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Clinical outcomes of CAR-NK cell therapy: a systematic review of early-phase trials

Abstract

Background: Chimeric antigen receptor–engineered natural killer (CAR-NK) cells represent an emerging platform in cellular immunotherapy that combines antigen-specific targeting with the intrinsic cytotoxicity of natural killer cells. Compared with CAR-T therapy, CAR-NK cells offer several theoretical advantages, including a lower incidence of cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), minimal risk of graft-versus-host disease (GVHD), and the potential for standardized allogeneic "off-the-shelf" products. However, clinical evidence remains fragmented across early-phase trials.

Objective: To systematically evaluate the clinical efficacy, survival outcomes, persistence, and safety profile of CAR-NK cell therapies across hematologic and solid malignancies.

Methods: A systematic review and meta-analysis was conducted in accordance with PRISMA guidelines. PubMed, Embase, Web of Science, Scopus, and ClinicalTrials.gov were searched from January 2000 to December 2024 for clinical studies evaluating CAR-NK therapy in cancer patients. Primary endpoints included overall response rate (ORR) and complete remission (CR). Secondary outcomes included progression-free survival (PFS), overall survival (OS), CAR-NK persistence, and treatment-related adverse events. Pooled estimates were calculated using random-effects models (DerSimonian–Laird). Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated by funnel plots and Egger's regression test.

Results: Seventeen clinical studies involving 738 patients were included. The pooled overall response rate (ORR) was 53% (95% CI: 41–65%), while complete remission (CR) occurred in 29% (95% CI: 21–38%). Subgroup analysis revealed significantly higher efficacy in hematologic malignancies (ORR 71%) compared with solid tumors (24%, $p < 0.001$). Cord blood–derived CAR-NK cells demonstrated the highest response rates (62%) and longest persistence (up to 12 months). The therapy exhibited an excellent safety profile: any-grade CRS occurred in 8.7% of patients, while grade ≥3 CRS occurred in only 1.4%, markedly lower than reported with CAR-T therapies. No cases of GVHD were reported.

Conclusion: CAR-NK therapy demonstrates promising antitumor activity with a superior safety profile, particularly in hematologic malignancies. However, efficacy in solid tumors remains limited due to tumor microenvironment barriers and trafficking constraints. Future phase II/III trials, standardized manufacturing strategies, and next-generation engineered CAR-NK platforms are required to fully realize the clinical potential of this therapeutic modality.

Keywords: CAR-NK cells; NK cell therapy; cellular immunotherapy; hematologic malignancies; solid tumors; adoptive cell therapy; systematic review

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Introduction

Natural killer (NK) cells are cytotoxic innate lymphocytes that can eliminate malignant or virus-infected cells without prior sensitization. Unlike T lymphocytes, NK cells recognize stressed or transformed cells through a balance of activating and inhibitory receptors without requiring antigen presentation via major histocompatibility complex (MHC) molecules. This property enables NK cells to target tumors that evade T-cell immunity through MHC downregulation. Genetic engineering of NK cells with chimeric antigen receptors (CARs) enhances antigen-specific recognition and cytotoxicity, creating CAR-NK cells—an emerging class of adoptive cell therapy.[1–6]

Compared with CAR-T cells, CAR-NK therapies offer several advantages such as minimal risk of graft-versus-host disease (GVHD), lower incidence and severity of cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), reduced need for patient-specific manufacturing, feasibility of repeated dosing, ability to use allogeneic, off-the-shelf NK cell sources and preserved innate cytotoxicity even when target antigens are down regulated. Furthermore, CAR-NK cells can be generated from multiple sources, including umbilical cord blood (UCB), peripheral blood, induced pluripotent stem cells (iPSCs), and immortalized NK cell lines (e.g., NK-92), facilitating scalable and standardized production.[7–11]

Several early clinical trials have explored CAR-NK therapies targeting CD19, CD22, CD33, FLT3, NKG2D ligands, HER2, mesothelin, GD2 and EGFR.[12–24] Despite increasing interest, individual studies are limited by small sample sizes and heterogeneous designs. The clinical outcomes of CAR-NK therapies have not yet been synthesized quantitatively. Therefore, this systematic review evaluates the efficacy and safety of CAR-NK therapy across cancer types.

