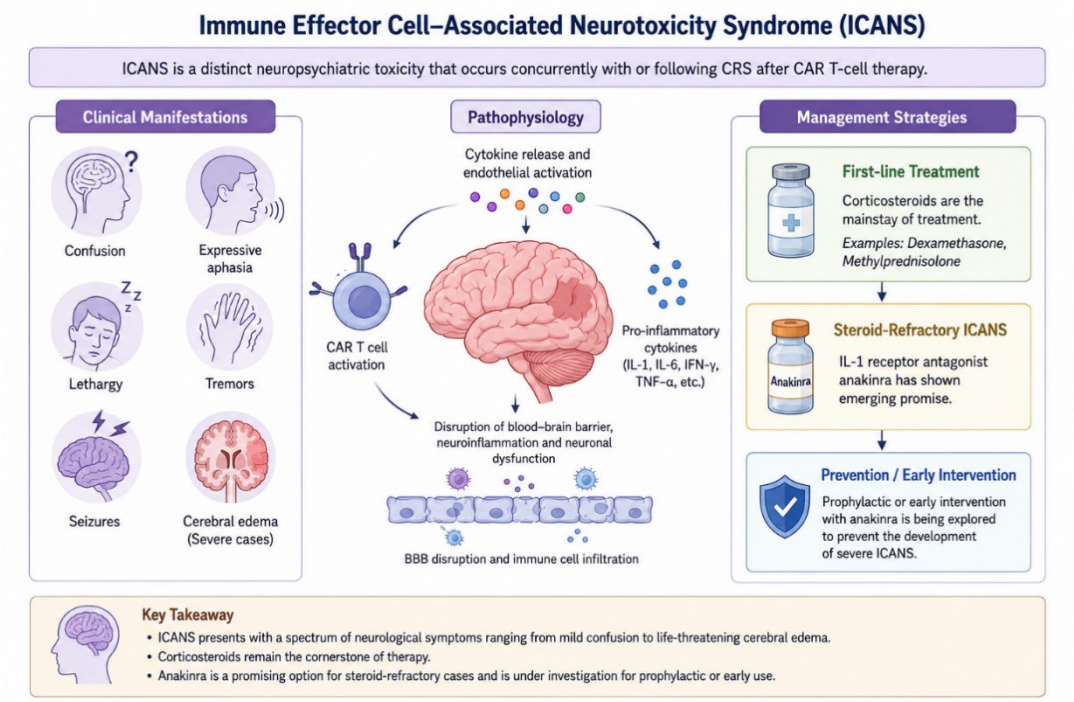

Figure 5. Symptoms, Pathophysiology and management of ICANS

Confusion, expressive aphasia, fatigue, tremors, seizures, and in extreme situations, cerebral edema are just a few of the symptoms it might cause [69]. Corticosteroid injection is the cornerstone of treatment [70]. For steroid-refractory cases, the IL-1 receptor antagonist anakinra has shown emerging promise. Furthermore, prophylactic or early intervention with anakinra is being explored as a strategy to prevent the development of severe ICANS [71].

5.3 Other Toxicities

CAR T-cell treatment is associated with several other adverse effects. B-cell aplasia and the resulting hypogammaglobulinemia are anticipated on-target, off-tumor consequences of CD19-directed therapies, necessitating long-term maintenance with intravenous immunoglobulin (IVIG) supplementation [72]. The profound lymphodepletion from conditioning chemotherapy and persistent B-cell aplasia significantly increase the risk of infections, mandating antimicrobial prophylaxis and close monitoring [73]. Rare but severe complications include hemophagocytic lymphohistiocytosis (HLH), a hyperinflammatory syndrome, and tumor lysis syndrome, particularly in patients with high-burden leukemias [74].

6. MECHANISMS OF RESISTANCE AND RELAPSE

Due to a variety of resistance mechanisms, a sizable percentage of patients eventually experience illness relapse despite high initial response rates [75].

6.1 Antigen Escape

Missing or changes in the respective antigen is the most common reason for recurrence in CD19-targeted treatments. This can occur through alternative splicing, leading to the production of CD19 isoforms that lack the epitope recognized by the CAR; through lineage switch, where leukemic cells transform to a myeloid or other non-B lineage phenotype; or through acquired genetic mutations (frameshift or nonsense) that abolish CD19 expression [76]. Strategies including sequential targeting, targeting more stable antigens, or dual-targeted CARs are developing against this [77].

