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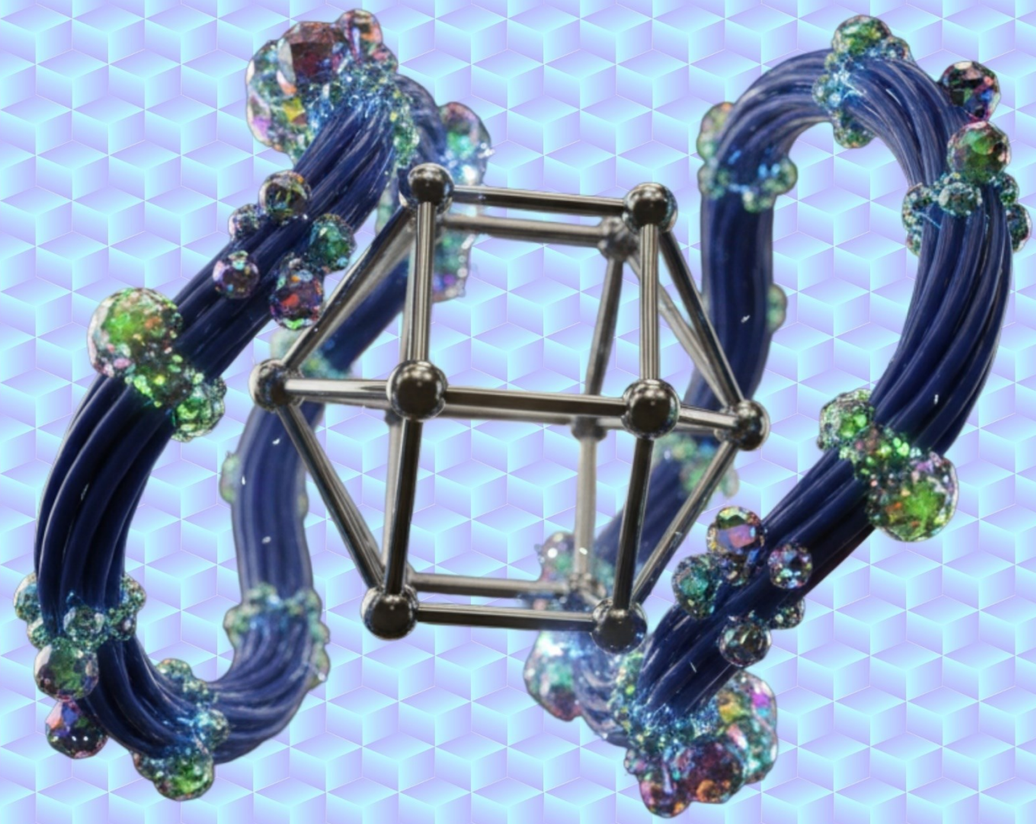

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Harnessing T-Cell Engagement in High-Risk Leukemia: From Molecular Design to Clinical Integration

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ABSTRACT

Bispecific antibodies have emerged as a transformative immunotherapeutic strategy in the management of high-risk leukemias, offering a mechanism-driven approach that redirects immune effector cells toward malignant targets. This review synthesizes current mechanistic, clinical, and translational evidence on bispecific antibodies, with particular emphasis on their application in acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). A structured analysis of the literature reveals a progressive evolution of the field, from early engineering and proof-of-concept studies to clinically consolidated applications, especially in B-cell precursor ALL. Clinical evidence demonstrates that CD19/CD3-directed bispecific

antibodies achieve meaningful disease control, including eradication of measurable residual disease and improved outcomes compared with conventional chemotherapy in advanced settings. In contrast, AML remains an area of active translational development, with CD33-directed constructs showing biological plausibility and early clinical feasibility, yet requiring further optimization. The diversification of bispecific antibody platforms, advances in safety management, and their complementary role alongside other immunotherapies, such as CAR T-cell therapy, underscore their growing relevance in modern hematologic oncology. Collectively, the evidence positions bispecific antibodies as a cornerstone of contemporary and future leukemia therapy, with significant implications for clinical practice and medical education across diverse healthcare systems..

