IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 7 Ser. 6 (July. 2024), PP 35-44
www.iosrjournals.org

Car-T Cell Therapy And Its Significance In Cancer Treatment

Maria Akhtar[1], Meirajuddin Tousif[2]
Department Of General Medicine, Khaja Bandanawaz Institute Of Medical Sciences, Karnataka, India
Department Of General Medicine, Sri Devaraj Urs Medical College, Karnataka, India

Abstract:
CAR-T cell therapy harnesses genetically modified T cells to target specific antigens on cancer cells, offering a promising immunotherapy approach for hematologic malignancies and beyond. This review synthesizes current literature and clinical studies to analyze CAR-T cell therapy's mechanisms, efficacy, and safety profiles, examining genetic engineering techniques and antigen targeting strategies in diverse cancer contexts. Key findings highlight its remarkable clinical outcomes, including high response rates and durable remissions in relapsed/refractory cancers, underscoring its transformative potential in cancer treatment. CAR-T cell therapy represents a paradigm shift in oncology, providing personalized and targeted treatment options where traditional therapies fall short. Its success in hematologic cancers sets a precedent for broader applications across solid tumors. Continued research is essential to optimize CAR-T therapy, focusing on enhancing durability, managing adverse events, and expanding accessibility. As innovation progresses, CAR-T cell therapy holds immense promise in shaping the future landscape of cancer treatment.

Keyword*: CAR-T cell therapy, Immunotherapy, Cancer treatment, Genetic engineering, Hematologic malignancies.*

Date of Submission: 08-07-2024 Date of Acceptance: 18-07-2024

I. Introduction

What is CAR-T Cell Therapy?

Chimeric Antigen Receptor T-cell (CAR-T) therapy is a type of immunotherapy that involves modifying a patient's T cells (a type of immune cell) to express CARs that can specifically recognize and attack cancer cells. This approach harnesses the body's immune system to fight cancer more effectively.

.

Mechanism

CAR T cell therapy involves several intricate steps to effectively target and eliminate cancer cells: The process involves collecting T cells from a patient, genetically engineering them to express CARs targeting specific cancer antigens, expanding these modified cells in the laboratory, and then infusing them back into the patient. Once administered, CAR-T cells can seek out and destroy cancer cells that express the target antigen.

Significance

CAR-T cell therapy represents a significant advancement in cancer treatment, particularly for hematologic malignancies like certain leukemias and lymphomas that have been resistant to conventional therapies. It has shown remarkable success in inducing long-term remissions in patients who have exhausted other treatment options, offering new hope for effective cancer management.

Objective of the Review

The primary aim of this essay review is to provide a comprehensive overview of CAR-T cell therapy, including its development, mechanism of action, clinical applications, advantages, challenges, and future directions. By synthesizing current research and clinical data, the review aims to inform readers about the state-of-the-art in CAR-T cell therapy and its potential to revolutionize cancer treatment.

Importance of Exploring CAR-T Cell Therapy:

1. **Transformative Potential**: CAR-T cell therapy has shown unprecedented efficacy in treating certain types of cancer, leading to complete remission in patients who had no other treatment options. Understanding this therapy's mechanisms, successes, and limitations is crucial for advancing cancer treatment.
2. **Ongoing Research and Innovation**: CAR-T cell therapy is a rapidly evolving field, with continuous research aimed at improving its safety, expanding its applicability to other types of cancer (including solid tumors), and

overcoming resistance. By exploring CAR-T cell therapy, researchers and clinicians can identify areas for improvement and innovation, ultimately enhancing patient outcomes.

3. **Healthcare Impact**: Given the high costs and resource-intensive nature of CAR-T cell therapy, it is essential to explore its economic and logistical implications. This understanding can help healthcare systems and policymakers develop strategies to make this cutting-edge treatment more accessible and sustainable.
4. **Educational Value**: For medical professionals, researchers, and students, a thorough review of CAR-T cell therapy provides valuable insights into one of the most promising areas of oncology, fostering a deeper understanding of advanced cancer immunotherapies.

II. Overview Of CAR-T Cell Therapy

Mechanism of CAR-T Cells

Chimeric Antigen Receptor (CAR) technology is a groundbreaking advancement in cancer immunotherapy. CARs are synthetic molecules engineered to combine an antigen-binding domain, typically derived from monoclonal antibodies, with T-cell activation domains [1]. This design enables CAR-T cells to recognize and attack cancer cells effectively.

The structure of CARs consists of several key components. The extracellular portion includes a single-chain variable fragment (scFv) derived from the variable regions of antibodies, responsible for recognizing specific antigens on cancer cells. The transmembrane domain anchors the receptor in the T cell membrane. The intracellular signaling domains, often derived from CD3ζ and costimulatory molecules such as CD28 or 4-1BB, initiate T-cell activation upon antigen binding. This modular design allows CARs to be tailored to target a wide range of tumor-associated antigens, providing versatility and specificity in cancer treatment [1].

The process of engineering CAR-T cells involves several crucial steps, starting with the collection of T cells from the patient. These T cells are typically obtained through leukapheresis, a procedure that selectively removes white blood cells from the patient's blood. Once collected, the T cells are genetically modified to express CARs on their surface. This modification is usually achieved using viral vectors, such as lentiviruses or retroviruses, which deliver the CAR gene into the T cells' genome [1].

After the CAR gene is successfully integrated, the modified T cells are expanded in the laboratory to produce sufficient quantities for therapeutic use. This expansion phase ensures that millions of CAR-T cells are available to be infused back into the patient. Before infusion, patients often undergo lymphodepleting chemotherapy to reduce the number of regulatory T cells and other immune cells that might interfere with the efficacy of the CAR-T cells [1].

Once infused into the patient's body, CAR-T cells circulate through the bloodstream, seeking out and binding to target antigens expressed on the surface of cancer cells. This binding triggers the intracellular signaling domains of the CAR, leading to T-cell activation and proliferation. Activated CAR-T cells then execute their cytotoxic function through various mechanisms, including the release of cytotoxic granules containing perforin and granzymes, which induce apoptosis in target cells. Additionally, CAR-T cells secrete pro-inflammatory cytokines, such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), which enhance the immune response against the tumor [2].

One of the critical advantages of CAR-T cell therapy is its ability to mediate MHC-unrestricted tumor cell killing. Unlike conventional T cells, which require major histocompatibility complex (MHC) molecules to present antigens, CAR-T cells recognize antigens directly through their CARs. This MHC-independent recognition allows CAR-T cells to target cancer cells even when these cells have downregulated MHC molecules to evade immune detection [2].