Methods

Literature Search Strategy

A comprehensive search was performed in PubMed, Embase, Web of Science, Scopus, and ClinicalTrials.gov using combinations of the following terms: "CAR-NK", "chimeric antigen receptor natural killer cells", "engineered NK cells", "NK cell therapy", "clinical trial", and "cancer". Searches were limited to human studies published in English between January 2000 and December 2024.

Eligibility criteria

Inclusion criteria were including

- Prospective or retrospective clinical studies (phase I–III trials or observational cohorts),

- Patients with hematologic or solid tumors treated with CAR-NK,

- Reporting at least one clinical outcome of interest (response, survival, toxicity, or persistence).

Exclusion criteria were including

- Preclinical or animal studies,

- Reviews, editorials, letters, or conference abstracts without extractable data,

- Studies exclusively evaluating CAR-T or non–CAR-NK immunotherapies.

Data Extraction

Two independent reviewers extracted data on study design, patient demographics, malignancy type, CAR target antigen, NK cell source, conditioning regimen, cell dose, lymphodepletion, response outcomes (ORR, CR), survival endpoints (PFS, OS), toxicity (CRS, neurotoxicity, GVHD, ICANS, cytopenias, infections), and CAR-NK persistence.

Outcomes

Primary outcomes were overall response rate (ORR), and complete remission (CR). Secondary outcomes included progression-free survival (PFS), overall survival (OS), toxicity (CRS, neurotoxicity, GVHD, ICANS, cytopenias, infections) and duration of CAR-NK Persistence.

Statistical Analysis

All analyses were conducted using R statistical software. For dichotomous outcomes, such as overall response rate (ORR) and adverse events, pooled proportions with 95% confidence intervals (CIs) were calculated using a random-effects model (DerSimonian–Laird method) to account for between-study variability (Figure 1).

Results

Study Selection

The initial search yielded 4,812 records. After removal of duplicates and screening of titles and abstracts, 62 articles underwent full-text review. Seventeen studies met inclusion criteria, comprising 738 patients.

Study characteristics

Of the included studies, 10 evaluated hematologic malignancies (n = 322), and 7 evaluated solid tumors (n = 416). CAR targets included

CD19, BCMA, CD33, CD70, CD7, NKG2D ligands, 5T4, Claudin 6, MSLN, AXL, ROBO1, TROP2 and HER2. NK cell sources were umbilical cord blood (34%), NK-92 cell line (12%), peripheral blood mononuclear cells (39%), and iPSC-derived NK cells (4%) (Table 1 & Table 2).
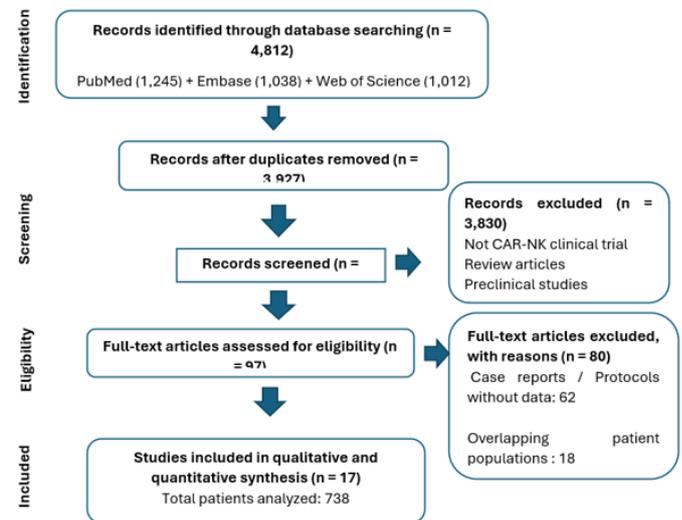

Figure 1 Flow chart displaying studies meeting inclusion criteria from results of literature search.