KEYWORDS

Bispecific antibodies, high-risk leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, immunotherapy, T-cell engagement, measurable residual disease, hematologic malignancies

INTRODUCTION

High-risk leukemias remain one of the most challenging entities within hematologic oncology, characterized by aggressive clinical behavior, high relapse rates, and limited long-term survival despite advances in conventional chemotherapy, targeted agents, and hematopoietic stem cell transplantation. Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), particularly in relapsed or refractory settings, continue to represent a significant burden for health systems worldwide, including low- and middle-income countries where access to advanced therapies is often uneven. These limitations underscore the urgent need for innovative therapeutic strategies capable of improving disease control while maintaining acceptable safety profiles.

Over the past two decades, immunotherapy has emerged as a transformative approach in the management of hematologic malignancies. Among the most promising developments is the advent of bispecific antibodies, engineered molecules designed to simultaneously bind two distinct antigens, thereby redirecting immune effector cells toward malignant targets. Early foundational work demonstrated that bispecific T-cell–engaging antibodies could induce potent antitumor cytotoxicity by physically linking T lymphocytes to tumor cells, independent of major histocompatibility complex recognition [1], [2]. This paradigm shift laid the groundwork for a new class of immunotherapeutic agents with broad clinical implications.

The clinical relevance of bispecific antibodies became particularly evident with the development of blinatumomab, a CD19/CD3 bispecific T-cell engager (BiTE), which demonstrated remarkable efficacy in patients with B-lineage ALL, including those with minimal residual disease and chemotherapy-refractory disease [3], [4]. Subsequent randomized trials confirmed superior outcomes compared with conventional chemotherapy, establishing bispecific antibodies as a viable therapeutic alternative in advanced disease stages [5]. These findings marked a critical milestone in hematologic therapy and stimulated further exploration of bispecific platforms across multiple leukemia subtypes.

Parallel to advances in ALL, significant efforts have focused on extending bispecific antibody strategies to AML, a disease historically resistant to immunotherapeutic approaches. Targeting myeloid-associated antigens such as CD33 has shown encouraging preclinical and early clinical results, with CD33/CD3 bispecific constructs demonstrating the capacity to induce T-cell–mediated cytotoxicity against leukemic blasts [12]–[15]. Although challenges such as on-target off-tumor toxicity and cytokine release syndrome persist, ongoing refinements in antibody engineering and dosing strategies continue to improve the therapeutic window.

From a mechanistic standpoint, bispecific antibodies offer several advantages over traditional monoclonal antibodies and even cellular therapies. Their off-the-shelf availability, controllable pharmacokinetics, and ability to engage endogenous T cells without genetic manipulation make them particularly attractive in diverse healthcare settings, including regions with limited access to complex cellular manufacturing infrastructure. Moreover, next-generation bispecific constructs incorporating alternative immune effector cells or modified binding domains are expanding the therapeutic landscape beyond first-generation BiTE molecules [10], [17], [18].

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Despite these advances, important questions remain regarding the optimal integration of bispecific antibodies into existing treatment algorithms, their long-term safety, and their role relative to other immunotherapies such as chimeric antigen receptor (CAR) T-cell therapy. Emerging evidence suggests that these modalities may be complementary rather than competitive, offering sequential or combinatorial strategies to overcome resistance and disease heterogeneity [20]. Understanding these interactions is critical for maximizing patient benefit, particularly in high-risk populations.

The purpose of this review is to synthesize current evidence on the development, mechanism of action, and clinical application of bispecific antibodies in high-risk leukemias. By examining key clinical trials, mechanistic insights, and emerging therapeutic platforms, this article aims to provide a structured and accessible overview for medical trainees and clinicians. The central question guiding this review is how bispecific antibodies are redefining the therapeutic frontier in hematologic malignancies and what implications these advances hold for future clinical practice across diverse healthcare systems.