Historical Development

Chimeric Antigen Receptor (CAR) T cell therapy has emerged as a revolutionary approach in cancer treatment, offering new hope to patients with previously incurable malignancies. The journey of CAR-T cell therapy began with the groundbreaking work of Zelig Eshhar in the late 1980s, who pioneered the concept of engineering T cells to express artificial receptors for targeting cancer cells [3]. This initial idea laid the foundation for the development of CAR-T cell therapy, marking the inception of a transformative field in oncology.

In 1993, a significant milestone was achieved with the first clinical trial of CAR-T cell therapy conducted by Dr. Carl June and his team at the University of Pennsylvania [4]. In this trial, autologous T cells engineered to express CARs targeting CD19 were infused into a patient with advanced lymphoma, demonstrating the feasibility of using genetically modified T cells for cancer treatment. This landmark study paved the way for subsequent clinical investigations into CAR-T cell therapy and sparked renewed interest in the field.

However, early trials faced challenges, including limited persistence and efficacy of CAR-T cells [5]. Despite these hurdles, researchers remained undeterred, striving to overcome obstacles and improve the therapeutic potential of CAR-T cell therapy. Over the years, significant advancements have been made, leading to notable milestones in the field.

In 2010, the U.S. Food and Drug Administration (FDA) approved the first CAR-T cell therapy, tisagenlecleucel (Kymriah), for the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL) [6]. This approval marked a historic moment in the development of CAR-T cell therapy, validating its efficacy and safety in a clinical setting. Subsequent approvals followed, including axicabtagene ciloleucel (Yescarta) for certain types of non-Hodgkin lymphoma, further solidifying the role of CAR-T cell therapy in cancer treatment.

The success of CAR-T cell therapy in hematologic malignancies has spurred interest in exploring its potential in solid tumors. While challenges such as tumor heterogeneity and immunosuppressive microenvironments present formidable obstacles, ongoing research efforts aim to address these issues and expand the application of CAR-T cell therapy beyond hematologic cancers [7].

Advances in CAR-T cell manufacturing have also played a crucial role in the evolution of the field. Automation and optimization of production processes have facilitated the scalable and efficient generation of CAR-T cells, enhancing their accessibility and broadening their therapeutic reach [8].

Types of CAR-T Cells

Over the past few decades, the development of CAR-T cells has evolved significantly through several generations, each characterized by specific enhancements aimed at improving their efficacy, persistence, and safety. This essay outlines the different generations of CAR-T cells and their unique characteristics, referencing pivotal studies in the field.

The concept of CAR-T cells emerged in the early 1990s, with the first generation of CARs designed to contain only the CD3ζ signaling domain. This generation, although groundbreaking, exhibited limitations such as suboptimal T cell activation and proliferation, leading to inadequate anti-tumor responses. The simplicity of the first-generation CARs highlighted the need for additional co-stimulatory signals to enhance their therapeutic potential [9].

To address these limitations, second-generation CAR-T cells were developed, incorporating one co-stimulatory domain, typically CD28 or 4-1BB, along with the CD3ζ domain. This addition significantly improved T cell activation, cytokine production, and persistence, resulting in more effective anti-tumor activity. Studies demonstrated that second-generation CAR-T cells exhibited superior proliferation and survival, which translated into enhanced clinical outcomes, particularly in hematologic malignancies [10].

Further advancements led to the development of third-generation CAR-T cells, which included two co-stimulatory domains in conjunction with the CD3ζ domain. This generation aimed to further amplify the activation signals and improve the functionality of CAR-T cells. Research indicated that third-generation CAR-T cells produced higher levels of cytokines and exhibited more robust anti-tumor activity compared to their predecessors. However, the clinical benefits over second-generation CAR-T cells were not as pronounced as initially anticipated [11].

The quest for optimal CAR-T cell therapy continued with the introduction of fourth-generation CAR-T cells, also known as "TRUCKs" (T cells Redirected for Universal Cytokine Killing). These cells are engineered to secrete cytokines upon antigen engagement, thereby recruiting and activating other immune cells in the tumor microenvironment. This approach not only targets the tumor cells directly but also modifies the tumor milieu to support a more comprehensive immune response. Fourth-generation CAR-T cells represent a significant leap in CAR-T cell technology, offering potential advantages in treating solid tumors, which have historically been challenging for CAR-T therapies [12].

Recent research has focused on refining CAR-T cell manufacturing protocols to enrich specific T cell subsets, such as stem cell memory T (T SCM) cells. These subsets are associated with better expansion and persistence, crucial determinants of clinical efficacy. Studies have shown that CAR-T cells derived from T SCM cells exhibit improved long-term survival and potent anti-tumor responses, highlighting the importance of selecting the right T cell subsets for CAR-T cell production [13].

Moreover, innovative strategies are being explored to enhance the safety profile of CAR-T cells. This includes the development of "smart" CARs that can switch on or off in response to specific signals, thereby minimizing the risk of severe toxicities. Additionally, dual CARs or bispecific CARs are designed to recognize multiple tumor antigens simultaneously, reducing the likelihood of tumor escape due to antigen loss [14].

III. Clinical Applications

Types of cancers for which CAR-T cell therapy is currently approved.

CAR-T cell therapy has been approved for use in treating several types of cancers, mainly focusing on hematological malignancies. Here is a list of cancers for which CAR-T cell therapy is currently approved:

Acute Lymphoblastic Leukemia (ALL)

CAR-T cell therapy is approved for pediatric and young adult patients with refractory or relapsed B-cell acute lymphoblastic leukemia (ALL) [15].

Diffuse Large B-Cell Lymphoma (DLBCL)

This therapy is used for adult patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy [15].

Primary Mediastinal Large B-Cell Lymphoma

CAR-T cell therapy is approved for treating primary mediastinal large B-cell lymphoma in relapsed or refractory cases [15].

High-Grade B-Cell Lymphoma

High-grade B-cell lymphoma is another type of cancer treated with CAR-T cell therapies for relapsed or refractory cases [15].

Mantle Cell Lymphoma (MCL)

CAR-T cell therapy is approved for adult patients with relapsed or refractory mantle cell lymphoma [15].

Follicular Lymphoma

CAR-T cell therapy is also used for treating relapsed or refractory follicular lymphoma [15].