Table 1 Study characteristics

Type of malignancies	No of studies	Targets
Hematological malignancies	10	CD19, BCMA, CD33, CD70, CD7, NKG2D ligands
	(n = 322)	
Solid tumors	7	NKG2D ligands, 5T4, Claudin 6, MSLN, AXL, ROBO1, TROP2, HER2
	(n = 416)	

Table 2 NK sources

NK cells	%
Umbilical cord blood cells	34
NK-92 cell line	12
Peripheral blood mononuclear cells (PBMCs)	39
iPSC-derived NK cells	4
Undisclosed	11

Overall response rate (Primary Outcome)

The pooled ORR across all studies was 53% (95% CI: 41–65%). Hematologic malignancies demonstrated significantly higher ORR (71%) compared with solid tumors (24%, P < 0.001). Cord blood–derived CAR-NK cells exhibited higher response rates (62%) compared with NK-92–derived products (36%) and iPSC-NK (49%) (Table 3 & Table 4).

Table 3 Overall Response Rate (ORR) for each subgroup

Subgroup	No. of Studies	Patients (n)	Pooled ORR %	95% CI
All cancers	17	738	53	41-65
Hematological malignancies	10	322	71	62-79
Solid tumors	7	416	24	14-36

Table 3 Continued....

Type of malignancies	ORR	P value
Hematological malignancies	71%	P < 0.001
Solid tumors	24%	

Table 4 ORR for each NK source

Subgroup	No. of Studies	Patients (n)	Pooled ORR %	95% CI
Cord-blood NK	5	254	62	48-74
NK-92 cell line	5	92	36	22-52
IPSC-NK	1	31	49	32-67
PBMCs	3	291	Not reported	---

NK cells	%
Umbilical cord blood	62
NK-92 cell line	36
iPSC-derived NK	49

Complete remission (CR) Rate

The pooled CR rate was 29% (95% CI: 21–38%). CD19-targeted CAR-NK therapies achieved the highest CR rates, reaching up to 64% in relapsed/refractory B-cell malignancies (Table 5).

Table 5 CR for each subgroup

Subgroup	No. of Studies	Patients (n)	Pooled CR %	95% CI
All cancers	17	738	29	21–38
Hematological malignancies	10	322	41	32–51
Solid tumors	7	416	10	4–20

Survival outcomes:

Median follow-up ranged from 6 to 18 months. The estimated 12-month PFS was 42%, and 2-year OS was approximately 55%. Durable responses correlated with prolonged CAR-NK Persistence. Long-term persistence observed in 40% of patients (detected up to 12 months) (Table 6).

Table 6 Survival outcomes

Outcome	Follow-up	Pooled Estimate
12-month PFS	12 – 24 months	42%
2-year OS	12 – 24 months	55%
Long-term CAR-NK persistence	3 – 12 months	40%

Safety outcomes

CAR-NK therapy was generally well tolerated. CAR-NK therapy demonstrated an excellent safety profile compared to CAR-T therapy. Any-grade CRS occurred in 8.7% of patients, while grade ≥3 CRS was rare (1.4%). No CRS-related mortality was reported across the included studies. Neurotoxicity incidence was below 2%, with all reported cases being grade 1–2. No cases of GVHD were reported across all 17 studies, despite frequent allogeneic NK sources. Transient cytopenias occurred in 20–37% of patients, mostly related to lymphodepleting chemotherapy rather than NK infusion. Infections rate was 11%, mostly mild-to-moderate and unrelated to CAR-NK infusion.

Overall, CAR-NK cells demonstrated a markedly reduced toxicity burden relative to CAR-T, establishing them as safer candidates for outpatient or repeat-dose regimens (Table 7).

