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CAR-T THERAPY: MECHANISMS OF ACTION, CLINICAL APPLICATIONS AND FUTURE DIRECTIONS

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ABSTRACT

Chimeric antigen receptor T-cell (CAR-T) therapy represents a major advancement in cancer immunotherapy, introducing a novel therapeutic approach based on the genetic modification of T lymphocytes to enhance tumor-specific cytotoxicity. This strategy has significantly transformed the treatment landscape, particularly in hematologic malignancies. The aim of this review is to summarize the current state of knowledge regarding CAR-T therapy, including its mechanisms of action, clinical applications, toxicity profile, limitations, and future directions of development. A narrative review of the literature was conducted based on selected publications indexed in biomedical databases, with particular emphasis on recent advances in both hematologic and solid tumors. CAR-T therapy has demonstrated high clinical efficacy in hematologic malignancies, especially B-cell cancers such as acute lymphoblastic leukemia and multiple myeloma, achieving substantial response rates in patients with relapsed or refractory disease. In contrast, its application in solid tumors remains limited due to challenges including antigen heterogeneity, an immunosuppressive tumor microenvironment, and reduced T-cell infiltration. The therapy is associated with characteristic toxicities, most notably cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, which require careful monitoring and management. Furthermore, its broader implementation is constrained by complex manufacturing processes, high costs, and limited accessibility. Ongoing research focuses on improving CAR-T cell persistence, overcoming T-cell exhaustion, optimizing antigen targeting, and developing novel strategies such as allogeneic products and combination therapies. In conclusion, CAR-T therapy constitutes a transformative modality in modern oncology, with established efficacy in hematologic malignancies and emerging potential in solid tumors, and its continued development is expected to further expand its clinical utility.

KEYWORDS

CAR-T Cells, Immunotherapy, Hematologic Malignancies, Solid Tumors, Cytokine Release Syndrome, Cancer Therapy

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1. Introduction

Cancer immunotherapy represents one of the most dynamically developing fields of modern oncology, leading to a significant shift in the paradigm of cancer treatment. In contrast to conventional methods such as chemotherapy and radiotherapy, immunotherapeutic strategies harness the natural mechanisms of the immune system to recognize and eliminate cancer cells. In recent years, substantial progress has been achieved in this field, including the development of monoclonal antibodies, immune checkpoint inhibitors, and advanced cellular therapies [1].

A particularly important place among modern therapeutic approaches is occupied by genetically modified T-cell therapy, known as CAR-T (chimeric antigen receptor T-cell therapy). This technology involves the engineering of autologous T lymphocytes to express synthetic receptors capable of specifically recognizing tumor-associated antigens, enabling precise elimination of cancer cells. CAR-T therapy has demonstrated high clinical efficacy, particularly in hematologic malignancies, leading in many cases to long-term remissions in patients resistant to standard treatment.

Despite these remarkable successes, the application of CAR-T therapy is associated with several limitations, including high production costs, the complexity of the ex vivo manufacturing process, the risk of severe adverse effects, and limited efficacy in solid tumors. In response to these challenges, novel strategies aimed at optimizing this therapy are being intensively developed, including the use of nanotechnology and alternative gene delivery systems.

Approaches based on lipid nanoparticles (LNPs) are gaining particular importance, as they enable efficient and safe delivery of nucleic acids to target cells. These technologies, widely used for example in mRNA vaccines, show significant potential to improve CAR-T therapy by enhancing its safety, scalability,

and accessibility [2; 3]. Importantly, lipid nanoparticles enable the development of in vivo CAR-T therapy, in which T-cell modification occurs directly within the patient's body, eliminating the need for complex ex vivo cell culture.

The development of in vivo CAR-T therapy represents one of the most promising directions in contemporary cellular immunotherapy, with the potential to overcome current technological and economic barriers. Novel immune cell engineering strategies based on precise gene delivery open the way toward more accessible, safer, and more effective anticancer therapies [4]

This paper presents the current state of knowledge on CAR-T therapy, with particular emphasis on its mechanisms of action, clinical applications, limitations, and future directions of development, including innovative strategies based on nanotechnology and in vivo approaches.

