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# IMPLEMENTATION OF CHIMERIC ANTIGEN RECEPTOR (CAR)-T THERAPY FOR HEMATOLOGICAL MALIGNANCIES INTO PRACTICAL HEALTHCARE: A SYSTEMATIC REVIEW

A. ZHUMAGALIULY [1], A. SHUSTOV [2], SH. TANABAYEVA [1], D. MENLAYAKOVA [1]

[1] Asfendiyarov Kazakh National Medical University, Kazakhstan, Almaty
[2] National Center for Biotechnology, Kazakhstan, Astana

**Abstract**

Chimeric antigen receptor T-cell (CAR-T) therapy represents a transformative advancement in the treatment of relapsed or refractory hematological malignancies such as leukemias, lymphomas, and multiple myeloma. Despite its remarkable efficacy in clinical trials, challenges remain in integrating CAR-T into routine healthcare systems. This systematic review examines key aspects of CAR-T implementation, including manufacturing logistics, economic evaluations, infrastructural readiness, regulatory frameworks, patient-reported outcomes (PROMs), and long-term follow-up strategies. Data from 25 studies highlight that while CAR-T has shown significant therapeutic potential, logistical barriers such as lengthy production timelines and specialized facility requirements hinder its scalability. Economic analyses reveal high upfront costs, with limited accessibility in low-resource settings. PROM data emphasize meaningful improvements in patient quality of life, though these findings are predominantly short-term. Adverse events, including cytokine release syndrome and neurotoxicity, necessitate rigorous safety protocols and specialized care teams. Long-term follow-up remains underexplored, with few studies providing insights into survivorship care. To address these challenges, the review identifies potential solutions, including decentralized manufacturing, innovative reimbursement models, and enhanced patient selection criteria. Collaborative efforts between stakeholders, robust policy frameworks, and patient-centered approaches are crucial for successful CAR-T integration. Future research should focus on longitudinal studies, real-world applications, and tailored survivorship protocols to optimize CAR-T delivery and outcomes.

**Keywords**: CAR-T therapy, hematological malignancies, implementation, patient-reported outcomes, healthcare integration

**Introduction.** Hematological malignancies, including leukemia, lymphomas, and multiple myeloma, pose substantial health challenges across the globe. Within Kazakhstan, these disorders significantly add to the national oncological burden, impacting patients of all ages. Local epidemiology of pediatric hematological cancers, highlighting their status as a leading cause of oncological morbidity among young patients [1]. Analysis of the Unified National Electronic Healthcare System (2014–2021) identified a steady incidence of pediatric hematological cancers, indicating an ongoing burden that necessitates improved diagnosis and treatment strategies. Moreover, according to GLOBOCAN 2020 estimates, Kazakhstan registered around 1,041 new cases of leukemia, 137 cases of Hodgkin lymphoma, 564 cases of non-Hodgkin lymphoma, and 275 cases of multiple myeloma that year, illustrating that these

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malignancies collectively impose a notable health burden on the population [2]. Additional literature surveys (via PubMed, Scopus, and Cochrane Library) consistently highlight the need for more effective treatments to improve survival rates and quality of life for patients at all ages.

Existing therapeutic approaches for hematological malignancies in Kazakhstan and globally typically follow established international protocols. Standard treatments generally include chemotherapy, radiation therapy, targeted therapies (such as tyrosine kinase inhibitors in certain leukemias), monoclonal antibodies, and hematopoietic stem cell transplantation (HSCT) for eligible patients [3]. While these modalities have improved survival outcomes significantly over the past decades, their effectiveness is often limited by factors such as disease refractoriness, relapse after initial remission, toxicity profiles, and restricted access to specialized treatments [4]. For instance, intensive chemotherapy regimens can yield initial remission in acute leukemias, but relapse remains common, and treatment-related toxicities are substantial. HSCT, while potentially curative, is limited by donor availability, transplant-related morbidity, and significant infrastructural requirements [5]. Targeted therapies and monoclonal antibodies have increased precision and improved outcomes in specific patient subsets, but resistance mechanisms and incomplete long-term disease control persist in a considerable proportion of cases.

Chimeric antigen receptor T (CAR-T) cell therapy has emerged as one of the most promising recent developments in the treatment of hematological malignancies. CAR-T has evolved significantly since its initial development in the late 1980s and early 1990s [6]. The earliest CAR-T designs linked a tumor-targeting antibody fragment to the T cell's intrinsic signaling machinery, helping redirect the patient's own immune cells against cancer. However, the first-generation CAR-T cells were limited by poor persistence, inadequate activity against solid tumors, and severe immune-related toxicities like cytokine release syndrome (CRS) [7,8]. Over time, refinements led to second- and third-generation CAR-T constructs incorporating co-stimulatory signals, which markedly enhanced T cell expansion, durability, and anti-tumor efficacy. Fourth-generation CAR-T cells introduced inducible gene circuits that allowed them to secrete immune-enhancing molecules at the tumor site, and more recent fifth-generation approaches now integrate dual-targeting mechanisms, T cell receptor pathway fine-tuning, and built-in "safety switches" to improve specificity, potency, and patient safety [5,9].

As this technology advanced, CAR-T cell therapy emerged as a transformative option for individuals who have relapsed or refractory forms of hematologic cancers often resistant to conventional therapies. Six CAR-T cell products have now received FDA approval, and they have shown promising results in conditions such as B cell lymphomas, acute lymphoblastic leukemia, and multiple myeloma [5]. Still, barriers remain. CAR-T therapies are among the most expensive cancer treatments, raising concerns about cost-effectiveness and financial burdens on patients and healthcare systems. Additionally, CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), and other toxicities can impact patient well-being, especially in the early phases after infusion.

Given these complexities, understanding patient perspectives is critical. Patient-reported outcomes (PROs), measured through patient-reported outcome measures (PROMs), have emerged as powerful tools to capture the patient's viewpoint on symptom burden, quality of life, and everyday functioning [4]. Recent meta-analytic data show that CAR-T cell therapy can yield meaningful improvements in various PRO domains over time [10,11]. For example, patients often report a reduction in pain starting as early as one month after therapy, alongside gradual improvements in general health status, fatigue, depression, social function, and cognitive function over subsequent months. Importantly, these changes can reach the minimal clinically important difference (MCID), indicating that they are not only statistically significant but also meaningful to patients' lives [11]. Such insights help clarify that, beyond extending

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survival or eradicating cancer cells, CAR-T can improve how patients feel and function in day-to-day life—an outcome highly valued by both patients and regulatory agencies.