Multiple Myeloma

CAR-T cell therapy is used for patients with relapsed or refractory multiple myeloma after multiple prior lines of therapy [15].

IV. FDA-Approved CAR-T Cell Therapies

1. Tisagenlecleucel

Tisagenlecleucel, also known as Kymriah, was the first CAR-T cell therapy approved by the FDA in 2017. It is used to treat pediatric and young adult patients with refractory or relapsed B-cell acute lymphoblastic leukemia (ALL) and adult patients with relapsed or refractory large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma [16].

2. Axicabtagene Ciloleucel

Axicabtagene ciloleucel, marketed as Yescarta, was approved shortly after Tisagenlecleucel in 2017. This therapy is indicated for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. It has shown significant remission rates in patients with DLBCL, primary mediastinal large B-cell lymphoma, and high-grade B-cell lymphoma [17].

3. Brexucabtagene Autoleucel

Brexucabtagene autoleucel, also known as Tecartus, was approved in 2020 for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL). It is the first and only CAR-T cell therapy approved for MCL, providing a new therapeutic option for this aggressive cancer [18].

4. Lisocabtagene Maraleucel

Lisocabtagene maraleucel, known as Breyanzi, received FDA approval in 2021. It is used to treat adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL, high-grade B-cell lymphoma, and primary mediastinal large B-cell lymphoma. Breyanzi has shown promise in delivering durable responses [19].

5. Idecabtagene Vicleucel

Idecabtagene vicleucel, or Abecma, was the first CAR-T cell therapy approved for multiple myeloma in 2021. It is indicated for adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy. This approval marks a significant advancement in the treatment options available for multiple myeloma patients [20].

6. Ciltacabtagene Autoleucel

Ciltacabtagene autoleucel, known as Carvykti, is another CAR-T cell therapy for multiple myeloma, approved in 2022. It is designed for patients who have relapsed or refractory disease after four or more prior lines of therapy, showing high response rates and potential for durable remissions [21].

7. Axicabtagene Ciloleucel for Follicular Lymphoma

In 2021, Axicabtagene ciloleucel was also approved for treating relapsed or refractory follicular lymphoma, marking its versatility in targeting various B-cell malignancies. This approval provides a new therapeutic option for patients with difficult-to-treat follicular lymphoma [18].

8. Tisagenlecleucel for Follicular Lymphoma

Following the success in treating DLBCL and ALL, Tisagenlecleucel received approval in 2022 for relapsed or refractory follicular lymphoma. This expanded the therapeutic reach of Tisagenlecleucel, demonstrating its efficacy in multiple types of B-cell lymphomas [17].

Efficacy in Various Cancer

Acute Lymphoblastic Leukemia (ALL)

Tisagenlecleucel has demonstrated remarkable efficacy in pediatric and young adult patients with relapsed or refractory B-cell Acute Lymphoblastic Leukemia (ALL). The pivotal ELIANA trial reported high remission rates, with a significant overall response rate and a manageable safety profile. This therapy has been more effective than standard chemotherapy in these challenging cases, providing a new lifeline for patients who have exhausted other treatment options [22].

Diffuse Large B-Cell Lymphoma (DLBCL)

Axicabtagene ciloleucel, approved for refractory large B-cell lymphoma, has shown durable responses in patients as evidenced by the ZUMA-1 trial. This therapy achieved a high percentage of complete remissions, demonstrating superior efficacy compared to salvage chemotherapy [23].Similarly, lisocabtagene maraleucel has exhibited significant efficacy in relapsed or refractory large B-cell lymphoma, with clinical trials highlighting its favorable safety profile and superior effectiveness relative to standard salvage chemotherapy [24].

Mantle Cell Lymphoma (MCL)

Brexucabtagene autoleucel has emerged as a highly effective treatment for relapsed or refractory mantle cell lymphoma. Clinical trials have shown high response rates and manageable safety, outperforming previously available treatment options [25].

Multiple Myeloma (MM)

Idecabtagene vicleucel has demonstrated high response rates in heavily pretreated multiple myeloma patients. Clinical trials revealed that this CAR-T therapy is superior to previous standard therapies for relapsed or refractory multiple myeloma, offering hope to patients with limited options [26].

Chronic Lymphocytic Leukemia (CLL)

For chronic lymphocytic leukemia, early-phase trials have indicated promising efficacy and a manageable safety profile for CAR-T therapy in relapsed or refractory cases. The results suggest that CAR-T therapy may be more effective than existing treatments, potentially transforming the treatment paradigm for CLL [27].

Follicular Lymphoma (FL)

Clinical trials have shown that CAR-T therapy provides significant benefits, including high response rates, for patients with follicular lymphoma. This therapy has been found to be more effective than traditional treatments for relapsed or refractory cases, highlighting its potential as a powerful new option in the therapeutic arsenal against FL [28].

Comparative effectiveness with other treatments

When comparing CAR-T therapy with other treatments, several key points emerge. For many hematological malignancies, CAR-T therapies have demonstrated higher response rates and longer durations of remission compared to standard treatments such as chemotherapy and salvage therapy [29,30,31,32,33,34]. The high specificity of CAR-T cells for their target antigens, coupled with their ability to persist and expand within the patient, contributes to their superior efficacy [35].

V. Advantages Of CAR-T Cell Therapy

CAR-T cell therapy represents a groundbreaking approach in cancer treatment, offering several distinct advantages. Firstly, it enables highly targeted treatment by genetically modifying T cells to express chimeric antigen receptors (CARs) that recognize specific tumor antigens, thus minimizing damage to healthy tissues [34].This precision reduces side effects commonly associated with conventional chemotherapy and radiation

therapy. Secondly, CAR-T cells persist in the body after infusion, providing sustained immune surveillance against cancer recurrence [34]. Moreover, CAR-T therapy has shown remarkable efficacy in treating hematologic malignancies like leukemia and lymphoma, where conventional therapies often fail. These advantages highlight CAR-T cell therapy's potential to revolutionize cancer treatment by offering personalized, targeted therapies that enhance patient outcomes while minimizing adverse effects.

Long-term Remission Rates and Survival Benefits of CAR T Cell Therapy

CAR T-cell therapy has demonstrated remarkable efficacy in achieving long-term remission and improving survival outcomes in patients with hematologic malignancies. Studies indicate sustained complete remission rates, reaching up to 90% in certain cohorts treated with anti-CD19 CAR T cells [35]. Prolonged progression-free survival and durable disease control have been consistently observed across clinical trials [36]. These outcomes underscore CAR T-cell therapy's potential to offer lasting benefits by targeting cancer cells specifically while sparing healthy tissues, thus enhancing patient quality of life and extending survival beyond traditional treatment options.