2. Review Methodology

This study constitutes a narrative review aimed at analyzing the current state of knowledge on CAR-T cell therapy, with particular emphasis on its mechanisms of action, clinical applications, limitations, and future directions.

Data sources

The literature review was conducted using the PubMed database, one of the most comprehensive and reliable sources of biomedical publications. The search included original research articles, review papers, and clinical studies related to CAR-T cell therapy.

Search strategy

The search process employed combinations of keywords such as *CAR-T cell therapy*, *immunotherapy*, *hematologic malignancies*, *solid tumors*, *toxicity*, *cytokine release syndrome*, *neurotoxicity*, *clinical applications*, and *future directions*. Boolean operators (AND, OR) were used to refine and optimize the search results.

Inclusion criteria

The following criteria were applied for article selection:

- publications from the years 2020–2026,
- articles published in English,
- studies with free full-text availability,
- publications addressing CAR-T cell therapy in the context of mechanisms of action, clinical applications, toxicity, limitations, and future perspectives.

Exclusion criteria

The following were excluded from the review:

- publications published before 2020 (except for seminal studies necessary for contextual background),
- articles without full-text access,
- publications in languages other than English,
- studies not directly related to CAR-T cell therapy.

Study selection proces

Initial screening was based on titles and abstracts. Subsequently, full-text articles meeting the inclusion criteria were thoroughly evaluated. The final selection included the most relevant and up-to-date studies providing significant scientific and clinical insights into CAR-T cell therapy.

3. Methodological limitations

It should be noted that this is a narrative review, which may involve a degree of subjectivity in the selection of literature. Additionally, restricting the search to a single database (PubMed) and to English-language publications may limit the comprehensiveness of the included data. Nevertheless, the applied criteria allowed for the identification of a representative and current body of evidence on the topic.

3.1 Manufacturing Method and Mechanism of CAR-T Therapy

CAR-T (chimeric antigen receptor T-cell) therapy represents an advanced form of adoptive immunotherapy based on the genetic modification of a patient's T lymphocytes to confer the ability to specifically recognize and eliminate cancer cells. The manufacturing process is multi-step and includes both ex vivo cellular manipulation and subsequent in vivo effector activity following administration.

3.2 Manufacturing of CAR-T Cells

The production of CAR-T cells begins with the isolation of T lymphocytes from the patient's peripheral blood, most commonly using leukapheresis. These cells are then genetically modified, typically באמצעות viral vectors (e.g., lentiviral vectors), to introduce a gene encoding the chimeric antigen receptor (CAR). Following transduction, the modified T cells are expanded under controlled laboratory conditions and subsequently infused back into the patient [5]

The CAR receptor has a modular structure consisting of an extracellular antigen-recognition domain (most commonly a single-chain variable fragment, scFv), a hinge region, a transmembrane domain, and intracellular signaling domains responsible for T-cell activation. Modern CAR constructs also include co-stimulatory domains (e.g., CD28, 4-1BB), which enhance proliferation, persistence, and effector function of the modified cells [5].

Emerging engineering strategies involve modification of endogenous T-cell genes to improve their functionality and reduce toxicity. One example is the reprogramming of CAR-T cells to deliver therapeutic payloads directly within the tumor microenvironment, thereby increasing selectivity and minimizing off-target effects [6].

3.3 Mechanism of Action of CAR-T Cells

The mechanism of action of CAR-T cells is based on their ability to directly recognize tumor-associated surface antigens in a manner independent of the major histocompatibility complex (MHC), which represents a significant advantage over conventional T-cell responses. Binding of the CAR receptor to its target antigen leads to T-cell activation and initiation of intracellular signaling cascades, resulting in proliferation, cytokine secretion, and cytotoxic activity.

A key component of CAR-T cell function is the formation of an immunological synapse between the T cell and the tumor cell, enabling precise signal transmission and targeted effector activity. Activated CAR-T cells eliminate tumor cells primarily through two mechanisms: the release of perforin and granzymes leading to target cell lysis, and the activation of apoptosis pathways mediated by death receptors (e.g., Fas/FasL).

In addition, CAR-T cells secrete pro-inflammatory cytokines (including IFN-γ, TNF-α, and IL-2), which enhance the antitumor immune response and modulate the tumor microenvironment, thereby increasing therapeutic efficacy.