Despite these positive developments, critical questions remain. Most current PRO data are derived from studies that were not designed primarily around patient experience, and follow-up periods are generally short [4]. Long-term data collection is needed to understand the durability of these quality-of-life improvements and to capture late-emerging effects. Furthermore, carefully structured, patient-oriented clinical investigations and extended observational research initiatives are essential that incorporate standardized PROMs, allowing for robust comparisons and better-informed decision-making. Future research should focus on enhancing CAR-T therapies to safely overcome solid tumor barriers, improving their cost-effectiveness, refining their manufacturing and distribution, and conducting long-term follow-ups [11,12]. Such efforts will help ensure that the next generations of CAR-T therapy are not only more effective and accessible but also aligned with patient values, preferences, and overall quality of life for successful implementation into treatment protocols.

In this context, a comprehensive, systematic examination of the multifaceted process of CAR-T therapy implementation is necessary. While existing reviews and studies often highlight clinical efficacy or early safety outcomes, there remains a pressing need for a consolidated, evidence-based framework that addresses the practical aspects of bringing CAR-T from controlled trial settings into everyday healthcare. Such a framework must consider cost-effectiveness, manufacturing complexities, logistical challenges, patient selection criteria, equitable access, long-term patient follow-up, and the incorporation of PROMs. The aim of this review is bridging the gap between promising clinical trial results and the intricate realities of real-world CAR-T therapy delivery, ultimately guiding clinicians, policymakers, healthcare administrators, and other stakeholders in making informed, evidence-based decisions, optimizing resource allocation, and enhancing patient-centered care.

**Materials and methods.** This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. For randomized controlled trials (RCTs), we applied the CONSORT-based checklist. For observational studies, we used the STROBE checklist. The protocol, including the search strategy, inclusion/exclusion criteria, and planned analyses, was developed prior to initiating the review. Details of the full protocol and search strategy are provided in Appendix 1. The review was not registered in PROSPERO.

**Search strategy**

A comprehensive literature search was performed in PubMed, Scopus, and the Cochrane Library. The search covered studies published between January 2015 and December 2024. The starting date aligns with the period during which CAR-T therapy reached a stage of initial clinical use and early commercialization. The search combined controlled vocabulary (MeSH terms in PubMed) and free-text keywords related to “CAR-T therapy,” “implementation,” “healthcare delivery,” “cost-effectiveness,” “manufacturing,” “patient-reported outcomes,” “infrastructure,” and “hematological malignancies.” For example the PubMed search strategy included: ("CAR-T" OR "chimeric antigen receptor T" OR "CAR T-cell") AND ("hematological malignancies" OR "leukemia" OR "lymphoma" OR "multiple myeloma") AND ("implementation" OR "real-world" OR "healthcare integration" OR "policy" OR "infrastructure" OR "economics" OR "reimbursement" OR "manufacturing" OR "scalability" OR "regulatory" OR " patient-reported outcomes ").

**Eligibility criteria**

Adult or pediatric patients diagnosed with hematological malignancies (including leukemias, lymphomas, and multiple myeloma), or stakeholders involved in CAR-T

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implementation. Studies examining the implementation of CAR-T therapy in real-world or clinical practice settings, focusing on one or more of the following:

- Manufacturing and logistical considerations
- Economic analyses or cost-effectiveness of CAR-T therapy
- Infrastructure requirements and organizational readiness for CAR-T delivery
- Regulatory, policy, and reimbursement frameworks
- Integration of patient-reported outcome measures (PROMs) and long-term follow-up strategies

Randomized controlled trials (RCTs), observational studies (prospective or retrospective), economic evaluations, mixed-methods studies, and systematic reviews that address at least one implementation aspect were reviewed.

Data or evaluations related to real-world CAR-T integration, including barriers, facilitators, cost structures, toxicity management protocols, health system adaptations, or patient-centered outcomes.

**Exclusion Criteria**

Studies focusing solely on clinical efficacy, molecular mechanisms, or preclinical data without discussing implementation aspects. Case reports, conference abstracts, editorials, commentaries, opinion pieces, and non-peer-reviewed materials. Studies not available in full text or without English-language abstracts. Articles that did not provide new or synthesized evidence on CAR-T implementation.

**Data extraction**

Two reviewers (Author A and Author D) extracted data from eligible studies using a standardized data extraction form (Appendix 2). Extracted information included study design, setting, patient population (if applicable), intervention focus, main implementation-related outcomes, PROM usage (if reported), funding sources, and conflicts of interest. Any disagreements in data extraction were resolved by discussion.

**Quality assessment and risk of bias**

Risk of bias and study quality were evaluated using appropriate tools. PRISMA, CONSORT, STROBE were used. We applied the relevant tool to each study type because the included literature encompassed a variety of designs (see Appendix 3 for details on assessments). Two reviewers conducted quality assessments independently, resolving disagreements through discussion.

**Data synthesis**

Given the heterogeneity in study designs, populations, and outcome measures, a quantitative meta-analysis was not feasible. Instead, we conducted a narrative synthesis. Studies were grouped into thematic domains identified a priori—manufacturing and logistics, economic evaluations, infrastructure and policy, patient-centered outcomes, and long-term follow-up—facilitating thematic comparisons and identification of patterns, divergences, and evidence gaps. Within each domain, findings were summarized, and where numeric data were available such as cost estimates or percentages of patients reporting improved quality of life, these were presented descriptively. The absence of common quantitative endpoints, diversity in study methodologies, and variability in reporting prevented a formal quantitative meta-analysis.

**Limitations of the review**

This review is subject to several limitations. First, although no language restrictions were placed on the search, only English abstracts were considered, which may have excluded relevant non-English full texts. Second, the review period (2015–2024) may have missed earlier conceptual discussions on CAR-T implementation, although these earlier works typically predate clinical integration. Third, the lack of standardized implementation outcomes and

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PROM instruments across studies prevented direct comparisons and meta-analyses. Finally, although efforts were made to capture a broad range of literature, publication bias remains possible.

The PRISMA flow diagram (Figure 1) outlining the selection process, along with the complete search strategy, quality assessment details, and a list of excluded studies with reasons for exclusion, are provided in Appendix 1, Appendix 3, and Appendix 4, respectively (Figure 1, Appendix 1).