Breakthroughs and advancements in CAR-T cell research.

Recent advancements in CAR-T cell research have yielded significant breakthroughs, enhancing the efficacy and application of this innovative therapy. Notably, CAR-T cells have been engineered to exhibit precise targeting of cancer cells, minimizing harm to healthy tissues and improving treatment outcomes. This specificity is particularly beneficial in hematological malignancies like leukemia and lymphoma, where CAR-T therapies have shown remarkable success [37].

Additionally, CAR-T cells are designed as a "living drug," capable of proliferating and persisting within the patient's body, which ensures sustained cancer surveillance and long-term remission. Recent studies have also highlighted innovations such as universal CAR-T cells, which can potentially treat a broader range of cancers and reduce manufacturing complexities [38]. These advancements represent a significant leap forward in the fight against cancer, promising more effective and durable treatments.

VI. Challenges And Limitations

Side Effects and Toxicities of CAR-T cell therapy

CAR-T cell therapy, a groundbreaking treatment for certain cancers, has shown significant promise but is not without side effects and toxicities. The most common adverse effects include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) [39]. CRS, characterized by a severe inflammatory response, and ICANS, involving neurological symptoms, present substantial challenges in treatment management [40]. Long-term outcomes of CAR-T cell therapy also highlight persistent toxicities such as cytopenias and hypogammaglobulinemia, which can lead to increased infection risks and prolonged recovery periods [41].

Gastrointestinal adverse events are also notable, affecting patients' quality of life post-treatment [42]. Additionally, cardiovascular toxicities and hematologic toxicities, including prolonged cytopenias, are significant concerns [43]. Infection risks remain high due to immune suppression, necessitating vigilant monitoring and management [44]. Despite these challenges, understanding and mitigating these toxicities are crucial for improving the safety and efficacy of CAR-T cell therapy in clinical practice.

Challenges in making the therapy widely accessible.

CAR-T cell therapy, a groundbreaking cancer treatment, faces significant challenges due to its high costs, impacting healthcare systems and accessibility. The therapy's expense often exceeds $400,000, driven by the intricate and personalized production process, which involves extensive laboratory and clinical resources [45,46]. These high costs create substantial financial burdens for patients, insurers, and healthcare providers, limiting the widespread adoption of this promising treatment.

Additionally, logistical and economic barriers further hinder accessibility. Patients in rural or low-resource settings struggle with limited access to specialized treatment centers and the necessary follow-up care [45].The stringent regulatory requirements for CAR-T cell therapy also constrain its availability, preventing broader patient populations from benefiting [45,46].

Efforts to address these challenges include optimizing production processes to reduce costs, improving insurance coverage, and developing universal CAR-T cells for more efficient and affordable production. Overcoming these hurdles is crucial to making CAR-T cell therapy a viable and accessible option for all patients in need [45,46].

Mechanisms of resistance to CAR-T cell therapy.

CAR-T cell therapy has shown remarkable success in treating various malignancies, but resistance remains a significant challenge. Primary resistance occurs when cancer cells evade initial CAR-T therapy, while secondary resistance involves relapse after an initial response. Mechanisms of resistance include antigen loss, tumor microenvironment factors, and CAR-T cell exhaustion [47].

Antigen loss, where cancer cells downregulate or mutate the target antigen, is a major hurdle. Researchers are developing dual-targeting CAR-T cells that can recognize multiple antigens to address this issue [48].The immunosuppressive tumor microenvironment, characterized by regulatory T cells, myeloid-derived suppressor cells, and cytokines, also hinders CAR-T cell efficacy. Strategies to modulate this environment include combining CAR-T cells with immune checkpoint inhibitors or using genetically modified CAR-T cells to secrete cytokines that counteract suppression [49].

CAR-T cell exhaustion, a state of functional decline due to chronic antigen exposure, is another significant resistance mechanism. Enhancing CAR-T cell persistence and function through genetic modifications and optimizing the CAR structure are ongoing research areas. This includes using costimulatory domains and modifying CAR signaling pathways to prevent exhaustion [50].

VII. Future Directions And Research

Next-Generation CAR-T Cells - Developments in enhancing CAR-T cell efficacy and safety.

Next-generation CAR-T cell therapies represent a promising frontier in cancer treatment, focusing on enhancing therapeutic outcomes and broadening applicability. Recent advancements leverage gene engineering and synthetic biology to augment CAR-T cell functionality and durability within the patient's system [51]. Innovations include targeting new antigens and refining manufacturing processes to improve treatment efficacy while minimizing adverse effects [52]. These developments aim to overcome current limitations, such as tumor antigen escape and treatment-related toxicities, by integrating novel technologies that enhance specificity and persistence. As clinical trials continue to evaluate these next-generation therapies [53], the future holds promise for personalized and more effective treatments against various malignancies.

Exploring the synergy between CAR-T cells and other cancer treatments (e.g., checkpoint inhibitors).

The integration of CAR-T cell therapy with checkpoint inhibitors represents a promising strategy in cancer treatment. CAR-T cells enhance targeted tumor cell killing, while checkpoint inhibitors like PD-1 and CTLA-4 blockers prevent immune evasion mechanisms. Studies emphasize their combined potential in improving therapeutic outcomes across various cancers [54,55]. This synergistic approach aims to bolster immune responses, extending durability and efficacy beyond conventional treatments. Ongoing research focuses on optimizing combination dosing and managing immune-related adverse events to maximize clinical benefit.

Tailoring CAR-T cell therapy to individual patient profiles and genetic backgrounds.

CAR-T cell therapy is evolving towards personalized medicine, aiming to optimize treatment outcomes by tailoring therapies to individual patient profiles and genetic backgrounds. This approach integrates genetic profiling to enhance CAR-T cell efficacy and safety. By identifying specific biomarkers and genetic variations influencing therapy response and toxicity [56], personalized CAR-T strategies strive to minimize adverse effects and improve patient survival rates [57].

Advancements in genetic sequencing and bioinformatics enable precise targeting of cancer cells while sparing normal tissues [58]. Research focuses on optimizing CAR-T cell design and delivery mechanisms, exploring novel technologies to enhance specificity and persistence in diverse patient populations [59]. This personalized approach holds promise for transforming cancer treatment paradigms, moving towards more effective and tailored therapies.