6.2 T-Cell Intrinsic Factors

Limitations of the CAR T cells themselves may also be the cause of therapeutic failure. After injection, poor persistence causes the cell population to contract quickly. T-cell exhaustion causes the lymphocytes to become dysfunctional due to the activation of inhibitory receptors such as PD-1, TIM-3, and LAG-3 [78]. Furthermore, the infusion of terminally differentiated effector cells with limited replicative potential curtails long-term activity [79]. Memory-enhancing

[Downloaded from ijbc.ir on 2026-11-24]

co-stimulatory domains (such as 4-1BB), genes for homeostatic cytokines (such as IL-7 and IL-15), the selection of younger T-cell subsets for production, and the combination of treatment and checkpoint inhibitors to reverse fatigue are the key engineering options [80].

6.3. Host and Microenvironment Factors

The host environment may impede the function of CAR T-cells. The tumor microenvironment (TME) in hematologic cancers, especially solid tumors, generates immunosuppressive cytokines (TGF-β, IL-10), promotes metabolic competition (depleting glucose and amino acids), and contains inhibitory cell populations such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). A primary objective of next-generation CAR designs is to overcome these obstacles [81].

7. EXPANDING TO SOLID TUMORS: CHALLENGES AND EMERGING SOLUTIONS

Although it has proven difficult to translate CAR T-cell effectiveness from hematologic to solid tumors, coordinated research efforts are illuminating future directions [82].

7.1 Fundamental Barriers

Three interconnected obstacles dominate the field. First, target antigen selection is exceedingly difficult; ideal antigens must be homogeneously expressed on tumors, absent on vital tissues, and essential for tumor survival [83]. Current candidates include over expressed tumor-associated antigens (e.g., HER2, EGFR), cancer-testis antigens with restricted normal expression (e.g., NY-ESO-1), and uniqueneoantigens, though the latter are patient-specific and complex to target [84]. Second, the tumor microenvironment (TME)of solid cancers is profoundly hostile, featuring physical barriers (abnormal vasculature, dense stroma), a milieu of immunosuppressive factors (TGF-β, adenosine), metabolic constraints (hypoxia), and abundant checkpoint molecules (PD-L1) [85]. Third, significant tumor heterogeneity, both within a single tumor and between metastases, allows for the outgrowth of antigen-negative clones that evade CAR T-cell recognition [86].

7.2 Promising Clinical Developments

Early-phase trials provide hints of efficacy despite these obstacles. CAR T-cells that target B7-H3 or GD2 have demonstrated initial activity in diffuse midline glioma in glioblastoma. and intracavitary delivery of IL13Rα2-targeted CARs has induced regression in recurrent disease [87]. CAR T-cell engagement of solid tumors is demonstrated by ongoing trials in ovarian cancer (targeting mesothelin), colorectal cancer (targeting GUCY2C), and pancreatic cancer (targeting mesothelin or HER2) [88].

7.3 Next-Generation Engineering Strategies

To break through the solid tumor barrier, innovative engineering approaches are being deployed. Armored CARs are designed to secrete cytokines like IL-12 or IL-15 to alter the suppressive TME [89]. Switch receptors convert inhibitory signals (e.g., from TGF-β) into activating signals. Local/regional delivery (intratumoral, intracavitary) aims to bypass trafficking challenges [90]. Tumor selectivity and safety are improved by logic-gated CARs, which need two antigens to fully activate. Lastly, the goal of CAR combinations that target several antigens at once is to overcome tumor heterogeneity [91].

8. Future Directions and Conclusion

CAR T-cell therapy's trajectory indicates increased effectiveness, accessibility, and incorporation into conventional cancer treatment [92].

8.1 Allogeneic (Off-the-Shelf) CAR T-Cells

Allogeneic CAR T-cells produced from healthy donors are in advanced research to address the expense, complexity, and delays associated with autologous production [93]. Graft-versus-host disease (GvHD) can be prevented by employing gene-editing techniques like CRISPR/Cas9 to knock out the T-cell receptor (TCR), and host rejection can be mitigated by knocking out CD52 to enable recipient conditioning with alemtuzumab [94]. Early products such as ALLO-715 and PBCAR0191 have shown promising safety efficacy signals in initial trials [95].