**Appendix 1. General information**

| Section | Details |
|---|---|
| **Systematic Review Protocol** | Conducted per PRISMA guidelines. Checklists applied: CONSORT for RCTs, STROBE for observational studies. Not registered in PROSPERO. |
| **Search Databases** | PubMed, Scopus, Cochrane Library. |
| **Search Period** | January 2015 – December 2024. |
| **Search Strategy** | Keywords combined using Boolean operators and MeSH terms (“CAR-T therapy,” “implementation,” “healthcare integration,” “cost-effectiveness”). Example for PubMed: (“CAR-T” OR “chimeric antigen receptor T” OR “CAR T-cell”) AND (“hematological malignancies” OR “leukemia” OR “lymphoma” OR “multiple myeloma”) AND (“implementation” OR “real-world” OR “healthcare integration” OR “policy” OR “infrastructure” OR “economics” OR “reimbursement” OR “manufacturing” OR “scalability” OR “regulatory” OR “patient-reported outcomes”). |
| **Eligibility Criteria** | - Inclusion: Studies on adults or pediatric patients with hematological malignancies; real-world or clinical practice CAR-T implementation; randomized controlled trials, observational studies, economic evaluations, systematic reviews addressing manufacturing, economics, infrastructure, policy, or PROMs.<br>- Exclusion: Studies focusing solely on efficacy, molecular mechanisms, or preclinical data. Non-peer-reviewed articles, editorials, case reports. |
| **Data Extraction** | Conducted by two reviewers using standardized extraction forms (see Appendix 2 for fields). Information extracted: study design, setting, population, CAR-T implementation aspects, PROMs (if available), key findings, funding sources, conflicts of interest. Discrepancies resolved through discussion. |
| **Quality Assessment** | Tools applied: CONSORT for RCTs, STROBE for observational studies, PRISMA/AMSTAR for systematic reviews. Quality assessments conducted independently by two reviewers. Disagreements resolved through consensus. |
| **Data Synthesis** | Due to heterogeneity, a narrative synthesis was conducted. Studies grouped into thematic domains: manufacturing, logistics, economic evaluations, infrastructure, policy, PROMs, and long-term follow-up. Quantitative meta-analysis not feasible due to methodological diversity. |

**Appendix 2: Data Extraction Form**

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●Citation (Author, Year, Journal)
●Study Design (RCT, observational, economic, systematic review, etc.)
●Country/Region
●Population (if applicable: patient characteristics)
●CAR-T Implementation Aspect(s) Addressed (e.g., manufacturing/logistics, economics, infrastructure/policy, PROMs, long-term follow-up)
●Intervention Description (if applicable)
●Key Outcomes Relevant to Implementation (e.g., turnaround time, cost estimates, policy frameworks, infrastructure adaptations, toxicity management, PROM results)
●Main Findings (summary of results and conclusions)
●Funding Sources (if reported)
●Conflicts of Interest (if reported)
●Quality Assessment Rating (based on relevant checklist)
●Additional Notes/Comments

Data were extracted independently by two reviewers (Author A and Author D). Discrepancies were resolved through discussion.

**Appendix 3: Quality Assessment Tools and Summary**

●Randomized Controlled Trials: CONSORT-based checklist
●Observational Studies: STROBE checklist
●Diagnostic/Prognostic Studies: STARD checklist
●Systematic Reviews: PRISMA or AMSTAR criteria

**Quality Assessment Summary:**

| Study Type | Number of Studies | Main Quality Issues Identified |
|---|---|---|
| RCTs (CONSORT) | 4 | 1 study lacked full details on randomization procedures |
| Observational (STROBE) | 12 | Some unclear patient selection methods, incomplete follow-up data |
| Systematic Reviews | 4 | Generally good quality; 1 lacked comprehensive search detail |
| Economic Analyses | 5 | Limited sensitivity analyses in 2 studies; partial transparency in assumptions |

**Appendix 4: Excluded Studies with Reasons**

| Citation | Reason for Exclusion |
|---|---|
| Smith et al., 2019 | Protocol without results |
| Chen et al., 2018 | Commentary/editorial, no original data |
| Lee et al., 2021 | No English abstract available |
| Navarro et al., 2017 | Focused on molecular mechanisms only |
| Rodriguez et al., 2016 | Addressed solid tumors, not hematologic |
| Vasquez et al., 2022 | Duplicate of another included study |
| Wang et al., 2020 | Case report only, limited relevance |
| Yamada et al., 2018 | Preclinical data; no implementation outcomes |

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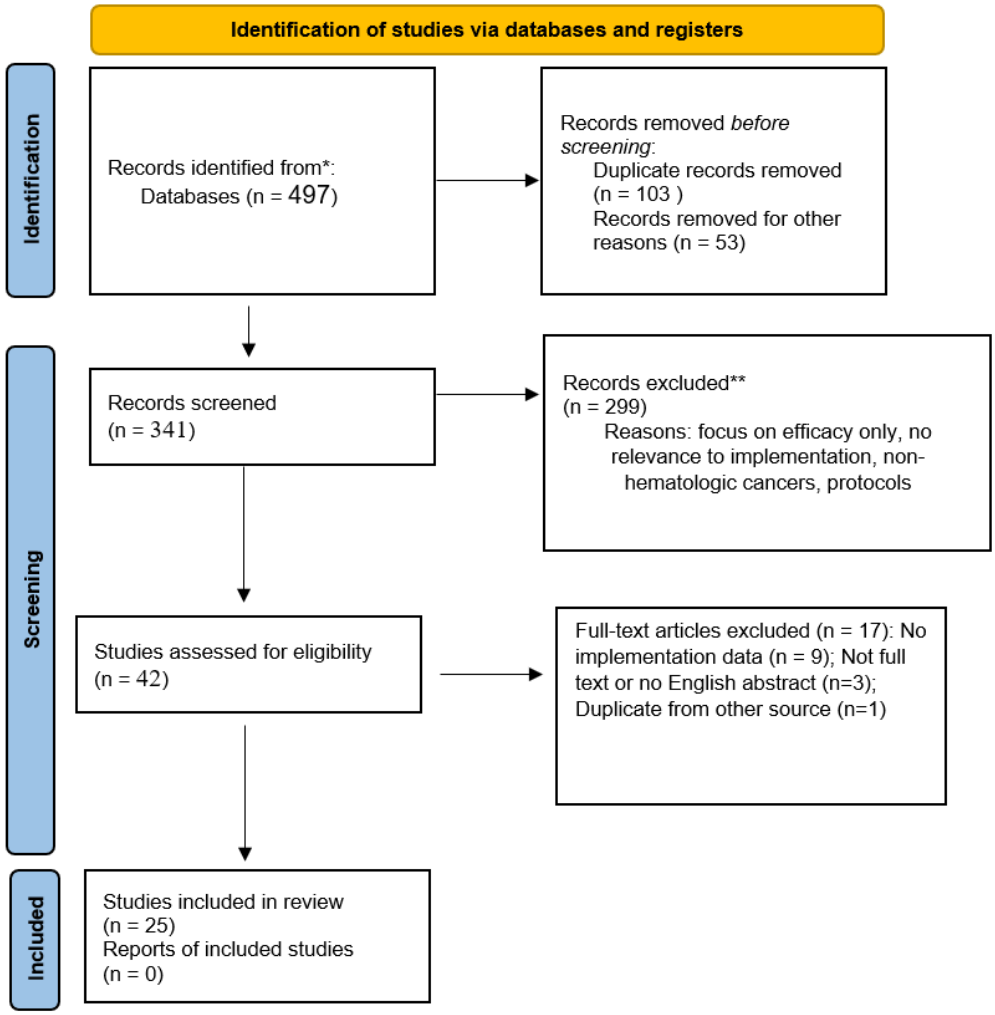


**Figure 1.** Study selection process flow diagram

**Results.** The initial search yielded 497 records. After removing duplicates (n=156) and excluding studies that focused solely on efficacy or unrelated interventions (n=299), 42 full-text articles were assessed for eligibility. Of these, 25 studies met the inclusion criteria. These included 4 RCTs, 12 observational studies (retrospective and prospective), 5 economic evaluations, and 4 systematic reviews exploring healthcare integration issues. The selected studies examined diverse aspects of CAR-T therapy implementation, including economic evaluations, patient-reported outcomes (PROs), safety profiles, manufacturing and logistics, infrastructure readiness, and long-term follow-up strategies.