VIII. Conclusion

CAR-T cell therapy stands at the forefront of modern oncology, offering groundbreaking treatment possibilities that significantly diverge from conventional therapeutic approaches. Its capacity to achieve high response rates and durable remissions in patients with relapsed or refractory hematologic malignancies illustrates its profound clinical impact. The tailored nature of CAR-T therapy, driven by sophisticated genetic engineering and precise antigen targeting, exemplifies a shift towards more personalized and effective cancer treatments.

Despite its remarkable success, challenges remain, particularly in optimizing the therapy's durability, managing adverse effects, and expanding its application to solid tumors. Ongoing research is pivotal in addressing these challenges and enhancing the overall efficacy and safety of CAR-T cell therapy. As we continue to refine these therapies and broaden their accessibility, the promise of CAR-T cell therapy becomes increasingly evident.

In conclusion, CAR-T cell therapy not only transforms the treatment landscape for hematologic cancers but also paves the way for future innovations in oncology. Its potential to extend beyond hematologic

malignancies and offer solutions where traditional therapies have failed underscores its critical role in shaping the future of cancer treatment. Through sustained research and development, CAR-T cell therapy is poised to redefine our approach to combating cancer, heralding a new era of targeted and personalized medicine.

References

[1]. Feins S, Kong W, Williams Ef, Milone Mc, Fraietta Ja. An Introduction To Chimeric Antigen Receptor (Car) T-Cell Immunotherapy For Human Cancer. Am J Hematol. 2019 May;94(S1):S3-S9. Doi: 10.1002/Ajh.25418. Epub 2019 Feb 18. Pmid: 30680780..

[2]. Benmebarek Mr, Karches Ch, Cadilha Bl, Lesch S, Endres S, Kobold S. Killing Mechanisms Of Chimeric Antigen Receptor (Car) T Cells. Int J Mol Sci. 2019 Mar 14;20(6):1283. Doi: 10.3390/Ijms20061283. Pmid: 30875739; Pmcid: Pmc6470706.

[3]. Mitra A, Barua A, Huang L, Ganguly S, Feng Q, He B. From Bench To Bedside: The History And Progress Of Car T Cell Therapy. Front Immunol. 2023 May 15;14:1188049. Doi: 10.3389/Fimmu.2023.1188049. Pmid: 37256141; Pmcid: Pmc10225594.

[4]. Mitra A, Barua A, Huang L, Ganguly S, Feng Q, He B. From Bench To Bedside: The History And Progress Of Car T Cell Therapy. Front Immunol. 2023 May 15;14:1188049. Doi: 10.3389/Fimmu.2023.1188049. Pmid: 37256141; Pmcid: Pmc10225594.

[5]. Uscanga-Palomeque Ac, Chávez-Escamilla Ak, Alvizo-Báez Ca, Saavedra-Alonso S, Terrazas-Armendáriz Ld, Tamez-Guerra Rs, Rodríguez-Padilla C, Alcocer-González Jm. Car-T Cell Therapy: From The Shop To Cancer Therapy. Int J Mol Sci. 2023 Oct 28;24(21):15688. Doi: 10.3390/Ijms242115688. Pmid: 37958672; Pmcid: Pmc10649325.

[6]. Zhang X, Li Jj, Lu Ph. Advances In The Development Of Chimeric Antigen Receptor-T-Cell Therapy In B-Cell Acute Lymphoblastic Leukemia. Chin Med J (Engl). 2020 Feb 20;133(4):474-482. Doi: 10.1097/Cm9.0000000000000638. Pmid: 31977556; Pmcid: Pmc7046249.

[7]. Dana H, Chalbatani Gm, Jalali Sa, Mirzaei Hr, Grupp Sa, Suarez Er, Rapôso C, Webster Tj. Car-T Cells: Early Successes In Blood Cancer And Challenges In Solid Tumors. Acta Pharm Sin B. 2021 May;11(5):1129-1147. Doi: 10.1016/J.Apsb.2020.10.020. Epub 2020 Nov 2. Pmid: 34094824; Pmcid: Pmc8144892.

[8]. Miliotou An, Papadopoulou Lc. Car T-Cell Therapy: A New Era In Cancer Immunotherapy. Curr Pharm Biotechnol. 2018;19(1):5-18. Doi: 10.2174/1389201019666180418095526. Pmid: 29667553..

[9]. Mitra A, Barua A, Huang L, Ganguly S, Feng Q, He B. From Bench To Bedside: The History And Progress Of Car T Cell Therapy. Front Immunol. 2023 May 15;14:1188049. Doi: 10.3389/Fimmu.2023.1188049. Pmid: 37256141; Pmcid: Pmc10225594.

[10]. Yekehfallah V, Karimipoor M, Falak R, Hosseini Es, Abbaszadegan Mr, Sharifzadeh S, Forouzandeh Moghadam M. Generation And Functional Characterization Of Plap Car-T Cells: Implications For Adoptive Cell Therapy. Cancers (Basel). 2022 Sep 22;14(19):4717. Doi: 10.3390/Cancers14194717. Pmid: 36139135; Pmcid: Pmc9527644.

[11]. Petersen Ct, Krenciute G. Next Generation Car T Cells For The Immunotherapy Of Hematologic Malignancies. Cancers (Basel). 2019 Mar 11;11(3):289. Doi: 10.3390/Cancers11030289. Pmid: 30863720; Pmcid: Pmc6468968.

[12]. Arcangeli S, Bardelli M, Rotiroti Mc, Simonelli L, Magnani Cf, Biondi A, Biagi E. Next-Generation Manufacturing Protocols Enriching T Scm Car T Cells Can Overcome Disease-Specific T Cell Defects In Pediatric And Adult Patients With B-Cell Acute Lymphoblastic Leukemia. Cancers (Basel). 2020 Jul 2;12(7):1810. Doi: 10.3390/Cancers12071810. Pmid: 32636841; Pmcid: Pmc7408578.

[13]. Tomasik J, Biernacka A, Fiutak K, Wilk M, Knyszynski A, Rzepecki P, Knyszynski A. Next Generations Of Car-T Cells - New Therapeutic Opportunities Beyond Oncology. Acta Biochim Pol. 2022;69(4):849-860. Doi: 10.18388/Abp.2020_5651. Pmid: 36389658.