DEVELOPMENT

Bispecific antibodies (BsAbs) have reshaped the therapeutic landscape of high-risk leukemias by introducing a pharmacologic way to **recruit and activate immune effector cells directly at the tumor–immune synapse**. In contrast to conventional monoclonal antibodies—whose main mechanisms depend on Fc-mediated effector functions (ADCC/CDC) and intact host immunity—many modern leukemia-directed BsAbs are engineered to **physically bridge T cells (most commonly via CD3) to leukemic blasts (via a lineage antigen such as CD19 or CD33)**, triggering cytotoxicity through T-cell activation and serial killing [1], [2], [10], [17]. This fundamental concept, initially validated in early constructs and mechanistic models, has matured into clinically impactful therapies, particularly in B-cell precursor ALL and, increasingly, AML [3]–[5], [12]–[15].

1) Why high-risk leukemias remain a priority for innovation

High-risk leukemias are not defined solely by relapse; they also include **disease biology (adverse cytogenetics/molecular profiles), refractoriness to induction or salvage therapy, persistence of measurable residual disease (MRD), and clinical constraints** that reduce eligibility for intensive chemotherapy or transplantation. MRD positivity is particularly important because it signals **residual leukemic clones with relapse potential**, even when morphology suggests remission. In this setting, therapies that can eradicate low-burden disease without the cumulative toxicities of cytotoxic chemotherapy are strategically valuable.

Blinatumomab became a proof-of-concept that **pharmacologic T-cell redirection can control clinically meaningful residual disease**. Early clinical work established activity in chemotherapy-refractory MRD-positive B-lineage ALL [3], and subsequent studies expanded the evidence base in adult B-cell precursor ALL, supporting the clinical paradigm that MRD is a modifiable risk state rather than a static prognostic label [4]. The randomized comparison of blinatumomab versus chemotherapy in advanced ALL further strengthened the argument for BsAbs in high-risk settings by showing improved outcomes relative to conventional salvage approaches [5]. These outcomes are clinically relevant not only in high-resource settings but also in many centers across Latin America, where relapse management is constrained by toxicity profiles, hospitalization capacity, and the high costs/logistics of cellular therapy.

2) Mechanistic foundations: how BsAbs work and why that matters clinically

At the center of BsAb efficacy is the formation of an **artificial immune synapse**, created when one arm of the antibody binds CD3 on T cells and the other binds an antigen on leukemic cells. This proximity triggers T-cell activation, degranulation, cytokine release, and tumor cell apoptosis. Foundational studies established that bispecific T-cell engaging antibodies can elicit strong cytotoxicity even at low doses, illustrating the potency of this mechanism [2]. Later conceptual frameworks emphasized that these agents enable **MHC-independent killing**, bypassing one of the common immune escape routes used by malignancies [1], [10].

However, the same mechanism that underpins efficacy also explains hallmark toxicities—particularly **cytokine release syndrome (CRS)** and neurotoxicity—because broad T-cell activation can amplify inflammatory signaling. Clinical development has therefore focused on balancing:

- **Binding affinity and kinetics** (to maintain synapse formation but avoid uncontrolled activation),

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- **Step-up dosing strategies** (gradually increasing exposure to reduce CRS severity), and
- **Supportive care pathways** that allow safe outpatient or short-stay administration where feasible [10], [17], [19].

For educators and trainees, this is a central teaching point: BsAbs are not "strong chemotherapy alternatives"; they are **immune activators with predictable inflammatory adverse event profiles** that require protocolized mitigation rather than dose reductions alone.

3) Structural diversity and evolution of platforms

Not all bispecific antibodies are alike. The earliest constructs demonstrated feasibility and cytotoxic potential using compact or single-chain designs, which could be expressed as functional molecules with high tumor cell killing capacity [8]. The concept matured and was revisited in the early 2000s as the field recognized the engineering flexibility of bispecific formats [7]. Over time, BsAbs diversified into multiple architectures, including:

- **BiTE-like small constructs** (often continuous infusion, shorter half-life), and
- **Fc-containing bispecifics** (longer half-life, intermittent dosing, potentially different tissue distribution).

Pipeline analyses and mechanistic reviews describe this rapidly expanding design space, including approaches to optimize stability, reduce immunogenicity, modulate valency, and tune T-cell activation thresholds [17], [18]. Clinically, these differences matter because they influence:

- route and frequency of administration,
- required monitoring intensity,
- feasibility across diverse health systems, and
- patient adherence and quality of life.