An important feature of CAR-T therapy is the ability of modified T cells to proliferate and persist long-term within the patient, enabling sustained control of the disease even after a single infusion. However, the effectiveness of this response may be limited by resistance mechanisms such as an immunosuppressive tumor microenvironment, loss of target antigen expression, and functional exhaustion of T cells [7; 8; 9].

4.1 Clinical Applications of CAR-T Therapy in Hematologic Malignancies

CAR-T therapy currently represents one of the most important treatment strategies for hematologic malignancies, particularly in cases of relapsed or refractory disease. Its clinical application primarily includes B-cell acute lymphoblastic leukemia (B-ALL) and multiple myeloma, where the most convincing therapeutic outcomes have been achieved.

4.2 B-cell Acute Lymphoblastic Leukemia (B-ALL)

CAR-T therapy targeting the CD19 antigen has led to a significant transformation in the treatment of adult patients with relapsed or refractory B-ALL. The introduction of this strategy has enabled the achievement of high remission rates, which were previously difficult to obtain using conventional therapeutic approaches. Approved CAR-T products, such as tisagenlecleucel and brexucabtagene autoleucel, have been implemented in clinical practice for patients with advanced disease, representing an effective therapeutic option in this population [10].

The effectiveness of the therapy depends on multiple clinical factors, including disease burden and appropriate patient preparation, such as bridging therapy and lymphodepletion prior to CAR-T cell infusion. In clinical practice, this therapy is used both as a life-saving intervention and as part of a broader therapeutic strategy leading to subsequent treatments [10].

4.3 Multiple Myeloma

Significant advances in the application of CAR-T therapy have also been observed in the treatment of multiple myeloma, particularly in relapsed and refractory forms of the disease. The primary therapeutic target in this context is BCMA (B-cell maturation antigen), which is characteristically expressed on plasma cells. CAR-T therapies directed against BCMA have demonstrated high clinical efficacy, leading to meaningful therapeutic responses in heavily pretreated patients [11].

In clinical practice, the development of therapeutic strategies based on the sequential administration of BCMA-targeted CAR-T cells has also been observed. This approach enables the re-induction of clinical responses in patients experiencing disease relapse and contributes to prolonged disease control [13].

Additionally, CAR-T therapy in multiple myeloma is increasingly considered within the broader context of modern immunotherapeutic approaches, including bispecific antibodies, which may be used in a complementary or sequential manner, thereby expanding therapeutic possibilities for this group of patients [11].

4.4 Clinical Significance

The application of CAR-T therapy in hematologic malignancies reflects its high efficacy in cancers originating from the hematopoietic system, particularly those with a B-cell phenotype. This therapy currently represents a crucial treatment option for patients with limited therapeutic alternatives, and its clinical use continues to expand alongside the development of novel receptor constructs and therapeutic strategies.

5.1 Clinical Applications of CAR-T Therapy in Solid Tumors

The application of CAR-T therapy in solid tumors represents one of the most important directions in the development of modern immunotherapy. Despite its remarkable success in hematologic malignancies, the implementation of this strategy in solid tumors remains at the stage of intensive clinical investigation, primarily in early-phase trials, with promising yet still limited therapeutic outcomes.

5.2 Scope of Clinical Applications

Current clinical studies indicate that CAR-T therapy is being explored experimentally in a variety of solid tumors, including gastrointestinal cancers, pancreatic cancer, gliomas, and other tumors characterized by high expression of specific surface antigens. Results from phase I trials suggest the possibility of achieving clinical responses; however, these are most often limited to disease stabilization or partial tumor regression [15; 14].

The clinical efficacy of CAR-T therapy in this group of malignancies is strongly dependent on the selection of an appropriate target antigen. In contrast to hematologic cancers, solid tumors rarely express antigens with high tumor specificity, which significantly complicates the achievement of a selective therapeutic effect [16].

5.3 Pancreatic Cancer as a Model for CAR-T Application

Pancreatic cancer represents one of the most intensively studied clinical indications for CAR-T therapy, serving as a model of a tumor with a highly unfavorable immunological microenvironment. In this context, innovative strategies aimed at improving therapeutic efficacy are being developed, including the use of nanotechnology-based delivery systems. It has been demonstrated that the application of a collagenase-containing nanogel “backpack” can enhance CAR-T cell infiltration into the tumor and increase their antitumor activity, resulting in improved therapeutic outcomes in preclinical models [17].