[14]. Chen L, Flies Db. Car-T Cell Therapy For Lung Cancer: Potential And Perspective. Thorac Cancer. 2022 Mar;13(6):799-810. Doi: 10.1111/1759-7714.14327. Pmid: 35289077.

[15]. Mitra A, Barua A, Huang L, Ganguly S, Feng Q, He B. From Bench To Bedside: The History And Progress Of Car T Cell Therapy. Front Immunol. 2023 May 15;14:1188049. Doi: 10.3389/Fimmu.2023.1188049. Pmid: 37256141; Pmcid: Pmc10225594.

[16]. Ahmad A, Uddin S, Steinhoff M. Car-T Cell Therapies: An Overview Of Clinical Studies Supporting Their Approved Use Against Acute Lymphoblastic Leukemia And Large B-Cell Lymphomas. Int J Mol Sci. 2020 May 30;21(11):3906. Doi: 10.3390/Ijms21113906. Pmid: 32486160; Pmcid: Pmc7312930.

[17]. Chen Yj, Abila B, Mostafa Kamel Y. Car-T: What Is Next? Cancers (Basel). 2023 Jan 21;15(3):663. Doi: 10.3390/Cancers15030663. Pmid: 36765623; Pmcid: Pmc9913679.

[18]. Sengsayadeth S, Savani Bn, Oluwole O, Dholaria B. Overview Of Approved Car-T Therapies, Ongoing Clinical Trials, And Its Impact On Clinical Practice. Ejhaem. 2021 Nov 24;3(Suppl 1):6-10. Doi: 10.1002/Jha2.338. Pmid: 35844299; Pmcid: Pmc9175669.

[19]. Wang Jy, Wang L. Car-T Cell Therapy: Where Are We Now, And Where Are We Heading? Blood Sci. 2023 Nov 2;5(4):237-248. Doi: 10.1097/Bs9.0000000000000173. Pmid: 37941917; Pmcid: Pmc10629745.

[20]. Ahmad A, Uddin S, Steinhoff M. Car-T Cell Therapies: An Overview Of Clinical Studies Supporting Their Approved Use Against Acute Lymphoblastic Leukemia And Large B-Cell Lymphomas. Int J Mol Sci. 2020 May 30;21(11):3906. Doi: 10.3390/Ijms21113906. Pmid: 32486160; Pmcid: Pmc7312930.

[21]. Wang V, Gauthier M, Decot V, Reppel L, Bensoussan D. Systematic Review On Car-T Cell Clinical Trials Up To 2022: Academic Center Input. Cancers (Basel). 2023 Feb 4;15(4):1003. Doi: 10.3390/Cancers15041003. Pmid: 36831349; Pmcid: Pmc9954171.

[22]. Maude Sl, Laetsch Tw, Buechner J, Rives S, Boyer M, Bittencourt H, Bader P, Verneris Mr, Stefanski He, Myers Gd, Qayed M, De Moerloose B, Hiramatsu H, Schlis K, Davis Kl, Martin Pl, Nemecek Er, Yanik Ga, Peters C, Baruchel A, Boissel N, Mechinaud F, Balduzzi A, Krueger J, June Ch, Levine Bl, Wood P, Taran T, Leung M, Mueller Kt, Zhang Y, Sen K, Lebwohl D, Pulsipher Ma, Grupp Sa. Tisagenlecleucel In Children And Young Adults With B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018 Feb 1;378(5):439-448. Doi: 10.1056/Nejmoa1709866. Pmid: 29385370; Pmcid: Pmc5996391.

[23]. Jallouk Ap, Gouni S, Westin J, Feng L, Mistry H, Steiner Re, James J, Noorani M, Horowitz S, Puebla-Osorio N, Fayad Le, Iyer Sp, Hawkins M, Flowers Cr, Ahmed S, Nastoupil Lj, Kebriaei P, Shpall Ej, Neelapu Ss, Nieto Y, Strati P. Axicabtagene Ciloleucel In Relapsed Or Refractory Large B-Cell Lymphoma Patients In Complete Metabolic Response. Haematologica. 2023 Apr 1;108(4):1163-1167. Doi: 10.3324/Haematol.2022.281954. Pmid: 36384251; Pmcid: Pmc10071112.

[24]. Mohty R, Moreno Vanegas Y, Chavez Jc, Kharfan-Dabaja Ma. Lisocabtagene Maraleucel For Relapsed Or Refractory Large B-Cell Non-Hodgkin Lymphoma. Expert Rev Anticancer Ther. 2023 Feb;23(2):121-126. Doi: 10.1080/14737140.2023.2171397. Epub 2023 Jan 24. Pmid: 36662602.

[25]. Mian A, Hill Bt. Brexucabtagene Autoleucel For The Treatment Of Relapsed/Refractory Mantle Cell Lymphoma. Expert Opin Biol Ther. 2021 Apr;21(4):435-441. Doi: 10.1080/14712598.2021.1889510. Epub 2021 Mar 11. Pmid: 33566715.

[26]. Munshi Nc, Anderson Ld Jr, Shah N, Madduri D, Berdeja J, Lonial S, Raje N, Lin Y, Siegel D, Oriol A, Moreau P, Yakoub-Agha I, Delforge M, Cavo M, Einsele H, Goldschmidt H, Weisel K, Rambaldi A, Reece D, Petrocca F, Massaro M, Connarn Jn, Kaiser S,

Patel P, Huang L, Campbell Tb, Hege K, San-Miguel J. Idecabtagene Vicleucel In Relapsed And Refractory Multiple Myeloma. N Engl J Med. 2021 Feb 25;384(8):705-716. Doi: 10.1056/Nejmoa2024850. Pmid: 33626253.

[27]. Todorovic Z, Todorovic D, Markovic V, Ladjevac N, Zdravkovic N, Djurdjevic P, Arsenijevic N, Milovanovic M, Arsenijevic A, Milovanovic J. Car T Cell Therapy For Chronic Lymphocytic Leukemia: Successes And Shortcomings. Curr Oncol. 2022 May 18;29(5):3647-3657. Doi: 10.3390/Curroncol29050293. Pmid: 35621683; Pmcid: Pmc9139644.

[28]. S. Nastoupil Et Al., "Car-T Therapy In Relapsed Follicular Lymphoma," J. Clin. Oncol., Vol. 38, No. 15, Pp. 1572-1582, 2020. [Online]. Available: Https://Pubmed.Ncbi.Nlm.Nih.Gov/31743215/.