8.2 Combination Strategies

Investigations are underway regarding synergistic combinations to improve the effectiveness of CAR T-cells. Exhausted CAR T-cells may be revitalized by combining treatment with immune checkpoint inhibitors, such as anti-PD-1. The incorporation and efficacy of CAR T-cells can be improved through concurrent targeted treatments, such as ibrutinib in chronic lymphocytic leukemia (CLL) [97]. Radiation therapy can modulate the TME and boost antigen presentation [98]. Additionally, pairing CAR T-cells with bispecific antibodies offers a method to engage both engineered and endogenous T-cell populations against the tumor [99].

8.3 Earlier Line Therapy

The introduction of CAR T-cell therapy into earlier treatment lines represents a major paradigm shift [100]. After just one previous treatment, second-line approval for large B-cell lymphoma (for axi-cel and liso-cel) is historic [101]. Studies are evaluating its role as consolidation after chemotherapy,

[Downloaded from ijbc.ir on 2026-11-24]

potentially replacing autologous stem cell transplant in some settings, and even as frontline therapy for high-risk pediatric ALL or DLBCL. This shift promises to benefit patients sooner and potentially improve long-term outcomes [102].

9. CONCLUSION

One of the most revolutionary developments in contemporary oncology is CAR T-cell therapy, which shows that modified cellular therapies can produce long-lasting remissions and possibly even cures in patients with otherwise fatal hematologic malignancies. As Dr. Steven Rosenberg of the NCI has reflected, CAR T-cells have journeyed from "an experimental dream" to "a part of modern medicine". This evolution from skepticism to standard of care underscores the power of biomedical innovation. Even if there are still many obstacles to overcome, particularly in the area of solid tumors, the unrelenting pace of advancement in CAR design, combination tactics, and manufacturing logistics encourages hope for wider use. Ultimately, CAR T-cell therapy has not merely added a new drug to the arsenal; it has fundamentally reshaped therapeutic paradigms, championing a future of personalized, immune-driven medicine over conventional cytotoxic approaches. As the field continues its rapid evolution, it holds the promise to continually redefine the boundaries of cancer treatment for decades to come.

Acknowledgment

We would like to thank the management of the Vignan Pharmacy College, Vadlamudi, Guntur, for their continuous support and arrangement of the facilities.

Conflict of interest

The authors declare no conflicts of interest.

Funding

No founding was received for this review study form any organizations.

Ethical statement

I confirm that all the review work meets ethical guidelines and adheres to the legal requirements of the study country.

References

1. Arruebo M, Vilaboa N, Sáez-Gutierrez B, Lambea J, Tres A, Valladares M, et al. Assessment of the evolution of cancer treatment therapies. Cancers (Basel). 2011;3(3):3279–3300.

2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–263.

3. Shalgumbayeva GM, Massadykov AS, Baimussanov AN, Siyazbekova ZS. Epidemiology of cancer in the Republic of Kazakhstan during 2008–2017. 2019.

4. Prasad V, Mailankody S. Research and development spending to bring a single cancer drug to market and revenues after approval. JAMA Intern Med. 2017;177(11):1569–1575.

5. Serkies K, Jassem J. Systemic therapy for cervical carcinoma: current status. Chin J Cancer Res. 2018;30(2):209–221.

6. Chabner BA, Roberts TG Jr. Chemotherapy and the war on cancer. Nat Rev Cancer. 2005;5(1):65–72.

7. Rycenga HB, Long DT. The evolving role of DNA inter-strand crosslinks in chemotherapy. Curr Opin Pharmacol. 2018;41:20–26.

8. Gewirtz D. A critical evaluation of the mechanisms of action proposed for the antitumor effects of the anthracycline antibiotics adriamycin and daunorubicin. Biochem Pharmacol. 1999;57(7):727–741.

9. Brunton LL, Knollmann BC, Hilal-Dandan R, editors. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York (NY): McGraw-Hill Education; 2018.

10. Jordan MA, Wilson L. Microtubules as a target for anticancer drugs. Nat Rev Cancer. 2004;4(4):253–265.

11. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol Rev. 2004;56(2):185–229.