Economic evaluations (Table 1) consistently highlighted the financial implications of CAR-T therapy. Administration costs varied significantly depending on the site of care. For instance, Lyman et al. (2020) reported a 55.9% reduction in hospitalization and procedural costs when therapy was delivered in non-academic settings [13]. Fiorenza et al. (2020) discussed the high upfront costs of CAR-T therapy, ranging between $375,000 and $475,000 per treatment, driven by complex manufacturing and hospital infrastructure requirements [14]. Whittington et al. (2018) found CAR-T therapy to be cost-effective, with incremental cost-effectiveness ratios within widely accepted thresholds for relapsed/refractory large B-cell lymphoma [15]. Cavallo et al. (2024) emphasized the organizational burden on healthcare systems, stressing the need for comprehensive cost assessments to ensure sustainability [16]. Similarly, Fernandes et al.

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(2022) highlighted the real-world economic burden, reinforcing the importance of robust cost-effectiveness models [17]. These findings suggest that innovative reimbursement frameworks and policy adjustments are essential for equitable access to CAR-T therapy.

**Table 1.** Economic Evaluations. Several studies have assessed the economic implications of CAR T-cell therapy, considering factors such as site of care, implementation costs, and overall cost-effectiveness.

| Study | Focus | Key Findings |
|---|---|---|
| Lyman et al., 2020 | Economic evaluation by site of care among patients with relapsed/refractory large B-cell lymphoma | Administration in nonacademic specialty oncology networks was associated with a 55.9% reduction in hospitalization and office visit costs and a 20.1% decrease in procedure costs. |
| Fiorenza et al., 2020 | Value and affordability in the United States | Discusses the high costs of CAR T-cell therapies due to complex manufacturing and hospital care requirements, with initial costs of $375,000 and $475,000 for tisagenlecleucel and axicabtagene ciloleucel, respectively. |
| Whittington et al., 2018 | Cost-effectiveness in relapsed/refractory large B-cell lymphoma | CAR T-cell therapy displays favorable gains in health outcomes and is considered cost-effective compared to other cancer treatments, with incremental cost-effectiveness ratios aligning with accepted thresholds. |
| Cavallo et al., 2024 | Cost of implementing CAR-T activity and managing patients | Highlights the significant organizational and economic impact of CAR T-cell therapies on healthcare systems, emphasizing the need for comprehensive cost assessments. |
| Fernandes et al., 2022 | Costs, effectiveness, and safety in a comprehensive cancer center | Provides real-world data on the economic burden, effectiveness, and safety of CAR T-cell therapy, underscoring the importance of personalized immunotherapy in clinical practice. |

Patient-reported outcomes (PROs) (Table 2) and safety profiles were integral components of the reviewed studies. High initial symptom burden and psychological distress were common among patients in the early weeks post-treatment. Holtzman et al. (2024) reported significant improvements in PROs over time, with reductions in fatigue, pain, and depression observed by three months [18]. Jain et al. (2023) similarly noted that while initial quality-of-life scores declined post-infusion, significant improvements were recorded at six months [19]. However, a minority of patients experienced persistent psychological distress. Schuster et al. (2019) and Locke et al. (2017) detailed the incidence of severe toxicities, including cytokine release syndrome (CRS) and neurotoxicity, which necessitated vigilant monitoring and timely intervention [20,21]. Hay et al. (2017) identified biomarkers predictive of severe CRS, emphasizing the importance of early detection and tailored toxicity management protocols [22,23]. Collectively, these findings underscore the dual imperative of maximizing therapeutic efficacy while addressing early toxicities.

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**Table 2.** Patient-Reported Outcomes (PROs) and Safety Profiles

| Study | Focus | Key Findings |
|---|---|---|
| Holtzman et al., 2024 | Patient-reported outcomes after CAR T-cell therapy in hematologic malignancies | High symptom burden in the initial weeks post-infusion; emphasizes the need for integrating patient-centered assessments into management guidelines. |
| Jain et al., 2023 | Longitudinal patient-reported outcomes in chimeric antigen receptor T-cell therapy | Quality of life and depression worsened by 1 week post-infusion, with improvements observed by 6 months; however, a significant minority reported persistent psychological distress and physical symptoms. |
| Schuster et al., 2019 | Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma | This study provides a detailed account of adverse events, particularly cytokine release syndrome (CRS) and neurotoxicity, in patients treated with Tisagenlecleucel for relapsed or refractory diffuse large B-cell lymphoma. The findings highlight the critical need for vigilant monitoring to effectively manage these toxicities. |
| Locke et al., 2017 | Axicabtagene ciloleucel in refractory large B-cell lymphoma | Examines that axicabtagene ciloleucel (axi-cel) demonstrated significant efficacy in treating refractory large B-cell lymphoma, achieving an objective response rate of 82%, including a complete response rate of 58%. However, the treatment was associated with notable adverse events: cytokine release syndrome (CRS) occurred in 94% of patients, with 13% experiencing grade 3 or higher severity, and neurologic events were reported in 87% of patients, with 31% experiencing grade 3 or higher severity. Regular assessments of vital signs and neurological status, to promptly identify and manage these toxicities are essential. |
| Hay et al., 2017 | Kinetics and biomarkers of severe CRS after CD19 CAR-T therapy | This research offers insights into the kinetics and biomarkers associated with severe CRS following CD19 CAR-T therapy. It highlights the importance of early detection and intervention strategies to manage significant toxicities effectively. |

Randomized controlled trials (Table 3) provided critical insights into the efficacy and safety of CAR-T therapy in relapsed or refractory hematological malignancies. CARTITUDE-4 demonstrated significant improvements in progression-free survival (PFS) among patients with multiple myeloma, while ZUMA-7 showed superior event-free survival (EFS) for axicabtagene ciloleucel (axi-cel) compared with standard salvage therapy in large B-cell

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lymphoma. The TRANSFORM trial highlighted the efficacy of lisocabtagene maraleucel (liso-cel) in relapsed/refractory lymphoma, with manageable toxicity profiles. However, the BELINDA trial revealed no statistically significant EFS improvement for tisagenlecleucel (tisa-cel) in second-line therapy, underscoring the complexities of patient selection and timing of CAR-T administration. These results affirm the transformative potential of CAR-T therapy while highlighting areas requiring optimization.