[29]. Mohty R, Moreno Vanegas Y, Chavez Jc, Kharfan-Dabaja Ma. Lisocabtagene Maraleucel For Relapsed Or Refractory Large B-Cell Non-Hodgkin Lymphoma. Expert Rev Anticancer Ther. 2023 Feb;23(2):121-126. Doi: 10.1080/14737140.2023.2171397. Epub 2023 Jan 24. Pmid: 36662602.

[30]. Jallouk Ap, Gouni S, Westin J, Feng L, Mistry H, Steiner Re, James J, Noorani M, Horowitz S, Puebla-Osorio N, Fayad Le, Iyer Sp, Hawkins M, Flowers Cr, Ahmed S, Nastoupil Lj, Kebriaei P, Shpall Ej, Neelapu Ss, Nieto Y, Strati P. Axicabtagene Ciloleucel In Relapsed Or Refractory Large B-Cell Lymphoma Patients In Complete Metabolic Response. Haematologica. 2023 Apr 1;108(4):1163-1167. Doi: 10.3324/Haematol.2022.281954. Pmid: 36384251; Pmcid: Pmc10071112.

[31]. Mian A, Hill Bt. Brexucabtagene Autoleucel For The Treatment Of Relapsed/Refractory Mantle Cell Lymphoma. Expert Opin Biol Ther. 2021 Apr;21(4):435-441. Doi: 10.1080/14712598.2021.1889510. Epub 2021 Mar 11. Pmid: 33566715.

[32]. Wang Y, Jain P, Locke Fl, Maurer Mj, Frank Mj, Munoz Jl, Dahiya S, Beitinjaneh Am, Jacobs Mt, Mcguirk Jp, Vose Jm, Goy A, Andreadis C, Hill Bt, Dorritie Ka, Oluwole Oo, Deol A, Paludo J, Shah B, Wang T, Banerjee R, Miklos Db, Rapoport Ap, Lekakis L, Ghobadi A, Neelapu [5] Ss, Lin Y, Wang Ml, Jain Md. Brexucabtagene Autoleucel For Relapsed Or Refractory Mantle Cell Lymphoma In Standard-Of-Care Practice: Results From The Us Lymphoma Car T Consortium. J Clin Oncol. 2023 May 10;41(14):2594-2606. Doi: 10.1200/Jco.22.01797. Epub 2023 Feb 8. Pmid: 36753699; Pmcid: Pmc10489553.

[33]. Munshi Nc, Anderson Ld Jr, Shah N, Madduri D, Berdeja J, Lonial S, Raje N, Lin Y, Siegel D, Oriol A, Moreau P, Yakoub-Agha I, Delforge M, Cavo M, Einsele H, Goldschmidt H, Weisel K, Rambaldi A, Reece D, Petrocca F, Massaro M, Connarn Jn, Kaiser S, Patel P, Huang L, Campbell Tb, Hege K, San-Miguel J. Idecabtagene Vicleucel In Relapsed And Refractory Multiple Myeloma. N Engl J Med. 2021 Feb 25;384(8):705-716. Doi: 10.1056/Nejmoa2024850. Pmid: 33626253.

[34]. Jogalekar Mp, Rajendran Rl, Khan F, Dmello C, Gangadaran P, Ahn Bc. Car T-Cell-Based Gene Therapy For Cancers: New Perspectives, Challenges, And Clinical Developments. Front Immunol. 2022 Jul 22;13:925985. Doi: 10.3389/Fimmu.2022.925985. Pmid: 35936003; Pmcid: Pmc9355792.

[35]. Cappell Km, Sherry Rm, Yang Jc, Goff Sl, Vanasse Da, Mcintyre L, Rosenberg Sa, Kochenderfer Jn. Long-Term Follow-Up Of Anti-Cd19 Chimeric Antigen Receptor T-Cell Therapy. J Clin Oncol. 2020 Nov 10;38(32):3805-3815. Doi: 10.1200/Jco.20.01467. Epub 2020 Oct 6. Pmid: 33021872; Pmcid: Pmc7655016.

[36]. Mi Jq, Zhao Wh, Chen Lj, Fu W, Wang By, Xu J, Liu J, Jin Sw, Zhu H, Du J, Jiang H, Sun H, Jia Y, Fan Xh, Li Jy, Hou J, Chen Z, Zhang Wg, He Al, Chen Sj. P874: Long-Term Remission And Survival In Patients With Relapsed Or Refractory Multiple Myeloma After Treatment Of Lcar-B38m Car-T – At Least 5-Year Follow-Up In Legend-2. Hemasphere. 2023 Aug 8;7(Suppl):E9841889. Doi: 10.1097/01.Hs9.0000970400.98418.89. Pmcid: Pmc10431000.

[37]. De Marco Rc, Monzo Hj, Ojala Pm. Car T Cell Therapy: A Versatile Living Drug. Int J Mol Sci. 2023 Mar 27;24(7):6300. Doi: 10.3390/Ijms24076300. Pmid: 37047272; Pmcid: Pmc10094630.

[38]. Lin H, Cheng J, Mu W, Zhou J, Zhu L. Advances In Universal Car-T Cell Therapy. Front Immunol. 2021 Oct 6;12:744823. Doi: 10.3389/Fimmu.2021.744823. Pmid: 34691052; Pmcid: Pmc8526896.

[39]. Chohan Kl, Siegler El, Kenderian Ss. Car-T Cell Therapy: The Efficacy And Toxicity Balance. Curr Hematol Malig Rep. 2023 Apr;18(2):9-18. Doi: 10.1007/S11899-023-00687-7. Epub 2023 Feb 10. Pmid: 36763238; Pmcid: Pmc10505056.

[40]. Shaikh S, Shaikh H. Cart Cell Therapy Toxicity. [Updated 2023 Apr 19]. In: Statpearls [Internet]. Treasure Island (Fl): Statpearls Publishing; 2024 Jan-. Available From: Https://Www.Ncbi.Nlm.Nih.Gov/Books/Nbk592426/

[41]. Cappell, K.M., Kochenderfer, J.N. Long-Term Outcomes Following Car T Cell Therapy: What We Know So Far. Nat Rev Clin Oncol 20, 359–371 (2023). Https://Doi.Org/10.1038/S41571-023-00754-1

[42]. Abu-Sbeih H, Tang T, Ali Fs, Luo W, Neelapu Ss, Westin Jr, Okhuysen Pc, Foo Wc, Curry Jl, Richards Dm, Ge Ps, Wang Y. Gastrointestinal Adverse Events Observed After Chimeric Antigen Receptor T-Cell Therapy. Am J Clin Oncol. 2019 Oct;42(10):789-796. Doi: 10.1097/Coc.0000000000000596. Pmid: 31478934.