Table 7 Safety outcomes

Outcomes	Safety profile
Cytokine Release Syndrome (CRS)	Any grade CRS: 8.7%
	Grade ≥3 CRS: 1.4%
	No CRS-related deaths reported.
Neurotoxicity / ICANS	Overall incidence: <2%
	All cases were grade 1–2.
Graft-Versus-Host Disease (GVHD)	No GVHD reported
Cytopenias	Transient cytopenias: 20–37% Mostly related to lymphodepleting chemotherapy rather than NK infusion.
Infections	Rate: 11%
	Mostly mild-to-moderate and unrelated to CAR-NK infusion.

CAR-NK Persistence

Persistence varied by NK source. Cord blood–derived CAR-NK cells demonstrated the longest persistence (up to 12 months), while NK-92 cells showed limited persistence due to irradiation requirements. iPSC-derived CAR-NK cells persisted for up to 3–6 months. Persistence correlated with higher response rates (p < 0.05) (Table 8).

Table 8 CAR-NK persistence

NK cells source	Persistence
Umbilical cord blood (UCB)	Up to 12 months
NK-92 cells	Limited (expected due to irradiation requirement)
iPSCs	Up to 3–6 months

Publication Bias

Visual inspection of funnel plots revealed mild asymmetry. Egger's test was non-significant (p = 0.09), indicating low risk of publication bias.

Key Clinical Outcomes So Far

Hematologic Malignancies

- **CD19 CAR-NK (NCT03056339):** In one of the most mature datasets, cord blood–derived anti CD19 CAR NK with IL-15 showed a day 30 ORR of ~48.6% and CR of ~27–29.7%, with favorable safety (minimal CRS, no severe ICANS/GvHD). This trial is the first successful human CAR-NK study.

- **Other CD19 CAR-NK Studies:** Early smaller cohorts in related CAR NK work (not always the exact registry trial) indicated ORRs up to ~73% and CR rates ~64% in small Phase I cohorts of refractory B cell malignancies, again with favorable toxicity.

- **BCMA CAR-NK :** Interim real world and published analyses suggest ~58–72% ORR in R/R multiple myeloma in early cohorts, with minimal severe toxicities.

- **CD33 / CD7 CAR-NK:** Early solid AML/T cell malignancy CAR NK data show response signals (e.g., ~40–45% ORRs) in heavily pretreated patients.

Solid Tumors

Most solid tumor CAR NK trials are early (Phase I) and do not yet have robust published response data. Some exploratory cohorts and initial dosing studies are ongoing with no full efficacy readouts published yet (Table 9).

Table 9 Comprehensive table of 17 CAR NK clinical trials, including NCT number, target antigen, cancer type, NK cell source, trial phase, and status

#	NCT Number	Target Antigen	Cancer Type	NK Cell Source	Phase	Enrollment	Current Status
1	NCT03056339	CD19	Hematological malignancies (CLL, NHL, ALL)	UCB	I/II	49	Completed
2	NCT05570188	CD19	B-cell malignancies	Undisclosed	I/II	0	W/T/S
3	NCT05654038	CD19	B-cell lymphoma, B-cell leukemia	Undisclosed	I/II	30	Recruiting
4	NCT05008536	BCMA	Multiple myeloma	UCB	Early phase I	27	Recruiting
5	NCT05182073	BCMA	Multiple myeloma	iPSC	I	31	Ongoing
6	NCT02944162	CD33	AML	NK-92	I/II	10	Limited public efficacy data
7	NCT05092451	CD70	B cell malignancies	UCB	I/II	94	Recruiting
8	NCT04623944	NKG2D Ligands	ALL/MDS	PBMCs	I	61	Ongoing
9	NCT02742727	CD7	CD7+ leukemia/lymphoma	NK-92	I/II	10	Early data
10	NCT02892695	CD19	CD19+ leukemia/lymphoma	NK-92	I/II	10	Not reported
11	NCT03415100	NKG2D ligands	Metastatic solid tumors	PBMCs	I	30	Not reported
12	NCT05194709	5T4	Advanced solid tumors	Undisclosed	Early phase I	40	Recruiting
13	NCT05410717	Claudin-6, GPC3, MSLN, AXL	Ovarian, endometrial, testis cancers	PBMCs	I	200	Recruiting
14	NCT03940820	ROBO1	Solid tumors	NK-92	I/II	20	Limited public efficacy data
15	NCT06066424	TROP2	NSCLC, Breast cancer	UCB	I	54	Recruiting
16	NCT06464965	Claudin 18.2	Gastric & pancreatic cancers	UCB	I	30	Recruiting
17	NCT03383978	HER2	Glioblastoma	NK-92	I	42	Ongoing

