Global Journal of Research in
Biology and Pharmacy
Journal homepage: https://gsjournals.com/gjrbp/
ISSN: 2980-4221 (Online)

(REVIEW ARTICLE)

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CAR-T AND CAR-NK CELL THERAPIES FOR HEMATOLOGIC MALIGNANCIES AND SOLID TUMORS: OVERCOMING RESISTANCE AND TOXICITY

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Global Journal of Research in Biology and Pharmacy, 2024, 03(02), 001–005

Publication history: Received on 12 March 2024; revised on 22 April 2024; accepted on 26 April 2024

Article DOI: https://doi.org/10.58175/gjrbp.2024.3.2.0041

ABSTRACT

Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of relapsed or refractory hematologic malignancies, with durable remissions observed in B-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma, multiple myeloma, and other B-cell malignancies. However, significant challenges persist, including antigen escape, limited persistence, immunosuppressive tumor microenvironments, and potentially life-threatening toxicities such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome. Moreover, efficacy in solid tumors remains limited due to heterogeneous antigen expression, poor trafficking, and immunosuppressive barriers. CAR-natural killer (NK) cells have emerged as a promising alternative or complement to CAR-T cells, offering potential advantages including lower risk of graft-versus-host disease, reduced cytokine release syndrome, and the possibility of allogeneic off-the-shelf products. This review critically examines recent clinical progress in CAR-T and CAR-NK cell therapies through early 2024, focusing on mechanisms of resistance and strategies to overcome them, as well as toxicity management. It discusses innovations such as dual-targeting CARs, armored CARs, logic-gated CARs, and allogeneic platforms. While CAR-T therapy has achieved remarkable success in hematologic cancers, extending these benefits to solid tumors and broader patient populations will require continued advances in cell engineering, combination therapies, and a deeper understanding of the tumor–immune interface.

Keywords: CAR-T Cells; CAR-NK Cells; Hematologic Malignancies; Solid Tumors; Cytokine Release Syndrome; Antigen Escape

1 INTRODUCTION

Chimeric antigen receptors are synthetic receptors that redirect immune effector cells to recognize and eliminate cells expressing a specific target antigen. CARs typically consist of an extracellular antigen-binding domain, a hinge and transmembrane region, and intracellular signaling domains derived from T-cell receptor components and co-stimulatory molecules. First-generation CARs contained only CD3ζ signaling, while second- and third-generation CARs incorporate one or more co-stimulatory domains such as CD28 or 4-1BB, enhancing proliferation, persistence, and effector function.

The approval of tisagenlecleucel in 2017 for pediatric and young adult B-cell acute lymphoblastic leukemia marked a milestone in cancer immunotherapy. Since then, several CD19-directed CAR-T products have been approved for various B-cell lymphomas, and B-cell maturation antigen (BCMA)-directed CAR-T therapies have been approved for multiple myeloma. These therapies have produced unprecedented response rates in heavily pretreated patients, but many patients still relapse or experience severe toxicities. In solid tumors, results have been less impressive, with limited clinical responses and significant challenges related to antigen selection, trafficking, and the immunosuppressive tumor microenvironment.

Natural killer cells possess intrinsic anti-tumor activity and can be engineered with CARs to enhance specificity and cytotoxicity. CAR-NK cells offer several potential advantages, including a lower risk of cytokine release syndrome and neurotoxicity, lack of graft-versus-host disease when derived from allogeneic sources, and the possibility of off-the-shelf administration. Early clinical trials of CAR-NK cells have shown encouraging safety and efficacy in hematologic malignancies, and efforts are underway to expand their use to solid tumors.

This review critically evaluates recent advances in CAR-T and CAR-NK cell therapies, with a focus on mechanisms of resistance, toxicity management, and strategies to improve efficacy, particularly in solid tumors.

2 CAR-T CELL THERAPY IN HEMATOLOGIC MALIGNANCIES

2.1 B-Cell Acute Lymphoblastic Leukemia

CD19-directed CAR-T therapy has produced high complete remission rates in relapsed or refractory B-cell acute lymphoblastic leukemia. The ELIANA trial of tisagenlecleucel in children and young adults demonstrated an overall remission rate of 81% at three months, with durable responses and an acceptable safety profile. Long-term follow-up has shown that a subset of patients achieve sustained remissions, potentially cure. However, relapse remains a major problem, often due to loss of CD19 expression (antigen escape) or poor CAR-T persistence. Strategies to address antigen escape include dual-targeting CARs (e.g., CD19/CD22) and sequential infusions. Enhancing persistence through co-stimulatory domain selection (e.g., 4-1BB versus CD28) and optimizing manufacturing processes are active areas of research.