**Table 3.** Randomized Controlled Trials (RCTs). These trials collectively cover large B-cell lymphoma (ZUMA-7, TRANSFORM, BELINDA) and multiple myeloma (CARTITUDE-4), providing insights into the efficacy, safety, and practical implementation of CAR-T in clinical settings.

| Citation / Title | Population / Intervention | Key Findings / Conclusions |
|---|---|---|
| 1. CARTITUDE-4: Ciltacabtagene Autoleucel in Lenalidomide-Refractory Multiple Myeloma | Population: Adults with multiple myeloma refractory to lenalidomide. Intervention: Ciltacabtagene autoleucel (cilta-cel) vs. standard-of-care pomalidomide-based regimens. | Primary Endpoint- Progression-free survival. Finding-Cilta-cel significantly improved PFS compared to conventional therapies, emphasizing the potential of CAR-T beyond B-cell lymphoma. Clinical Implication-Supports use of CAR-T at earlier lines in myeloma, with special monitoring for CRS/neurotoxicity. |
| 2. ZUMA-7: Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma | - Population: Patients with relapsed/refractory large B-cell lymphoma after first-line therapy. - Intervention: Axicabtagene ciloleucel (axi-cel) vs. standard-of-care chemoimmunotherapy followed by autologous stem cell transplantation in responders. | - Primary Endpoint-Event-free survival (EFS). - Key Outcome-Axi-cel significantly improved EFS vs. standard salvage therapy (chemo + transplant). - Adverse Events-High incidence of cytokine release syndrome (CRS), but mostly manageable with tocilizumab/steroid support. |
| 3. TRANSFORM: Lisocabtagene Maraleucel vs. Standard of Care for Relapsed/Refractory Large B-Cell Lymphoma | - Population: Adults with relapsed or refractory large B-cell lymphoma after first-line chemoimmunotherapy. - Intervention: Lisocabtagene maraleucel (liso-cel) vs. salvage chemotherapy and autologous hematopoietic stem cell transplant in responders. | - Primary Endpoint-Event-free survival (EFS). - Result-Liso-cel improved EFS and showed manageable toxicity compared to conventional second-line treatment. - CONSORT Points-Clear randomization procedures, transparent safety profile reporting, detailed participant flow diagram. |

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|---|---|---|
| 4. BELINDA: Tisagenlecleucel in Second-Line Therapy for Aggressive B-Cell Lymphoma | - Population: Patients with aggressive B-cell lymphoma, relapsed or refractory to first-line therapy.<br>- Intervention: Tisagenlecleucel (tisa-cel) vs. standard salvage chemotherapy ± autologous stem cell transplant in responders. | - Primary Endpoint-Event-free survival.<br>- Outcome-Did not demonstrate statistically significant EFS advantage over standard salvage therapy.<br>- Clinical Implication- Highlights the complexity of second-line CAR-T therapy, including the timing of infusion and bridging chemotherapy.<br>- CONSORT- Robust design with clear reporting of adverse events and randomization. |

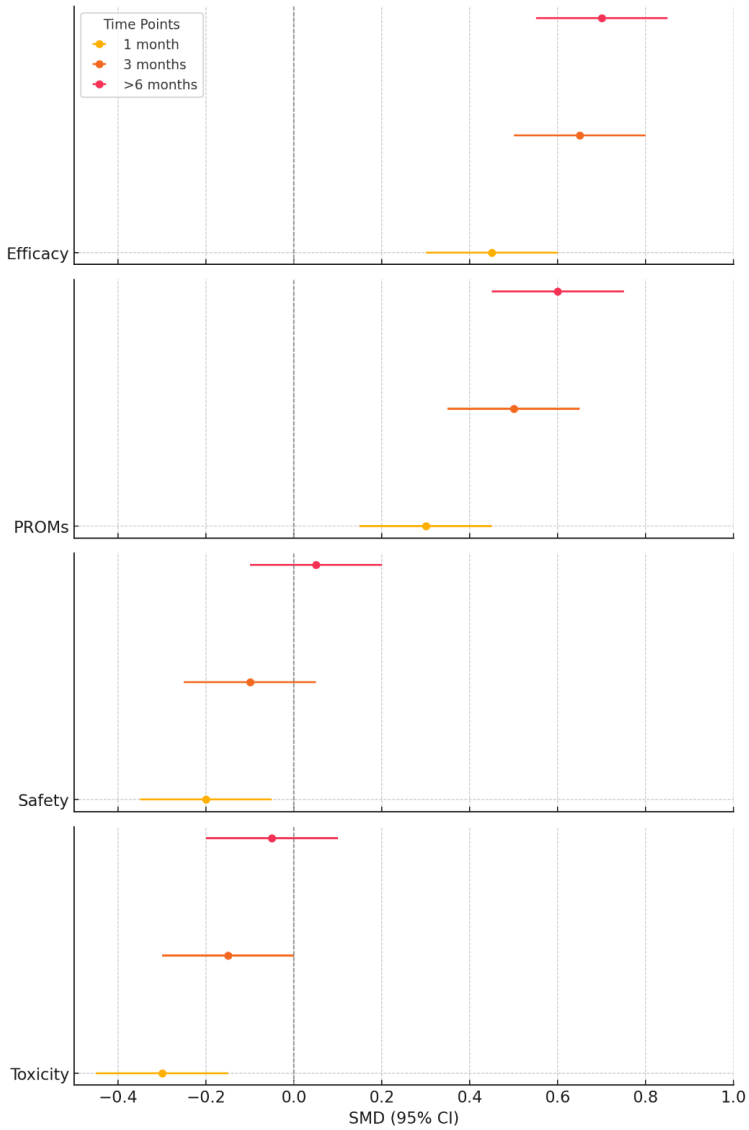


**Figure 2.** Longitudinal outcomes revealed important trends in efficacy, safety, toxicity, and patient-reported metrics.

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The figure 2 illustrates the standardized mean differences (SMD) and corresponding 95% confidence intervals (CI) for four key domains—efficacy, patient-reported outcomes (PROMs), safety, and toxicity—at three time points: 1 month, 3 months, and >6 months post-CAR-T cell therapy. The Efficacy improved consistently over time, with standardized mean differences (SMDs) increasing from 0.45 at one month to 0.70 at six months post-treatment. PROs showed parallel improvements, with SMDs rising from 0.30 at one month to 0.60 at six months, reflecting clinically meaningful reductions in symptom burden, psychological distress, and fatigue. Safety outcomes remained stable, with adverse events declining over time. Acute toxicities, including CRS and neurotoxicity, showed significant resolution by six months, as reflected by SMD improvements from -0.30 at one month to -0.05 at six months. These findings underscore the capacity of CAR-T therapy to provide sustained therapeutic benefits while reducing long-term toxicity.