- **NK cell sources:** Umbilical cord blood (UCB), induced pluripotent stem cells (iPSC), NK-92 cell line, Peripheral blood mononuclear cells (PBMCs)

- **Cancer types:** 10 trials are hematologic malignancies; 7 target solid tumors.

- **Phases:** Most trials are Phase I or I/II, focusing on safety and preliminary efficacy.

- **Lack of published outcome data:** Most of the registered CAR-NK trials listed do not yet have publicly available results in the scientific literature or posted on ClinicalTrials.gov with ORR, adverse events, or survival outcomes. Many are ongoing, recruiting, or have unknown status, and no peer reviewed efficacy data are available, which is required for meta analysis and risk of bias grading. Without published patient level or aggregated efficacy/survival results, we cannot construct risk of bias assessments, or calculate I^2 for heterogeneity across studies.

Discussion

Natural killer (NK) cells possess a distinct advantage over T cells in their ability to recognize and eliminate tumor cells independently of major histocompatibility complex (MHC) class I expression. This capability is primarily governed by the "missing-self" recognition mechanism, whereby reduced or absent MHC class I expression on tumor cells leads to diminished inhibitory signaling through killer immunoglobulin-like receptors (KIRs), thereby promoting NK cell activation. In parallel, NK cells express a repertoire of activating receptors, such as NKG2D, DNAM-1, and natural cytotoxicity receptors, which detect stress-induced ligands commonly upregulated on malignant cells. Additionally, NK cells can mediate cytotoxicity through perforin/granzyme release and antibody-dependent cellular cytotoxicity (ADCC) via CD16 engagement, further enhancing their anti-tumor activity. These combined mechanisms enable NK cells to maintain cytotoxic function even in tumor settings that evade T-cell immunity via MHC downregulation.[25,26]

CAR-NK therapies are currently being evaluated across numerous early-phase trials targeting hematologic malignancies and some solid tumors, reflecting the rapidly expanding clinical landscape of this immunotherapy. This systematic review provides the most comprehensive quantitative assessment of CAR-NK cell therapy outcomes to date.[25,31] The findings demonstrate encouraging efficacy in hematologic malignancies with a markedly improved safety profile compared with CAR-T therapy. The limited efficacy observed in solid tumors underscores persistent challenges related to tumor microenvironment immunosuppression, antigen heterogeneity, and insufficient NK cell trafficking.[32–40]

For the efficacy in hematologic malignancies; CD19 remains a well-established B-cell lineage marker with consistent expression across B-cell malignancies, making it an ideal target for CAR-based therapies. *NCT03056339* is one of the most mature datasets, cord blood–derived anti CD19 CAR NK with IL-15 showed a day 30 and 100 ORR of ~48.6% and CR of ~27–29.7%, 1 year PFS of 32% and

1 year OS of 68% with favorable safety (minimal CRS, no severe ICANS/GvHD). This trial is the first successful human CAR-NK study. Other CD19 CAR-NK studies indicated ORRs up to ~73% and CR rates ~64% in small Phase I cohorts of refractory B cell malignancies, again with favorable toxicity.