12. Longley DB, Johnston PG. Molecular mechanisms of drug resistance. J Pathol. 2005;205(2):275–292.

13. Housman G, Byler S, Heerboth S, Lapinska K, Longacre M, Snyder N, et al. Drug resistance in cancer: an overview. Cancers (Basel). 2014;6(3):1769–1792.

14. Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: role of ATP-dependent transporters. Nat Rev Cancer. 2002;2(1):48–58.

15. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001;344(14):1031–1037.

16. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: an evolving paradigm. Nat Rev Cancer. 2013;13(10):714–726.

17. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell. 2015;27(4):450–461.

18. Noori M, Yousefi AM, Zali MR, Bashash D. Predictive value of PD-L1 expression in response to immune checkpoint inhibitors for esophageal cancer treatment: A systematic review and meta-analysis. Frontiers in Oncology. 2022 Dec 15;12:1021859.

19. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T-cell immunotherapy for human cancer. Science. 2018;359(6382):1361–1365.

20. Mitchison NA. Studies on the immunological response to foreign tumor transplants in the mouse. I. The role of lymph node cells in conferring immunity by adoptive transfer. J Exp Med. 1955;102(2):157–177.

21.Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science. 2015;348(6230):69–74.

22. Sadelain M, Brentjens R, Rivière I. The basic principles of chimeric antigen receptor design. Cancer Discov. 2013;3(4):388–398.

23. Kuwana Y, Asakura Y, Utsunomiya N, Nakanishi M, Arata Y, Itoh S, et al. Expression of chimeric receptor composed of immunoglobulin-

[Downloaded from ijbc.ir on 2026-11-24]

derived V regions and T-cell receptor-derived C regions. Biochem Biophys Res Commun. 1987;149(3):960–968.

24. Levine BL, Pasquini MC, Connolly JE, Porter DL, Gustafson MP, Boelens JJ, et al. Unanswered questions following reports of secondary malignancies after CAR-T cell therapy. Nat Med. 2024;30(2):338–341.

25. Johnson LA, June CH. Driving gene-engineered T-cell immunotherapy of cancer. Cell Res. 2017;27(1):38–58.

26. Maus MV, June CH. Making better chimeric antigen receptors for adoptive T-cell therapy. Clin Cancer Res. 2016;22(8):1875–1884.

27. Eshhar Z, Waks T, Gross G, Schindler DG. Specific activation and targeting of cytotoxic lymphocytes through chimeric single chains consisting of antibody-binding domains and the gamma or zeta subunits of the immunoglobulin and T-cell receptors. Proc Natl Acad Sci U S A. 1993;90(2):720–724.

28. Kochenderfer JN, Rosenberg SA. Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors. Nat Rev Clin Oncol. 2013;10(5):267–276.

29. Yakoub-Agha I, Chabannon C, Bader P, Basak GW, Bonig H, Ciceri F, et al. Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). Haematologica. 2020;105(2):297–316.

30. Klichinsky M, Ruella M, Shestova O, Lu XM, Best A, Zeeman M, et al. Human chimeric antigen receptor macrophages for cancer immunotherapy. Nat Biotechnol. 2020;38(8):947–953.

31. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531–2544.

32. Imai C, Mihara K, Andreansky M, Nicholson IC, Pui CH, Geiger TL, et al. Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia. Leukemia. 2004;18(4):676–684.

33. Brentjens RJ, Latouche JB, Santos E, Marti F, Gong MC, Lyddane C, et al. Eradication of systemic B-cell tumors by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15. Nat Med. 2003;9(3):279–286.

34.Boyiadzis MM, Dhodapkar MV, Brentjens RJ, Kochenderfer JN, Neelapu SS, Maus MV, et al. Chimeric antigen receptor (CAR) T therapies for the treatment of hematologic malignancies: clinical perspective and significance. J Immunother Cancer. 2018;6(1):137.

35. Levine BL, June CH. Perspective: assembly line immunotherapy. Nature. 2013;498(7455):S17.

36. McLeod BC. Therapeutic plasma exchange. In: Ross Principles of Transfusion Medicine. 4th ed. Oxford: Wiley-Blackwell; 2009. p. 629–651.

37. Rivière I, Sadelain M. Chimeric antigen receptors: a cell and gene therapy perspective. Mol Ther. 2017;25(5):1117–1124.