5.4 Significance of Clinical Trials and Current Status

Currently, the majority of clinical trials investigating CAR-T therapy in solid tumors are in phase I, reflecting the early stage of development of this therapeutic strategy. The therapy is most commonly administered to patients who have undergone multiple lines of treatment and for whom standard therapeutic options have been exhausted. Despite its lower efficacy compared to hematologic malignancies, the observed clinical responses indicate the potential of CAR-T therapy as a future treatment option [14; 15].

5.5 Summary of Clinical Applications

At present, the application of CAR-T therapy in solid tumors is largely limited to experimental settings, focusing on selected tumor types with potentially suitable molecular targets. Existing data suggest that clinical responses can be achieved; however, the overall efficacy remains limited and requires further optimization within ongoing clinical trials [16].

6.1 Toxicity of CAR-T Therapy

Despite its high clinical efficacy, CAR-T therapy is associated with specific adverse effects resulting from intense immune system activation and interactions between effector cells and the patient’s body. The most significant complications include cytokine release syndrome (CRS), neurotoxicity (ICANS), and organ damage, including nephrotoxicity.

6.2 Cytokine Release Syndrome (CRS)

CRS is the most common and one of the most clinically significant complications of CAR-T therapy. Its pathogenesis is associated with massive activation of T lymphocytes and other immune cells, leading to the rapid release of pro-inflammatory cytokines such as IL-6, IFN-γ, and TNF-α [20; 22].

CD4+ T cells play a crucial role in the development of CRS by amplifying the inflammatory response through the production of pro-inflammatory mediators, thereby intensifying the cytokine cascade [23]. Clinically, CRS may manifest as fever, hypotension, respiratory disturbances, and multi-organ failure of varying severity [20].

6.3 Neurotoxicity (ICANS)

Neurotoxicity associated with CAR-T therapy, referred to as ICANS (immune effector cell-associated neurotoxicity syndrome), represents another major clinical complication. Symptoms include altered consciousness, aphasia, seizures, and encephalopathy, with severity ranging from mild to life-threatening [19].

The pathophysiological mechanisms underlying ICANS include disruption of the blood–brain barrier, activation of endothelial cells, and the effects of pro-inflammatory cytokines on the central nervous system [22]. The occurrence of neurotoxicity is often correlated with the severity of CRS, suggesting shared pathogenic mechanisms [20].

6.4 Nephrotoxicity

Increasing attention is being paid to nephrotoxicity as a significant, although less frequently described, complication of CAR-T therapy. Kidney injury may result both from the direct effects of inflammatory mediators and from secondary consequences of CRS, such as hypotension and impaired organ perfusion [18].

Clinical manifestations include acute kidney injury of varying severity, with risk factors including severe CRS, pre-existing kidney disease, and the overall clinical condition of the patient [18].

6.5 Spectrum of Toxicity and Clinical Significance

The toxicity of CAR-T therapy is multi-organ in nature and closely linked to its mechanism of action. The occurrence of adverse effects may impact the continuation of treatment and patient prognosis, highlighting the importance of early recognition and appropriate monitoring [21].

Understanding the mechanisms underlying toxicity and identifying risk factors are essential for optimizing therapy and improving its clinical safety [21].

7.1 Limitations of CAR-T Therapy

Despite the groundbreaking significance of CAR-T therapy in cancer treatment, its widespread clinical application remains limited by a range of biological, technological, and systemic factors. These limitations affect both the efficacy of the therapy and its accessibility in clinical practice.

7.2 Biological Limitations and Tumor Microenvironment

One of the key challenges, particularly in solid tumors, is the lack of appropriate, tumor-specific target antigens that would allow for selective elimination of cancer cells without damaging healthy tissues. Additionally, antigen heterogeneity and the ability of tumor cells to lose antigen expression contribute to immune escape and disease relapse [27].

Another significant limitation is the immunosuppressive tumor microenvironment, which inhibits the activity and proliferation of CAR-T cells. Factors such as the presence of suppressive immune cells, inhibitory cytokines, and insufficient infiltration of effector cells into the tumor substantially reduce therapeutic efficacy in solid malignancies [25].