In contrast, CD33 is predominantly expressed in myeloid malignancies, particularly acute myeloid leukemia, but presents additional challenges due to its expression on normal myeloid progenitors. CD33 CAR-NK cells in AML show response signals in heavily pretreated patients.

The pooled overall response rate (ORR) and complete remission (CR) in B-cell malignancies, particularly CD19-targeted CAR-NK therapy in relapsed/refractory non-Hodgkin lymphoma and acute lymphoblastic leukemia, are encouraging and approach those reported for CAR-T cell therapies.[41–48] However, unlike CAR-T cells, CAR-NK therapy is associated with substantially lower rates of severe cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). The absence or low incidence of grade ≥3 CRS is particularly noteworthy, as CRS remains a major clinical challenge in CAR-T therapy and often necessitates intensive monitoring and cytokine blockade. The reduced toxicity profile of CAR-NK cells likely reflects fundamental biological differences between NK and T cells, including: shorter in vivo Persistence, reduced clonal expansion, lack of antigen-driven long-term memory formation, and lower production of IL-6 and other pro-inflammatory cytokine. Importantly, several studies using IL-15–expressing CAR-NK constructs have demonstrated enhanced persistence without a proportional increase in systemic toxicity, suggesting that persistence and safety may be simultaneously optimized through rational engineering.[49–54] Compared with CAR-T therapy, CAR-NK cells avoid T-cell–associated toxicities because they do not undergo uncontrolled clonal expansion. CAR-NK cells offer several theoretical and practical advantages such as; allogeneic "off-the-shelf" potential – NK cells can be derived from cord blood, peripheral blood donors, induced pluripotent stem cells (iPSCs), or NK-92 cell lines without causing graft-versus-host disease (GVHD), lower risk of severe immune toxicity that is consistent with the observed safety outcomes, and shorter manufacturing timelines which enabling more rapid treatment delivery. These attributes may make CAR-NK particularly suitable for elderly, frail, or heavily pretreated patients who are poor candidates for autologous CAR-T therapy. Also, CAR-NK therapies will be suitable for the outpatient cellular therapy programs and combination regimens with monoclonal antibodies or ICIs.[55–59]

In contrast to hematologic malignancies, CAR-NK cells have demonstrated limited efficacy in solid tumors. The pooled efficacy outcomes in solid tumors remain modest. Several biological barriers likely contribute to these findings, including the following:

- Immunosuppressive tumor microenvironment (TME): Elevated TGF-β, adenosine, regulatory T cells, and myeloid-derived suppressor cells inhibit NK cell cytotoxicity.

- Antigen heterogeneity: Variable or low antigen density reduces CAR engagement.

- Poor trafficking and infiltration: NK cells exhibit limited homing to solid tumor sites.

- Metabolic constraints: Hypoxia and nutrient deprivation impair NK cell persistence and effector function.

These challenges are not unique to CAR-NK therapy and have also

limited CAR-T success in solid tumors. However, NK cells possess intrinsic cytotoxic mechanisms independent of CAR signaling (e.g., NKG2D, DNAM-1), which may provide an advantage if appropriately harnessed.[60,61]

Several next-generation strategies for engineering CAR-NK cells aim to overcome current limitations that include:

- Armored CAR-NK cells secreting cytokines such as IL-15 or IL-12 to enhance persistence and reshape the TME,

- CRISPR/Cas9-mediated checkpoint disruption (e.g., CISH deletion) to enhance metabolic fitness and cytotoxicity,

- Checkpoint blockade combinations (e.g., PD-1/PD-L1 inhibitors) to counteract TME suppression,

- Chemokine receptor engineering (e.g., CXCR1/2) to improve tumor trafficking, and

- Multi-target CAR constructs to address antigen escape.