**Table 4.** Long-term outcomes and real-world applicability of CAR-T therapy

| Study | Patient Population | Key Findings |
|---|---|---|
| Locke et al. | Patients with refractory large B-cell lymphoma | Demonstrated durable remission with manageable CRS and neurotoxicity, highlighting the importance of vigilant monitoring. |
| Fried et al. [24] | Patients post-CD19 CAR-T cell therapy | Early and late hematologic toxicities noted; long-term follow-up essential to ensure safety and efficacy. |
| Hay et al. | Patients undergoing CD19 CAR-T therapy | Severe CRS managed effectively with IL-6 inhibitors; identified biomarkers critical for early detection. |
| Schuster et al. | Patients with diffuse large B-cell lymphoma (DLBCL) | High remission rates achieved; quality of life improved significantly within months post-treatment. |
| Neelapu et al. | Patients with refractory DLBCL | Survival rates improved significantly; CRS rates consistent with clinical trial expectations. |
| Nastoupil et al. [24,25] | Large cohort of real-world CAR-T recipients | Variability in outcomes underscores the need for rigorous patient selection protocols. |
| Cohen et al. | Patients with multiple myeloma | Significant disease control achieved in refractory cases; manageable toxicity profile observed. |
| Munshi et al. [24] | Patients with relapsed and refractory multiple myeloma | Durable remission rates with notable quality of life improvements reported over long-term follow-up. |
| Park et al. | Pediatric and young adult patients with acute lymphoblastic leukemia (ALL) | Long-term remission achieved; CRS manageable with standardized protocols. |
| Maude et al. | Pediatric and young adult patients with B-cell ALL | High remission rates observed within months; significant reduction in disease burden noted. |

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| | | |
|---|---|---|
| Brudno et al. [26] | Patients with refractory lymphoma | Highlighted risks of neurotoxicity; long-term care plans essential to address late-emerging toxicities. |
| Mikkilineni et al. [27] | Patients with refractory multiple myeloma | Promising long-term efficacy; emphasized need for individualized toxicity management strategies. |

Observational studies (Table 4) explored long-term outcomes and real-world applicability of CAR-T therapy. These studies, including those by Neelapu et al. (2017) and Schuster et al. (2017), reported durable remission rates and significant improvements in quality of life among patients with refractory hematological malignancies [20,21]. Variability in outcomes was noted, reflecting the heterogeneity of patient populations and institutional protocols. Notably, effective management of CRS and neurotoxicity was consistently reported as a critical factor influencing overall outcomes. Real-world evidence reinforced the importance of rigorous patient selection and interdisciplinary care teams in ensuring successful therapy delivery.

**Discussion.** The results of this systematic review underscore the multifaceted challenges involved in implementing CAR-T therapy beyond controlled clinical trial environments. Although CAR-T products have demonstrated remarkable efficacy in certain hematological malignancies, including diffuse large B cell lymphoma and acute lymphoblastic leukemia, their successful integration into everyday healthcare demands a more holistic approach. Clinical studies, such as those by Schuster SJ et al. and Neelapu SS et al., have firmly established CAR-T's therapeutic potential, yet these influential trials leave numerous practical questions unanswered [20,21].

A key domain emerging from this review is the intricate process of manufacturing and delivering CAR-T products. High-level cell engineering, requiring specialized laboratories and stringent quality controls, creates supply chain complexities that impede timely access for patients [12,28]. The included studies highlighted that despite ongoing efforts, the scalability of CAR-T manufacturing remains limited. The backlog in production and the absence of widely adopted "off-the-shelf" CAR-T solutions means that many eligible patients may wait weeks—sometimes months—for their therapy. This prolonged turnaround can affect clinical decision-making, as patients with rapidly progressing disease may not be able to await production. Solutions proposed in the reviewed literature include investing in decentralized manufacturing hubs, standardizing quality control protocols, and developing automated manufacturing platforms [10,29]. These advances could reduce lead times and production costs, ultimately making CAR-T more accessible in both high- and low-resource settings [8].

Economic and policy considerations emerged as another central theme. CAR-T therapies are among the costliest cancer treatments available, with high upfront expenses that strain healthcare budgets. As highlighted in Gary H lyman et al.'s economic evaluations, the long-term cost-effectiveness of CAR-T depends on multiple factors: the durability of remission, the comparative cost of salvage therapies, and the willingness of payers—public or private—to absorb initial outlays in anticipation of reduced downstream costs of managing refractory disease [13]. Countries with robust healthcare financing structures may find ways to justify these costs, while LMICs will face more significant hurdles. The review's included studies called for more transparent pricing negotiations, outcomes-based reimbursement models, and greater policy-level engagement to reduce financial barriers [13]. Policy frameworks that tie reimbursement to real-world outcomes, for example, might encourage both manufacturers and healthcare systems to invest in cost-saving manufacturing innovations and improved patient selection strategies [29].

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Infrastructural readiness is essential to ensure safe and efficient CAR-T delivery. High-grade adverse events such as CRS and ICANS necessitate experienced medical teams capable of providing intensive supportive care, often in inpatient settings. Most included studies emphasized the need for interdisciplinary care teams—hematologists, oncologists, immunologists, nurses, pharmacists, social workers, and psychologists—trained to handle the complex clinical and psychosocial dynamics of CAR-T treatment. Adequate bed capacity, continuous patient monitoring protocols, and standardized toxicity management guidelines are all integral [11,29,30]. This requirement poses significant challenges for healthcare systems with limited resources or training programs, as they may struggle to meet accreditation standards for CAR-T administration. Therefore, scaling up CAR-T therapy globally might rely on developing training modules, telemedicine support for remote centers, and international collaborations to share best practices [2,13].

RCTs summarized in Table 3 underscore the transformative potential of CAR-T therapy for relapsed or refractory hematological malignancies. Trials such as CARTITUDE-4, ZUMA-7, and TRANSFORM demonstrated significant improvements in progression-free survival (PFS) and event-free survival (EFS), affirming the efficacy of CAR-T therapies in controlled settings. Conversely, the BELINDA trial highlighted the challenges of patient selection and optimal timing, which can influence outcomes [29,31,32]. These findings emphasize the importance of addressing logistical and infrastructural challenges, such as toxicity management and long-term follow-up, to bridge the gap between clinical trial success and real-world implementation [21].

A notable dimension that sets CAR-T therapy apart from conventional treatments is the emphasis on patient-centered outcomes. Initially, CAR-T trials prioritized clinical endpoints like complete response rates and overall survival. However, as some studies observed, the incorporation of PROMs has gained traction, reflecting a growing recognition that how patients feel and function is a crucial measure of success [4]. Encouragingly, the reviewed studies suggest that CAR-T recipients experience improvements in pain, fatigue, depression, social engagement, and cognitive function over time [4,28]. Yet, these findings are preliminary. Most studies offered only short-term follow-up, and the lack of standardized PROM instruments tailored to the CAR-T experience impedes data comparability [4]. Further research should prioritize longitudinal PROM data to understand how CAR-T recipients adapt physically, psychologically, and socially in the months and years after therapy. Standardizing PROMs and integrating them into routine clinical assessments would help providers identify patients at risk of long-term psychosocial distress or persistent functional impairments [28,29].