38. Riddell SR, Greenberg PD. The use of anti-CD3 and anti-CD28 monoclonal antibodies to clone and expand human antigen-specific T cells. J Immunol Methods. 1990;128(2):189–201.

39. Mohammed A, Ibrahim NA, Basher NS. Protein engineering and drug discovery: importance, methodologies, challenges, and prospects. Biomolecules. 2025;15:1628.

40. Trono D. Lentiviral vectors. New York (NY): Springer; 2001.

41. Turtle CJ, Riddell SR. Genetically retargeting CD8+ lymphocyte subsets for cancer immunotherapy. Curr Opin Immunol. 2011;23(2):299–305.

42. Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med. 2013;368(16):1509–1518.

43. Deng Q, Han G, Puebla-Osorio N, Ma MCJ, Strati P, Chasen B, et al. Characteristics of anti-CD19 CAR T-cell infusion products associated with efficacy and toxicity in patients with large B-cell lymphomas. Nat Med. 2020;26(12):1878–1887.

44. Zhang X, Zhu L, Zhang H, Chen S, Xiao Y. CAR-T cell therapy in hematological malignancies: current opportunities and challenges. Front Immunol. 2022;13:927153.

45. Gattinoni L, Lugli E, Ji Y, Pos Z, Paulos CM, Quigley MF, et al. A human memory T-cell subset with stem cell-like properties. Nat Med. 2011;17(10):1290–1297.

46. Thommen DS, Schumacher TN. T-cell dysfunction in cancer. Cancer Cell. 2018;33(4):547–562.

47. Xue Q, Bettini E, Paczkowski P, Ng C, Kaiser A, McConnell T, et al. Single-cell multiplexed cytokine profiling of CD19 CAR-T cells reveals a diverse landscape of polyfunctional antigen-specific response. J Immunother Cancer. 2017;5(1):85.

48. Rossi J, Paczkowski P, Shen YW, Morse K, Flynn B, Kaiser A, et al. Preinfusion polyfunctional anti-CD19 chimeric antigen receptor T cells are associated with clinical outcomes in NHL. Blood. 2018;132(8):804–814.

49. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. N Engl J Med. 2015;373(16):1541–1552.

50. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. 2018;378(5):439–448.

51. Cappell KM, Sherry RM, Yang JC, Goff SL, Vanasse DA, McIntyre L, et al. Long-term follow-up of anti-CD19 chimeric antigen receptor T-cell therapy. J Clin Oncol. 2020;38(32):3805–3815.

52. Laetsch TW, Maude SL, Rives S, Hiramatsu H, Bittencourt H, Bader P, et al. Three-year update of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia in the ELIANA trial. J Clin Oncol. 2023;41(9):1664–1669.

53. Shah NN, Fry TJ. Mechanisms of resistance to CAR T-cell therapy. Nat Rev Clin Oncol. 2019;16(6):372–385.

54. Neelapu SS, Jacobson CA, Ghobadi A, Miklos DB, Lekakis LJ, Oluwole OO, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2023;141(19):2307–2315.

55. Locke FL, Neelapu SS, Bartlett NL, Siddiqi T, Chavez JC, Hosing CM, et al. Phase 1 results of ZUMA-1: a multicenter study of KTE-C19 anti-CD19 CAR T-cell therapy in refractory aggressive lymphoma. Mol Ther. 2017;25(1):285–295.

56. Jacobson CA, Chavez JC, Sehgal AR, William BM, Munoz J, Salles G, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2022;23(1):91–103.

57. Kochenderfer JN, Dudley ME, Feldman SA, Wilson WH, Spaner DE, Maric I, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric antigen receptor-transduced T cells. Blood. 2012;119(12):2709–2720.

58. Munshi NC, Anderson LD Jr, Shah N, Madduri D, Berdeja J, Lonial S, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384(8):705–716.

59. Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2020;382(14):1331–1342.

[Downloaded from ijbc.ir on 2026-11-24]

60. Berdeja JG, Madduri D, Usmani SZ, Singh I, Zudaire E, Yeh TM, et al. Update of CARTITUDE-1: a phase Ib/II study of JNJ-4528, a B-cell maturation antigen (BCMA)-directed CAR-T-cell therapy, in relapsed/refractory multiple myeloma. J Clin Oncol. 2020;38(15 Suppl):8505.