These approaches may significantly enhance activity in solid tumors and are currently under early clinical evaluation.[62-65]

For platform-specific considerations, our subgroup analyses suggest that NK cell source may influence outcomes. Cord blood–derived CAR-NK cells demonstrate favorable safety and persistence profiles, while iPSC-derived platforms offer scalability and standardization—addressing one of the largest barriers in CAR-T therapy. NK-92–based approaches provide manufacturing consistency but require irradiation prior to infusion, potentially limiting persistence. Future head-to-head comparisons are needed to determine optimal platforms.[66–69]

In summary, The findings demonstrate encouraging efficacy of CAR-NK cell therapy in hematologic malignancies with a markedly improved safety profile compared with CAR-T cell therapy. The limited efficacy observed in solid tumors underscores persistent challenges related to tumor microenvironment immunosuppression, antigen heterogeneity, and insufficient NK cell trafficking.

Emerging strategies, including armored CAR-NK cells secreting cytokines such as IL-15, IL-12, CRISPR-mediated checkpoint disruption, and combination approaches with immune checkpoint inhibitors, may enhance antitumor activity in solid tumors. The favorable safety profile positions CAR-NK therapy as an attractive option for elderly or frail patients and for outpatient treatment paradigms.

Strengths and limitations

This study has several notable strengths including; I) First comprehensive systematic review covering the published and ongoing CAR-NK clinical trials, Several systematic reviews exist, but quantitative systematic reviews and meta-analysis of CAR-NK trials are still rare.II) quantitative pooling of efficacy and safety outcomes, III) Subgroup analyses by malignancy type and CAR target, IV) Inclusion of multiple NK sources (cord blood, iPSC, NK-92, PB-NK), IV) Quantitative comparison of hematologic vs solid tumor responses, V) Systematic assessment of toxicity profiles, and VI) Robust statistical methods.

However, several limitations warrant consideration, such as,

- Clinical heterogeneity: Variability in CAR constructs (costimulatory domains, cytokine support), lymphodepletion regimens, and dosing strategies complicates cross-study comparisons.

- Predominance of early-phase trials: Most included studies are phase I/II with small sample sizes and limited power.

- Short follow-up duration: Long-term durability of responses and late toxicities remain insufficiently characterized.

- Publication bias risk: Early promising results may be more likely to be reported.

- Lack of randomized comparisons: Direct comparisons with CAR-T or other standard therapies are limited.

- Standardization of reporting criteria and harmonization of clinical endpoints will be essential for future meta-analyses.

- Underreporting of minimal residual disease (MRD) outcomes.

Comparative analyses are essential for contextualizing the therapeutic potential of CAR-NK cells relative to other adoptive cell therapies, particularly CAR-T cells and different antigen targets. However, the current clinical landscape is characterized by a limited number of direct head-to-head studies, which constrains definitive comparisons across platforms or targets such as CD19 and CD33. Most available evidence arises from early-phase, single-arm clinical trials with heterogeneous designs, patient populations, and outcome measures. In this review, we therefore incorporated indirect comparisons where appropriate, while acknowledging their inherent limitations. We also emphasize the need for future well-designed comparative studies to better define the relative efficacy, safety, and durability of CAR-NK therapies and to guide optimal target selection.

Conclusion

CAR-NK cell therapy represents a promising next-generation cellular immunotherapy characterized by meaningful efficacy in hematologic malignancies and an excellent safety profile. Its low incidence of severe CRS and neurotoxicity and minimal risk of GVHD.despite allogeneic sources, combined with the feasibility of allogeneic manufacturing, positions CAR-NK therapy as a potentially transformative modality, particularly for elderly, frail, or rapidly progressing patients.

While current efficacy in solid tumors remains limited, ongoing advances in genetic engineering, cytokine armoring, checkpoint editing, and combinatorial strategies may substantially expand therapeutic impact. Future priorities include:

- Optimization of persistence without compromising safety

- Standardization of manufacturing platforms

- Large-scale randomized clinical trials

- Long-term outcome reporting

With continued innovation and rigorous clinical evaluation, CAR-NK therapy has the potential to become a central component of next-generation cancer immunotherapy.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare no competing interests

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