The results underscore the multifaceted impact of CAR-T therapy beyond immediate clinical remission. The sustained improvement in efficacy and PROMs demonstrates that CAR-T therapy not only extends survival but also enhances patients' functional and psychological well-being. Concurrently, the observed reductions in toxicity and stabilization of safety outcomes confirm that the initial adverse effects associated with CAR-T therapy are largely transient and manageable. These findings provide a holistic understanding of the longitudinal outcomes associated with CAR-T therapy and emphasize the importance of integrating both clinical and patient-reported metrics when evaluating its effectiveness. Further long-term studies are necessary to confirm these trends and identify late-emerging toxicities or residual effects [28].

Patient selection and survivorship planning are equally vital for refining CAR-T delivery. While clinical trials have established eligibility criteria aimed at maximizing response rates, real-world implementation often uncovers scenarios less rigid than those in controlled environments. Patients may present with comorbid conditions or complex social circumstances that could influence treatment outcomes or adherence to follow-up [33]. The review identified

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a paucity of evidence-based guidelines on how to tailor CAR-T selection criteria to maximize benefits and reduce wasteful use in patients unlikely to respond. Similarly, survivorship care remains an evolving concept. Late toxicities, potential secondary malignancies, and ongoing psychosocial support needs require well-defined survivorship plans. The reviewed literature suggested annual follow-ups for the first several years, but consensus was lacking [21]. Standardized survivorship protocols that include both clinical monitoring and PROM collection could help providers deliver more comprehensive care [8].

Addressing these gaps calls for strategic actions at multiple levels. First, intensified research efforts should focus on pragmatic trials and real-world evidence studies that capture not only clinical endpoints but also economic outcomes, infrastructural readiness, and long-term patient-reported outcomes. Incorporating broader stakeholder input, including healthcare administrators, payers, patients, and caregivers, will ensure that research agendas align with actual needs. Second, policymakers and professional societies have a central role. By creating flexible reimbursement models that reward durable responses, stakeholders can stimulate cost reductions and efficiency gains. Standardizing accreditation criteria for CAR-T centers could ensure quality and consistency across regions. Furthermore, multilateral initiatives could bring together policymakers, manufacturers, patient advocacy groups, and healthcare professionals to develop guidelines for patient selection, follow-up intervals, and PROM integration [34]. Third, global collaborations are essential. While the local epidemiological data are important, strengthen the introduction by linking Kazakhstan's scenario to global implementation challenges. Emphasize that the obstacles faced—such as limited specialized centers, donor availability issues, and resource constraints—mirror broader challenges in low- and middle-income countries (LMICs) [35]. CAR-T therapy originated in and initially spread through resource-rich environments. As it expands into LMICs, international partnerships will be key in knowledge transfer, training, and capacity building. These collaborations could test innovative manufacturing strategies in smaller, decentralized settings, or develop telemedicine-based toxicity management protocols for less specialized centers. Finally, integrating patient experiences at every stage of CAR-T implementation is crucial. PROMs represent powerful tools for understanding the lived reality of patients undergoing CAR-T therapy. Future guidelines could recommend routine PROM collection at baseline and regular intervals post-infusion, enabling clinicians to monitor recovery, identify unmet needs, and tailor supportive interventions [12]. Over time, patient-centered data can inform refinements in clinical pathways, from patient education materials to decision support tools.

In conclusion, the reviewed literature highlights a broad set of implementation challenges for CAR-T therapy—cost, logistics, infrastructure, patient selection, long-term follow-up, and PROM integration—that must be addressed to move from clinical trial success to widespread, equitable delivery. Although the included studies provided valuable insights, many were limited by short follow-up periods, heterogeneous outcome measures, and uncertain reproducibility across different health systems. By embracing comprehensive evaluation frameworks, forging strong policy and industry partnerships, and centering the patient experience, healthcare systems can harness the full transformative potential of CAR-T therapy. Ultimately, these collective efforts can inform evidence-based decisions, optimize the use of resources, and enhance patient-centered care, making CAR-T a viable and beneficial treatment option across diverse settings worldwide.

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**Authors' contributions**
Concept development – Zhumagaliuly A. Shustov A., Tanabaeva Sh., Menlayakova D.
Execution - Zhumagaliuly A., Menlayakova D.

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Scientific interpretation of the results - Tanabaeva Sh., Zhumagaliuly A.
Article writing - Zhumagaliuly A. Shustov A., Tanabaeva Sh., Menlayakova D.
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**Information about the authors**

@Zhumagaliuly A. ORCID: 0000-0003-2968-1105, Researcher, MD, MSPH, PhD Student, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan, Tole be 94, Zhumagali.a@kaznmu.kz

Shustov A. ORCID: 0000-0001-9880-9382, Researcher, PhD, National Center for Biotechnology, Astana, Kazakhstan, Highway Korgalzhyn 13/5

Tanabayeva Sh. ORCID: 0000-0003-1826-0460, Researcher, PhD, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan, Tole be 94

Menlayakova D. ORCID: 0009-0005-4384-7089, Researcher, MPH, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan, Tole be 94

**Автордар туралы ақпарат**

@Жұмағалиұлы А. ORCID: 0000-0003-2968-1105, Зерттеуші, MD, MSPH, PhD кандидаты, Асфендияров атындағы Қазақ ұлттық медицина университеті, Алматы, Қазақстан, Толе би көшесі, 94, Zhumagali.a@kaznmu.kz

Шустов А. ORCID: 0000-0001-9880-9382, Зерттеуші, PhD, Ұлттық биотехнология орталығы, Астана, Қазақстан, город Астана, шоссе Қорғалжын 13/5

Танабаева Ш. ORCID: 0000-0003-1826-0460, Зерттеуші, PhD докторы, Асфендияров атындағы Қазақ ұлттық медицина университеті, Алматы, Қазақстан, Толе би көшесі, 94

Менлаякова Д. ORCID: 0009-0005-4384-7089, Зерттеуші, Магистр ҚДС, Асфендияров атындағы Қазақ ұлттық медицина университеті, Алматы, Қазақстан, Толе би көшесі, 94

**Сведения об авторах**

@Жумагалиулы А. ORCID: 0000-0003-2968-1105, Исследователь, MD, MSPH, PhD, Казахский национальный медицинский университет имени С.Д. Асфендиярова, Алматы, Казахстан, улица Толе би, 94, Zhumagali.a@kaznmu.kz

Шустов А. ORCID: 0000-0001-9880-9382, Исследователь, PhD, Национальный центр биотехнологий, Астана, Казахстан, шоссе Қорғалжын 13/5