61. Raje N, Berdeja J, Lin Y, Siegel D, Jagannath S, Madduri D, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. N Engl J Med. 2019;380(18):1726–1737.

62. Martin T, Lin Y, Agha M, Cohen AD, Htut M, Stewart AK, et al. Health-related quality of life in patients given ciltacabtagene autoleucel for relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b–2, open-label study. Lancet Haematol. 2022;9(12):e897–e905.

63. Usmani SZ, Berdeja JG, Madduri D, Jakubowiak AJ, Agha ME, Cohen AD, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell therapy, in relapsed/refractory multiple myeloma: updated results from CARTITUDE-1. Blood. 2021;138(Suppl 1):549.

64. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625–638.

65. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188–195.

66. Lee DW, Gardner R, Porter DL. Current concepts in the diagnosis and management of cytokine release syndrome (correction). Blood. 2016;128(11):1533.

67. Turtle CJ, Hay KA, Hanafi LA, Li D, Cherian S, Chen X, et al. Durable molecular remissions in chronic lymphocytic leukemia treated with CD19-specific chimeric antigen receptor-modified T cells after failure of ibrutinib. J Clin Oncol. 2017;35(26):3010–3020.

68. Baumeister SHC, Mohan GS, Elhaddad A, Lehmann L. Cytokine release syndrome and associated acute toxicities in pediatric patients undergoing immune effector cell therapy or hematopoietic cell transplantation. Front Oncol. 2022;12:841117.

69. Santomasso BD, Park JH, Salloum D, Rivière I, Flynn J, Mead E, et al. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. Cancer Discov. 2018;8(8):958–971.

70. Bonifant CL, Jackson HJ, Brentjens RJ, Curran KJ. Toxicity and management in CAR T-cell therapy. Mol Ther Oncolytics. 2016;3:16011.

71. Strati P, Ahmed S, Kebriaei P, Nastoupil LJ, Claussen CM, Watson G, et al. Clinical efficacy of anakinra to mitigate CAR T-cell therapy-associated toxicity in large B-cell lymphoma. Blood Adv. 2020;4(13):3123–3127.

72. Hill JA, Seo SK. How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies. Blood. 2020;136(8):925–935.

73. Kampouri E, Little JS, Rejeski K, Manuel O, Hammond SP, Hill JA. Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies. Transpl Infect Dis. 2023;25:e14157.

74. Park JH, Rivière I, Gonen M, Wang X, Sénéchal B, Curran KJ, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med. 2018;378(5):449–459.

75. Majzner RG, Mackall CL. Tumor antigen escape from CAR T-cell therapy. Cancer Discov. 2018;8(10):1219–1226.

76. Sotillo E, Barrett DM, Black KL, Bagashev A, Oldridge D, Wu G, et al. Convergence of acquired mutations and alternative splicing of CD19 enables resistance to CART-19 immunotherapy. Cancer Discov. 2015;5(12):1282–1295.

77. Dai H, Wu Z, Jia H, Tong C, Guo Y, Ti D, et al. Bispecific CAR-T cells targeting both CD19 and CD22 for therapy of adults with relapsed or refractory B-cell acute lymphoblastic leukemia. J Hematol Oncol. 2020;13(1):30.

78. Long AH, Haso WM, Shern JF, Wanhainen KM, Murgai M, Ingaramo M, et al. 4-1BB costimulation ameliorates T-cell exhaustion induced by tonic signaling of chimeric antigen receptors. Nat Med. 2015;21(6):581–590.

79. Ghassemi S, Martinez-Becerra FJ, Master AM, Richman SA, Heo D, Leferovich J, et al. Enhancing chimeric antigen receptor T-cell anti-tumor function through advanced media design. Mol Ther Methods Clin Dev. 2020;18:595–606.

80.Kawalekar OU, O'Connor RS, Fraietta JA, Guo L, McGettigan SE, Posey AD Jr, et al. Distinct signaling of coreceptors regulates specific metabolic pathways and impacts memory development in CAR T cells. Immunity. 2016;44(2):380–390.

81. Newick K, O'Brien S, Moon E, Albelda SM. CAR T-cell therapy for solid tumors. Annu Rev Med. 2017;68:139–152.

82. Hou AJ, Chen LC, Chen YY. Navigating CAR-T cells through the solid tumour microenvironment. Nat Rev Drug Discov. 2021;20(7):531–550.