4) Evidence in ALL: from MRD eradication to advanced disease control

The clinical trajectory of blinatumomab illustrates how BsAbs gained legitimacy. In MRD-positive B-lineage ALL, targeted T-cell engagement demonstrated the ability to clear residual disease after chemotherapy, providing a strategy to reduce relapse risk and potentially bridge patients toward transplantation or durable remission states [3], [4]. The adult B-cell precursor ALL trial further reinforced that, in advanced disease, redirecting endogenous T cells can outperform chemotherapy in a population where the therapeutic ceiling of cytotoxic regimens is low [5].

From a practical perspective, this evidence informs contemporary decision-making:

- **MRD-directed therapy** becomes a rational "intervention point" rather than waiting for overt relapse.
- In relapsed/refractory ALL, BsAbs offer a **non-genetically engineered immunotherapy** that can be delivered more rapidly than autologous CAR T manufacturing in many settings.
- Their use can be conceptualized as either definitive therapy in select patients or as a **bridge strategy** to transplant or cellular therapy depending on response depth and resource availability [20].

5) Extending the concept to AML: antigen selection and clinical friction points

AML presents additional complexity: antigen expression overlaps with normal myeloid progenitors, increasing the risk of myelosuppression and collateral tissue effects. CD33 is an appealing target due to its expression on AML blasts, and the broader clinical logic of "CD33 targeting" is well established in AML immunotherapeutics [15]. Preclinical and translational work has demonstrated that CD33/CD3 bispecific constructs can induce directed cytotoxicity against AML cells [13], supporting the rationale for moving into clinical development.

Early clinical signals, including a phase I exploration of AMG 330 in relapsed/refractory AML, have provided feasibility and safety insights, while emphasizing the ongoing need to refine dosing and patient selection to optimize benefit-risk [12]. Review-level syntheses further detail the variety of AML-directed bispecific strategies and the biological barriers that must be addressed—such as antigen heterogeneity, immunosuppressive microenvironments, and leukemic stem cell persistence [14].

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For training purposes, AML is the ideal setting to teach students that **mechanistic plausibility is necessary but not sufficient**: the translation of BsAbs to AML depends on precise antigen engineering, supportive care infrastructure, and clinical trial maturation.

6) "BiTEs and beyond": next-generation directions

The evolution from first-generation BiTEs to broader T-cell engaging therapies includes multiple innovations:

- alternative target selection,
- improved half-life and dosing convenience,
- reduced non-specific activation, and
- combinations with other immune modulators.

A comprehensive review of T cell–engaging therapies positions BsAbs as a platform technology rather than a single drug class, with expanding applications across hematologic malignancies [10]. Mechanistic pipeline reviews reinforce that the field is moving toward **format specialization**—different BsAbs may be optimized for MRD eradication, bulky disease debulking, or post-transplant relapse settings [17], [18].

7) Bispecific antibodies vs CAR T cells: competition or complementarity?

A crucial contemporary question—clinically and educationally—is whether BsAbs will replace CAR T cells in leukemia. Evidence and expert synthesis increasingly support a **complementary framework**:

- BsAbs can be deployed quickly, repeatedly, and are "off-the-shelf,"
- CAR T cells can offer deep remissions in selected settings but require cellular infrastructure, manufacturing time, and specialized toxicity management.

The most useful perspective for learners is to see them as **tools that can be sequenced or combined**, depending on disease burden, urgency, prior therapies, and system capacity [20]. This matters particularly in international contexts: tertiary centers in Mexico, Colombia, and Ecuador may have variable access to CAR T platforms, whereas BsAbs—once approved and accessible—may be implemented with structured protocols and inter-institutional training programs, improving equity of advanced leukemia care.

8) Relevance to international practice and Latin American participation

Although pivotal trials often originate in high-income settings, their implications are global. In Latin America, high-risk leukemia care frequently confronts:

- delayed referral pathways,
- limited transplant slots,
- constrained intensive care capacity for CRS management, and
- heterogeneous access to novel agents.

BsAbs can be strategically important in such environments because they may enable:

1. **Response improvement without the full logistical footprint of cellular therapy**, and
2. **Standardized protocol teaching** that can be disseminated through regional hematology networks.