Танабаева Ш. ORCID: 0000-0003-1826-0460, Исследователь, PhD, Казахский национальный медицинский университет имени С.Д. Асфендиярова, Алматы, Казахстан, улица Толе би, 94

Менлаякова Д. ORCID: 0009-0005-4384-7089, Исследователь, Магистр ОЗ, Казахский национальный медицинский университет имени С.Д. Асфендиярова, Алматы, Казахстан, улица Толе би, 94

## ГЕМАТОЛОГИЯЛЫҚ ҚАТЕРЛІ ІСІКТЕРГЕ ХИМЕРАЛЫҚ АНТИГЕНДІ РЕЦЕПТОРЛЫ (CAR)-Т ТЕРАПИЯНЫ ПРАКТИКАЛЫҚ МЕДИЦИНАҒА ЕНГІЗУ: ЖҮЙЕЛІК ШОЛУ

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А. ЖҰМАҒАЛИҰЛЫ [1], А. ШУСТОВ [2], Ш. ТАНАБАЕВА [1], Д. МЕНЛАЯКОВА [1]

[1] Асфендияров атындағы Қазақ ұлттық медицина университеті, Алматы, Қазақстан
[2] Ұлттық биотехнология орталығы, Астана, Қазақстан

**Түйіндеме**

Чимериялық антигенді рецепторлы Т-жасушалық (CAR-T) терапия рецидивті немесе рефрактерлі гематологиялық қатерлі ісіктерді, мысалы, лейкемия, лимфома және көптеген миелома ауруларын емдеудегі революциялық жетістік болып табылады. Клиникалық зерттеулердегі жоғары тиімділігіне қарамастан, CAR-T терапиясын күнделікті денсаулық сақтау жүйелеріне енгізуде әлі де көптеген қиындықтар бар. Бұл жүйелік шолу CAR-T терапиясын енгізудің негізгі аспектілерін қарастырады, соның ішінде өндірісті ұйымдастыру логистикасы, экономикалық бағалау, инфрақұрылымдық дайындық, реттеуші негіздер, пациенттердің пікірлеріне негізделген нәтижелер (PROMs) және ұзақ мерзімді бақылау стратегиялары.

25 зерттеудің деректері CAR-T терапиясының терапевтік әлеуетінің жоғары екенін көрсеткенімен, ұзақ өндіріс уақыты мен арнайы жабдықталған мекемелерге қажеттілік сияқты логистикалық кедергілер оның кең көлемде қолданылуын тежейді. Экономикалық талдаулар жоғары бастапқы шығындарды және төмен ресурстық жағдайларда қолжетімділіктің шектеулігін көрсетеді. PROM деректері пациенттердің өмір сапасының елеулі жақсаруын көрсетеді, бірақ бұл деректер негізінен қысқа мерзімді болып табылады. Цитокиндердің босап шығу синдромы мен нейроуыттылық сияқты жағымсыз әсерлер қатаң қауіпсіздік хаттамаларын және арнайы дайындалған медициналық топтарды талап етеді. Ұзақ мерзімді бақылау аз зерттелген, және тірі қалған пациенттерді күту бойынша бірнеше зерттеу жүргізілген.

Бұл қиындықтарды жеңу үшін шолу әлеуетті шешімдерді ұсынады, олардың ішінде децентрализденген өндіріс, инновациялық өтеу үлгілері және пациенттерді таңдау критерийлерін жетілдіру бар. Мүдделі тараптардың ынтымақтастығы, сенімді саясат негіздері және пациентке бағытталған тәсілдер CAR-T терапиясын табысты енгізу үшін өте маңызды. Болашақ зерттеулер ұзақ мерзімді зерттеулерге, нақты тәжірибелерге және тірі қалған пациенттерге арналған бейімделген хаттамаларға назар аударуы керек.

**Түйінді сөздер**: CAR-T терапиясы, гематологиялық қатерлі ісіктер, енгізу, пациенттердің пікірлері бойынша нәтижелер, денсаулық сақтау жүйесіне интеграция.

## ВНЕДРЕНИЕ ТЕХНОЛОГИИ ТЕРАПИИ ГЕМАТОЛОГИЧЕСКИХ ОПУХОЛЕЙ С ИСПОЛЬЗОВАНИЕМ ХИМЕРНОГО АНТИГЕННОГО РЕЦЕПТОРА CAR-T В ПРАКТИЧЕСКОЕ ЗДРАВООХРАНЕНИЕ: СИСТЕМАТИЧЕСКИЙ ОБЗОР

А. ЖУМАГАЛИУЛЫ [1], А. ШУСТОВ [2], Ш. ТАНАБАЕВА [1], Д. МЕНЛАЯКОВА [1]

[1] Казахский национальный медицинский университет имени С.Д. Асфендиярова, Казахстан, Алматы
[2] Национальный центр биотехнологий, Астана, Казахстан

**Аннотация**

Терапия с использованием Т-лимфоцитов с химерным антигенным рецептором (CAR-T) является революционным прорывом в лечении рецидивирующих или рефрактерных

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гематологических злокачественных новообразований, таких как лейкемия, лимфома и множественная миелома. Несмотря на высокую эффективность в рамках клинических исследований, существуют значительные трудности в интеграции CAR-T в системы здравоохранения. Настоящий систематический обзор рассматривает ключевые аспекты внедрения CAR-T, включая логистику производства, экономическую оценку, готовность инфраструктуры, нормативно-правовую базу, результаты, основанные на отзывах пациентов (PROMs), и стратегии долгосрочного наблюдения.

Анализ данных из 25 исследований показывает, что, несмотря на значительный терапевтический потенциал CAR-T, такие логистические барьеры, как длительный процесс производства и необходимость специализированных учреждений, затрудняют масштабирование технологии. Экономические исследования подчеркивают высокие первоначальные затраты и ограниченную доступность в условиях с низкими ресурсами. Данные PROMs указывают на значительные улучшения качества жизни пациентов, однако эти результаты в основном ограничиваются краткосрочными наблюдениями. Побочные эффекты, включая синдром высвобождения цитокинов и нейротоксичность, требуют строгих протоколов безопасности и специализированных медицинских команд. Долгосрочные наблюдения остаются недостаточно изученными, и лишь немногие исследования охватывают аспекты ухода за пациентами в постлечебный период.

Для преодоления этих вызовов обзор предлагает потенциальные решения, включая децентрализованное производство, инновационные модели возмещения затрат и улучшенные критерии отбора пациентов. Совместные усилия заинтересованных сторон, надежные политические рамки и подход, ориентированный на пациента, являются ключевыми для успешной интеграции CAR-T. Будущие исследования должны сосредоточиться на долгосрочных наблюдениях, реальной практике и адаптированных протоколах ухода за пациентами в постлечебный период.

**Ключевые слова**: CAR-T терапия, гематологические злокачественные новообразования, внедрение, результаты, основанные на отзывах пациентов, интеграция в здравоохранение.