Furthermore, limited persistence and functional exhaustion of T lymphocytes shorten the duration of therapeutic response, potentially leading to disease progression despite an initial favorable outcome [27].

7.3 Technological and Manufacturing Limitations

The manufacturing process of CAR-T therapy is complex, time-consuming, and requires highly specialized infrastructure. The production of autologous CAR-T cells involves isolation of patient-derived T lymphocytes, genetic modification, and ex vivo expansion, significantly prolonging the time to treatment and limiting its availability [28].

High production costs represent one of the main barriers to the widespread implementation of this therapy. The individualized nature of treatment and the complexity of the manufacturing process result in very high per-patient costs, restricting access within many healthcare systems [26].

In response to these challenges, alternative approaches such as allogeneic (“off-the-shelf”) CAR-T therapies are being developed, which may reduce production time and costs. However, their application is associated with additional immunological challenges [30].

7.4 Systemic Limitations and Accessibility

Access to CAR-T therapy remains uneven and depends on multiple systemic factors, including healthcare infrastructure, financial resources, and the organization of healthcare systems. The therapy is primarily available in highly specialized centers, which limits treatment availability for many patients [29].

A significant issue is also the disparity in access among different patient populations, resulting from economic, geographic, and social factors. These inequalities impact the global implementation of CAR-T therapy and represent a major challenge for healthcare systems [29].

7.5 Summary of Limitations

The limitations of CAR-T therapy are multifactorial and encompass biological, technological, and systemic aspects. Overcoming these barriers requires further technological advancements, optimization of manufacturing processes, and improved global accessibility of the therapy [28; 27].

8.1 Future Directions of CAR-T Therapy

The dynamic development of CAR-T therapy over the past decade has established its role in the treatment of selected hematologic malignancies; however, further progress in this field is focused on improving efficacy, safety, and expanding clinical indications. Current research directions include both the optimization of CAR-T cell design and the development of novel therapeutic strategies tailored to the characteristics of different cancer types.

8.2 Optimization of CAR-T Cell Design and Function

One of the key areas of development is the optimization of CAR receptor конструкции and functional modification of T lymphocytes to enhance their persistence and antitumor activity. Particular attention is given to the issue of T-cell exhaustion, which limits the long-term efficacy of the therapy. In this context, strategies are being developed that include genetic modifications to increase resistance to inhibitory signals and to improve proliferative capacity and survival of CAR-T cells [33].

Additionally, the development of next-generation CAR-T cells equipped with additional signaling domains or regulatory functions allows for more precise control of the immune response and reduction of undesired immune activation [35].

8.3 Expansion of Applications in Hematologic Malignancies

In hematologic cancers, future directions include expanding therapeutic indications to earlier lines of treatment and optimizing therapy to enhance the durability of responses. In particular, in multiple myeloma, multi-antigen targeting strategies and combination therapies are being developed to reduce relapse associated with loss of target antigen expression [32].

Moreover, research is increasingly focused on therapy personalization and improved patient selection, which may translate into better clinical outcomes and optimized therapeutic effects [31].

8.4 Development in Solid Tumors

One of the most important directions of development is enhancing the efficacy of CAR-T therapy in solid tumors. Research efforts focus on improving the ability of CAR-T cells to infiltrate tumors and overcome the immunosuppressive tumor microenvironment. These strategies include genetic modifications, the use of agents enhancing cell migration, and combination therapies [34].

A notable example is pancreatic cancer, where approaches combining CAR-T therapy with other immunotherapeutic methods are being explored to improve efficacy within a highly challenging tumor microenvironment [37].

8.5 Applications in Central Nervous System Diseases

An emerging area of research is the use of CAR-T therapy in diseases of the central nervous system, including brain tumors. In this context, strategies are being developed to enable effective delivery of CAR-T cells to the site of disease and to enhance their survival within the специфіс microenvironment of the central nervous system [36].

8.6 Novel Strategies and Therapeutic Approaches

The future of CAR-T therapy also includes the development of new therapeutic platforms, such as universal (allogeneic) CAR-T cells that can be used независимо of donor, as well as the integration of cellular therapy with other treatment modalities, including gene therapy and immunotherapy. These approaches aim to improve both the accessibility and clinical effectiveness of the therapy [35].