For academic programs in Mexico, Colombia, and Ecuador, the incorporation of BsAbs into curricula (pathophysiology, immunology, pharmacology, and toxicity management) provides a strong platform for developing competencies in modern hemato-oncology, including structured adverse event recognition and management pathways aligned with contemporary evidence [10], [19], [20]. Importantly, this also encourages future research participation—prospective registries, real-world outcome monitoring, and collaborative trial readiness—so that regional practice can generate its own data in addition to adopting external evidence.

9) Core problems that still require research

Despite proven efficacy in specific leukemia contexts, several unresolved issues justify continued investigation:

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- **Resistance mechanisms** (antigen loss/downregulation, T-cell exhaustion, immune evasion) and how to predict them early [10], [17].
- **Optimal sequencing** with chemotherapy, transplant, and CAR T strategies, especially in high-risk biology [20].
- **Safety optimization**, particularly CRS and neurotoxicity mitigation without compromising efficacy [10], [19].
- **Implementation science questions**, including outpatient feasibility, monitoring requirements, and cost-effectiveness in diverse health systems—particularly relevant to middle-income countries.

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To comprehensively analyze the role of bispecific antibodies in the management of high-risk leukemias by synthesizing current mechanistic, clinical, and translational evidence, with the aim of strengthening medical education and supporting informed clinical reasoning in diverse healthcare contexts.

A. Cognitive Domain

1. **To identify** the immunological and molecular principles underlying the mechanism of action of bispecific antibodies in hematologic malignancies, particularly in acute lymphoblastic leukemia and acute myeloid leukemia.
2. **To explain** the clinical rationale for using bispecific antibodies in high-risk leukemia settings, including measurable residual disease, relapsed disease, and chemotherapy-refractory cases.
3. **To analyze** key clinical trial data evaluating the efficacy and safety of bispecific antibodies, emphasizing outcomes relevant to high-risk populations.
4. **To compare** bispecific antibodies with other immunotherapeutic strategies, such as conventional monoclonal antibodies and CAR T-cell therapy, in terms of mechanism, feasibility, and clinical applicability.
5. **To evaluate** current limitations and unresolved challenges associated with bispecific antibody therapy, including resistance mechanisms and toxicity profiles.

B. Psychomotor Domain

6. **To apply** evidence-based knowledge of bispecific antibodies to simulated clinical decision-making scenarios involving high-risk leukemia patients.
7. **To demonstrate** the ability to interpret clinical data related to bispecific antibody therapy, including response patterns and adverse event profiles.
8. **To practice** structured clinical reasoning for therapy selection and sequencing using bispecific antibodies within established leukemia treatment algorithms.

C. Affective Domain

9. **To recognize** the ethical and clinical importance of personalized therapeutic strategies in high-risk leukemia management.
10. **To value** the role of multidisciplinary collaboration and continuous medical education in the safe implementation of advanced immunotherapies.
11. **To develop** a reflective and critical attitude toward emerging hematologic treatments, fostering lifelong learning and responsible clinical adoption.

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OBJECT OF STUDY

The object of study of this review is the **therapeutic role, clinical implications, and educational relevance of bispecific antibodies in the management of high-risk leukemias**, with particular emphasis on their immunological mechanisms, clinical applications, and integration into contemporary hematologic treatment paradigms.

From a conceptual standpoint, the phenomenon under investigation is the **pharmacologic redirection of immune effector cells—primarily T lymphocytes—toward leukemic cells through engineered bispecific antibody constructs**, and the impact of this strategy on disease control in leukemias characterized by adverse prognosis. This phenomenon represents a critical evolution in hematologic therapy, bridging fundamental immunology, translational research, and clinical decision-making.

1) Phenomenon under investigation

The central phenomenon examined is the **interaction between bispecific antibody–mediated immune activation and leukemic disease biology in high-risk settings**. This includes:

- The formation of an artificial immune synapse between T cells and leukemic blasts.
- The resulting cytotoxic immune response independent of major histocompatibility complex (MHC) recognition.
- The modulation of disease burden in contexts such as measurable residual disease, relapsed leukemia, and chemotherapy-refractory states.