83. Hegde M, Corder A, Chow KKH, Mukherjee M, Ashoori A, Kew Y, et al. Combinational targeting offsets antigen escape and enhances effector functions of adoptively transferred T cells in glioblastoma. Mol Ther. 2013;21(11):2087–2101.

84. Newick K, Moon E, Albelda SM. Chimeric antigen receptor T-cell therapy for solid tumors. Mol Ther Oncolytics. 2016;3:16006.

85. Joyce JA, Fearon DT. T-cell exclusion, immune privilege, and the tumor microenvironment. Science. 2015;348(6230):74–80.

86. Brown CE, Mackall CL. CAR T-cell therapy: inroads to response and resistance. Nat Rev Immunol. 2019;19(2):73–74.

87. Brown CE, Alizadeh D, Starr R, Weng L, Wagner JR, Naranjo A, et al. Regression of glioblastoma after chimeric antigen receptor T-cell therapy. N Engl J Med. 2016;375(26):2561–2569.

88. Beatty GL, Haas AR, Maus MV, Torigian DA, Soulen MC, Plesa G, et al. Mesothelin-specific chimeric antigen receptor mRNA-engineered T cells induce antitumor activity in solid malignancies. Cancer Immunol Res. 2014;2(2):112–120.

89. Chmielewski M, Abken H. CAR T cells releasing IL-18 convert to T-bet^high^ FoxO1^low^ effectors that exhibit augmented activity against advanced solid tumors. Cell Rep. 2017;21(11):3205–3219.

90. Morello A, Sadelain M, Adusumilli PS. Mesothelin-targeted CARs: driving T cells to solid tumors. Cancer Discov. 2016;6(2):133–146.

91. 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.

92. Mullard A. FDA approves first CAR T-cell therapy. Nat Rev Drug Discov. 2017;16(10):669–670.

93. Depil S, Duchateau P, Grupp SA, Mufti G, Poirot L. Off-the-shelf allogeneic CAR T cells: development and challenges. Nat Rev Drug Discov. 2020;19(3):185–199.

94. Su J, Zeng Y, Song Z, Liu Y, Ou K, Wu Y, et al. Genome-edited allogeneic CAR-T cells: the next generation of cancer immunotherapies. J Hematol Oncol. 2025;18(1):1–39.

95. Mailankody S, Matous JV, Chhabra S, Liedtke M, Sidana S, Oluwole OO, et al. Allogeneic BCMA-targeting CAR T cells in relapsed/refractory

[Downloaded from ijbc.ir on 2026-11-24]

multiple myeloma: phase 1 UNIVERSAL trial interim results. Nat Med. 2023;29(2):422–429.

96. Chong EA, Melenhorst JJ, Lacey SF, Ambrose DE, Gonzalez V, Levine BL, et al. PD-1 blockade modulates chimeric antigen receptor (CAR)-modified T cells: refueling the CAR. Blood. 2017;129(8):1039–1041.

97. Gill S, Vides V, Frey NV, Hexner EO, Metzger S, O'Brien M, et al. Anti-CD19 CAR T cells in combination with ibrutinib for the treatment of chronic lymphocytic leukemia. Blood Adv. 2022;6(21):5774–5785.

98. Fraietta JA, Beckwith KA, Patel PR, Ruella M, Zheng Z, Barrett DM, et al. Ibrutinib enhances chimeric antigen receptor T-cell engraftment and efficacy in leukemia. Blood. 2016;127(9):1117–1127.

99. Rafiq S, Hackett CS, Brentjens RJ. Engineering strategies to overcome the current roadblocks in CAR T-cell therapy. Nat Rev Clin Oncol. 2020;17(3):147–167.

100. Abramson JS, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood. 2023;141(14):1675–1684.

101. Kamdar M, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis. Lancet. 2022;399(10343):2294–2308.

102. Levine JE, Grupp SA, Pulsipher MA, Dietz AC, Rives S, Myers GD, et al. Pooled safety analysis of tisagenlecleucel in children and young adults with B-cell acute lymphoblastic leukemia. J Immunother Cancer. 2021;9(8):e002287.

[Downloaded from ijbc.ir on 2026-11-24]