[43]. Patel Np, Doukas Pg, Gordon Li, Akhter N. Cardiovascular Toxicities Of Car T-Cell Therapy. Curr Oncol Rep. 2021 May 3;23(7):78. Doi: 10.1007/S11912-021-01068-0. Pmid: 33937946.

[44]. Stewart Ag, Henden As. Infectious Complications Of Car T-Cell Therapy: A Clinical Update. Ther Adv Infect Dis. 2021 Aug 24;8:20499361211036773. Doi: 10.1177/20499361211036773. Pmid: 34457269; Pmcid: Pmc8388233.

[45]. Edward R. Scheffer Cliff Et Al., High Cost Of Chimeric Antigen Receptor T-Cells: Challenges And Solutions. Am Soc Clin Oncol Educ Book 43, E397912(2023).
Doi:10.1200/Edbk_397912

[46]. Gajra A, Zalenski A, Sannareddy A, Jeune-Smith Y, Kapinos K, Kansagra A. Barriers To Chimeric Antigen Receptor T-Cell (Car-T) Therapies In Clinical Practice. Pharmaceut Med. 2022 Jun;36(3):163-171. Doi: 10.1007/S40290-022-00428-W. Epub 2022 Jun 7. Pmid: 35672571; Pmcid: Pmc9217916.

[47]. Shah Nn, Fry Tj. Mechanisms Of Resistance To Car T Cell Therapy. Nat Rev Clin Oncol. 2019 Jun;16(6):372-385. Doi: 10.1038/S41571-019-0184-6. Pmid: 30837712; Pmcid: Pmc8214555.

[48]. Rejeski K, Jain Md, Smith El. Mechanisms Of Resistance And Treatment Of Relapse After Car T-Cell Therapy For Large B-Cell Lymphoma And Multiple Myeloma. Transplant Cell Ther. 2023 Jul;29(7):418-428. Doi: 10.1016/J.Jtct.2023.04.007. Epub 2023 Apr 17. Pmid: 37076102; Pmcid: Pmc10330792.

[49]. Ruella M, Korell F, Porazzi P, Maus Mv. Mechanisms Of Resistance To Chimeric Antigen Receptor-T Cells In Haematological Malignancies. Nat Rev Drug Discov. 2023 Dec;22(12):976-995. Doi: 10.1038/S41573-023-00807-1. Epub 2023 Oct 31. Pmid: 37907724; Pmcid: Pmc10965011.

[50]. Edward R. Scheffer Cliff Et Al., High Cost Of Chimeric Antigen Receptor T-Cells: Challenges And Solutions. Am Soc Clin Oncol Educ Book 43, E397912(2023).
Doi:10.1200/Edbk_397912

[51]. Young Rm, Engel Nw, Uslu U, Wellhausen N, June Ch. Next-Generation Car T-Cell Therapies. Cancer Discov. 2022 Jul 6;12(7):1625-1633. Doi: 10.1158/2159-8290.Cd-21-1683. Pmid: 35417527; Pmcid: Pmc9262817.

[52]. Freitag F, Maucher M, Riester Z, Hudecek M. New Targets And Technologies For Car-T Cells. Curr Opin Oncol. 2020 Sep;32(5):510-517. Doi: 10.1097/Cco.0000000000000653. Pmid: 32657796.

[53]. Tomasik J, Jasiński M, Basak Gw. Next Generations Of Car-T Cells - New Therapeutic Opportunities In Hematology? Front Immunol. 2022 Oct 28;13:1034707. Doi: 10.3389/Fimmu.2022.1034707. Pmid: 36389658; Pmcid: Pmc9650233.
[54]. Grosser R, Cherkassky L, Chintala N, Adusumilli Ps. Combination Immunotherapy With Car T Cells And Checkpoint Blockade For The Treatment Of Solid Tumors. Cancer Cell. 2019 Nov 11;36(5):471-482. Doi: 10.1016/J.Ccell.2019.09.006. Pmid: 31715131; Pmcid: Pmc7171534.
[55]. Lv Y, Luo X, Xie Z, Qiu J, Yang J, Deng Y, Long R, Tang G, Zhang C, Zuo J. Prospects And Challenges Of Car-T Cell Therapy Combined With Icis. Front Oncol. 2024 Mar 20;14:1368732. Doi: 10.3389/Fonc.2024.1368732. Pmid: 38571495; Pmcid: Pmc10989075.
[56]. Messmer As, Que Ya, Schankin C, Banz Y, Bacher U, Novak U, Pabst T. Car T-Cell Therapy And Critical Care : A Survival Guide For Medical Emergency Teams. Wien Klin Wochenschr. 2021 Dec;133(23-24):1318-1325. Doi: 10.1007/S00508-021-01948-2. Epub 2021 Oct 6. Pmid: 34613477; Pmcid: Pmc8671280.
[57]. Fujiwara Y, Kato T, Hasegawa F, Sunahara M, Tsurumaki Y. The Past, Present, And Future Of Clinically Applied Chimeric Antigen Receptor-T-Cell Therapy. Pharmaceuticals (Basel). 2022 Feb 9;15(2):207. Doi: 10.3390/Ph15020207. Pmid: 35215319; Pmcid: Pmc8876595.
[58]. Neelapu Ss, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke Fl, Komanduri Kv, Lin Y, Jain N, Daver N, Westin J, Gulbis Am, Loghin Me, De Groot Jf, Adkins S, Davis Se, Rezvani K, Hwu P, Shpall Ej. Chimeric Antigen Receptor T-Cell Therapy - Assessment And Management Of Toxicities. Nat Rev Clin Oncol. 2018 Jan;15(1):47-62. Doi: 10.1038/Nrclinonc.2017.148. Epub 2017 Sep 19. Pmid: 28925994; Pmcid: Pmc6733403.
[59]. Frigault Mj, Maus Mv. State Of The Art In Car T Cell Therapy For Cd19+ B Cell Malignancies. J Clin Invest. 2020 Apr 1;130(4):1586-1594. Doi: 10.1172/Jci129208. Pmid: 32235098; Pmcid: Pmc7108913.