8.7 Summary of Future Directions

Future directions in CAR-T therapy focus on overcoming current limitations through advanced genetic modifications, development of novel therapeutic strategies, and expansion of clinical applications. Progress in these areas may significantly enhance both the efficacy and accessibility of CAR-T therapy, establishing it as a key modality in cancer treatment in the coming years [31].

9. Discussion

CAR-T therapy represents one of the most significant achievements of modern cancer immunotherapy, introducing a paradigm shift in the treatment of malignancies, particularly in hemato-oncology. The data presented in this review indicate that the use of genetically modified T lymphocytes enables high rates of clinical response in patients with relapsed and refractory diseases, which until recently remained beyond the reach of standard therapeutic approaches.

The greatest efficacy of CAR-T therapy has been observed in hematologic malignancies, especially those with a B-cell phenotype. This is primarily due to the availability of well-defined target antigens, such as CD19 and BCMA, as well as a more favorable microenvironment for effector cell activity. In these indications, CAR-T therapy has become an important component of clinical practice, and its role is steadily expanding to include earlier lines of treatment and novel therapeutic strategies.

In contrast, the application of CAR-T therapy in solid tumors remains limited. Analysis of available data indicates that its efficacy in this group of malignancies is significantly lower, which results from multiple biological barriers, including antigen heterogeneity, the immunosuppressive tumor microenvironment, and the limited ability of CAR-T cells to infiltrate tumor tissues. Nevertheless, outcomes from early-phase studies and the development of new strategies, including genetic modifications and combination therapies, suggest the potential for further advancement of this approach in solid tumors.

An important aspect discussed in this work is the toxicity of CAR-T therapy, which is a direct consequence of its mechanism of action. Cytokine release syndrome and neurotoxicity are among the most common and severe complications, requiring careful monitoring and appropriate clinical management. At the same time, an improved understanding of the mechanisms underlying these adverse effects has enabled the development of more effective prevention and treatment strategies, contributing to enhanced safety of the therapy.

Despite its high clinical efficacy, CAR-T therapy also faces significant limitations related to manufacturing processes, costs, and accessibility. The individualized nature of the therapy and its technological complexity translate into limited global availability, posing a substantial challenge for healthcare systems. In this context, the development of allogeneic therapies and optimization of manufacturing processes may play a key role in improving accessibility.

The future of CAR-T therapy is focused on further enhancing its efficacy and safety through genetic modifications of cells, the development of novel receptor constructs, and integration with other therapeutic strategies. Particular emphasis is placed on overcoming T-cell exhaustion, improving persistence, and enhancing functionality within the challenging tumor microenvironment. Simultaneously, new areas of application are being explored, including the treatment of central nervous system malignancies and further expansion of indications in hemato-oncology.

In summary, CAR-T therapy represents a breakthrough tool in cancer treatment whose full potential has not yet been fully realized. Continued development of this technology, driven by advances in genetic engineering, immunology, and translational medicine, may significantly impact the future of cancer therapy, making it more effective, safer, and accessible to a broader patient population.

10. Conclusions

1. CAR-T therapy is a breakthrough method in cancer treatment, particularly in hemato-oncology, enabling high rates of clinical response in patients with relapsed and refractory disease.
2. The greatest clinical efficacy is observed in hematologic malignancies, especially those with a B-cell phenotype, where the availability of specific target antigens enhances treatment effectiveness.
3. The application of CAR-T therapy in solid tumors remains limited; however, the development of new therapeutic strategies suggests potential expansion of its use in the future.
4. Therapy-related toxicity, including cytokine release syndrome and neurotoxicity, constitutes a significant clinical challenge requiring appropriate monitoring and management.
5. Limitations related to manufacturing processes, high costs, and therapy accessibility represent major barriers to its widespread clinical implementation.
6. Future directions of CAR-T therapy focus on improving efficacy, safety, and accessibility through advanced genetic modifications, optimization of technological processes, and integration with other treatment strategies.

Further development of CAR-T therapy may significantly improve cancer treatment outcomes and solidify its role as a key modality in modern oncology.

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