2.2 B-Cell Non-Hodgkin Lymphoma

Axicabtagene ciloleucel and lisocabtagene maraleucel are CD19-directed CAR-T products approved for relapsed or refractory large B-cell lymphoma. The ZUMA-1 and TRANSCEND trials demonstrated objective response rates of approximately 70–80%, with complete response rates of 50–60%, and a subset of patients achieving long-term remissions. However, cytokine release syndrome and neurotoxicity are common, particularly with axicabtagene ciloleucel, which uses a CD28 co-stimulatory domain and is associated with more rapid expansion and higher toxicity. Tisagenlecleucel is also approved for certain B-cell lymphomas. In mantle cell lymphoma, brexucabtagene autoleucel has shown efficacy, and in follicular lymphoma, axicabtagene ciloleucel and tisagenlecleucel have been approved. Despite high response rates, primary resistance and relapse remain issues, with mechanisms including loss of CD19, T-cell exhaustion, and an immunosuppressive tumor microenvironment.

2.3 Multiple Myeloma

BCMA-directed CAR-T therapies, idecabtagene vicleucel and ciltacabtagene autoleucel, have transformed the treatment of relapsed or refractory multiple myeloma. In the KarMMa and CARTITUDE-1 trials, overall response rates exceeded 70–90%, with a significant proportion achieving complete responses or better. Ciltacabtagene autoleucel, which contains two BCMA-binding domains, demonstrated particularly deep and durable responses. However, relapses occur, often associated with BCMA downregulation or loss, T-cell exhaustion, or development of anti-CAR immune responses. Dual-targeting CARs (e.g., BCMA/GPRC5D) and combination strategies are being evaluated to overcome resistance.

3 MECHANISMS OF RESISTANCE TO CAR-T THERAPY

3.1 Antigen Escape

Loss or downregulation of the target antigen is a major cause of relapse. In CD19-directed therapy, mutations, alternative splicing, or lineage switch can lead to loss of CD19 expression. In multiple myeloma, BCMA can be shed or downregulated, and selection of BCMA-low clones occurs. Dual-targeting CARs, which recognize two antigens simultaneously or sequentially, are designed to reduce the risk of antigen escape. For example, CD19/CD22 dual CARs in B-cell acute lymphoblastic leukemia and BCMA/GPRC5D dual CARs in multiple myeloma are in clinical trials.

3.2 CAR-T Cell Exhaustion and Poor Persistence

CAR-T cells can become exhausted due to chronic antigen stimulation, inhibitory receptor expression (e.g., PD-1, TIM-3, LAG-3), and metabolic dysfunction. Manufacturing processes that generate less differentiated, memory-like T cells may improve persistence. Use of 4-1BB co-stimulation, cytokine modulation (e.g., IL-7, IL-15), and combination with checkpoint inhibitors are being explored. Armored CARs that secrete cytokines or express dominant-negative receptors can resist immunosuppression.

3.3 Tumor Microenvironment

The tumor microenvironment in lymphomas and solid tumors contains immunosuppressive cells (regulatory T cells, myeloid-derived suppressor cells), inhibitory cytokines, and metabolic constraints. CAR-T cells may fail to traffic to tumor sites or be suppressed upon arrival. Strategies to overcome these barriers include engineering CAR-T cells with chemokine receptors, disrupting inhibitory pathways, and using combination therapies that modulate the microenvironment.

3.4 Host Immune Responses

Immunogenicity of CAR constructs, particularly murine-derived single-chain variable fragments, can lead to anti-CAR antibodies and reduced persistence. Humanized or fully human single-chain variable fragments may reduce immunogenicity. Repeated dosing and allogeneic CAR-T approaches also face immune rejection.

4 TOXICITY MANAGEMENT

4.1 Cytokine Release Syndrome

Cytokine release syndrome is a systemic inflammatory response caused by rapid CAR-T cell activation and cytokine release (IL-6, IFN-γ, TNF-α). Symptoms range from fever and fatigue to hypotension, hypoxia, and multiorgan failure. Management includes tocilizumab, an IL-6 receptor antagonist, and corticosteroids. Early recognition and grading using established criteria (e.g., ASTCT consensus grading) are essential. Risk factors include high tumor burden, high CAR-T dose, and CD28 co-stimulation. Prophylactic strategies and modified CAR designs are being investigated to reduce severity.

4.2 Immune Effector Cell-Associated Neurotoxicity Syndrome

Immune effector cell-associated neurotoxicity syndrome can manifest as confusion, aphasia, seizures, or cerebral edema. The pathophysiology involves endothelial activation, blood–brain barrier disruption, and cytokine-mediated neuroinflammation. Management includes corticosteroids and supportive care. Tocilizumab is less effective for neurotoxicity than for cytokine release syndrome. Risk factors overlap with cytokine release syndrome. Novel biomarkers and imaging modalities are being developed to predict and monitor neurotoxicity.

4.3 Other Toxicities

Prolonged cytopenias, B-cell aplasia with hypogammaglobulinemia, and infections are common after CAR-T therapy. On-target/off-tumor effects can cause serious adverse events, especially when targeting antigens expressed on normal tissues (e.g., BCMA on normal plasma cells). Rare but severe toxicities include hemophagocytic lymphohistiocytosis and tumor lysis syndrome. Long-term follow-up is needed to assess secondary malignancies and immune reconstitution.

5 CAR-T CELLS IN SOLID TUMORS

Despite extensive investigation, CAR-T therapy has shown limited efficacy in solid tumors. Obstacles include lack of truly tumor-specific antigens, heterogeneous antigen expression, poor T-cell infiltration, hostile tumor microenvironment, and T-cell dysfunction. Several antigens have been targeted, including HER2, EGFR, mesothelin, GD2, and Claudin 18.2, but response rates have generally been low. Notable exceptions include GD2-directed CAR-T in neuroblastoma, where some responses have been observed, and B7-H3-directed CAR-T in pediatric solid tumors. Strategies to improve solid tumor efficacy include:

- Dual-targeting and logic-gated CARs to increase specificity and reduce off-tumor toxicity.
- Armored CARs secreting cytokines or expressing chemokine receptors to enhance trafficking and function.
- Combination with checkpoint inhibitors, oncolytic viruses, or localized delivery to overcome immunosuppression.
- Next-generation CARs with enhanced signaling domains or synthetic biology circuits.

Despite these efforts, clinical translation remains challenging, and most trials are in early phases.

6 CAR-NK CELL THERAPY: AN EMERGING ALTERNATIVE

6.1 Advantages of CAR-NK Cells

Natural killer cells are innate immune cells capable of recognizing and killing tumor cells through multiple receptors, independent of antigen presentation. CAR-NK cells combine the specificity of CARs with NK cell biology. Potential advantages include:

- Lower risk of cytokine release syndrome and neurotoxicity: NK cells produce different cytokine profiles, particularly less IL-6.
- Reduced graft-versus-host disease: Allogeneic NK cells do not require HLA matching and can be used off-the-shelf.
- Multiple killing mechanisms: Besides CAR-mediated killing, NK cells retain intrinsic activating receptors (e.g., NKG2D, NKp30) that can target tumor cells.
- Shorter lifespan: This may reduce long-term toxicity but also limit persistence.

6.2 Clinical Experience

Early clinical trials of CAR-NK cells have shown promise. The most widely studied source is cord blood-derived NK cells engineered to express CD19 CAR and IL-15. In a phase 1/2 trial, CD19 CAR-NK cells produced complete responses in a majority of patients with relapsed or refractory B-cell malignancies, without significant cytokine release syndrome or neurotoxicity. Responses were rapid but sometimes transient, highlighting the need for strategies to enhance persistence. Other sources include induced pluripotent stem cell-derived NK cells and peripheral blood NK cells. Trials are underway in both hematologic and solid tumors. Challenges include manufacturing scalability, cryopreservation, and optimizing CAR construct design for NK cell signaling.

7 FUTURE PERSPECTIVES

The field of CAR-based cell therapy is evolving rapidly. Key directions include:

- Allogeneic off-the-shelf products: Gene-edited allogeneic CAR-T cells with deletion of TCR and HLA to avoid rejection and graft-versus-host disease.
- Armored and logic-gated CARs: Enhanced control over CAR activity and combination with cytokines or checkpoint blockade.
- Alternative cell sources: CAR-NK, CAR-macrophages, and CAR-γδ T cells may offer unique advantages.
- Overcoming solid tumor barriers: Combination with tumor microenvironment modulators, local delivery, and novel targeting strategies.
- Predictive biomarkers and personalized approaches: Identifying which patients are most likely to benefit and which toxicities they may experience.

As CAR-T therapy becomes more established, efforts to improve accessibility, reduce cost, and manage long-term side effects will be critical. CAR-NK cells may provide a more accessible and safer alternative, particularly for off-the-shelf use.

8 CONCLUSION

CAR-T cell therapy has transformed outcomes in relapsed or refractory hematologic malignancies, providing durable remissions in a substantial subset of patients. However, resistance and toxicity remain significant obstacles. Mechanisms of resistance include antigen escape, T-cell exhaustion, and immunosuppressive microenvironments. Toxicity management has improved with standardized grading and use of tocilizumab and corticosteroids, but severe events still occur. In solid tumors, efficacy is limited, and novel strategies are needed. CAR-NK cells offer a promising alternative with potential advantages in safety and off-the-shelf use. Continued advances in cell engineering, manufacturing, and combination therapies will be essential to realize the full potential of CAR-based immunotherapy across cancer types.

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