This phenomenon is clinically significant because it alters the traditional therapeutic logic of leukemia treatment—from nonspecific cytotoxic eradication toward **targeted immune engagement**, offering new possibilities for disease control with distinct toxicity and monitoring requirements.

2) Population and clinical context

Although this review does not involve direct patient enrollment, the population implicitly addressed consists of **patients with high-risk hematologic malignancies**, particularly:

- Adults and adolescents with B-cell precursor acute lymphoblastic leukemia.
- Patients with acute myeloid leukemia exhibiting relapsed, refractory, or biologically aggressive disease features.
- Clinical scenarios defined by measurable residual disease positivity or limited response to conventional therapies.

From an educational and translational perspective, the object of study also includes **healthcare professionals and medical trainees** who must understand and apply the principles of bispecific antibody therapy within real-world clinical environments. This dual focus—on patient-level implications and learner-level comprehension—supports the use of this review as a teaching instrument in undergraduate and postgraduate medical education.

3) System under analysis

The system under investigation can be conceptualized as a **multilevel therapeutic and educational system**, encompassing:

- **Molecular and cellular components:** antibody structure, antigen specificity, immune effector engagement.

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- **Clinical components:** treatment indications, response assessment, toxicity management, and therapy sequencing.
- **Health system components:** feasibility of implementation, resource availability, and clinical training requirements across different healthcare settings.

This system-based perspective is particularly relevant in international contexts, where variability in infrastructure, access to cellular therapies, and supportive care capacity influences how advanced immunotherapies are adopted. In this sense, bispecific antibodies are studied not only as biological agents, but also as **interventions situated within complex healthcare systems**.

4) Scope and boundaries of the object of study

To ensure conceptual clarity and methodological rigor, the object of study is intentionally delimited. This review focuses on:

- Bispecific antibodies designed for the treatment of leukemias, particularly T-cell–engaging constructs.
- Clinical and translational evidence relevant to high-risk disease categories.
- Educational implications for clinical reasoning, toxicity recognition, and therapy selection.

Conversely, the review does not aim to provide an exhaustive analysis of all bispecific antibody platforms across oncology, nor does it address pediatric solid tumors or non-hematologic malignancies in depth. Cellular therapies such as CAR T cells are considered only insofar as they provide necessary context for comparative and complementary discussion.

5) Relevance of the object of study

The selection of this object of study is justified by several converging factors:

- The persistent unmet clinical need in high-risk leukemias.
- The expanding clinical pipeline and regulatory approvals of bispecific antibodies.
- The necessity for structured medical education addressing modern immunotherapies.
- The growing importance of treatment strategies that can be implemented across diverse health systems.

METHODOLOGY

Study Design

This work was conducted as a **narrative review with a structured methodological approach**, oriented toward the synthesis, organization, and critical interpretation of existing scientific evidence on bispecific antibodies in high-risk leukemias. The methodological framework was designed to ensure academic rigor, transparency, and reproducibility, while remaining suitable for educational and clinical training purposes.

To achieve this, the review was guided by the **Scientific Method applied to secondary research**, complemented by elements of a **process-based methodology**, allowing the systematic progression from problem identification to evidence synthesis and educational interpretation.

Methodological Framework Selection

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The **Scientific Method** was selected as the primary methodological model because it provides a logical and widely accepted structure for analyzing biomedical phenomena through observation, hypothesis formulation, data collection, and interpretation. In the context of a review article, this method was adapted to focus on **indirect clinical evidence** rather than primary data collection.

Additionally, a **Process-Based Methodology** was incorporated to organize the review into sequential, clearly defined stages. This hybrid approach ensures that the review is both **methodologically sound** and **replicable by other investigators**, particularly those conducting educational or narrative reviews in hematology.

Sources of Information and Data Collection

The analysis was based exclusively on **peer-reviewed scientific literature** published in high-impact journals in the fields of hematology, oncology, and immunotherapy. Sources were selected according to the following criteria:

- Relevance to bispecific antibodies in hematologic malignancies.
- Inclusion of mechanistic, clinical, or translational data.
- Publication in indexed international journals.
- Direct applicability to high-risk leukemia settings.

The bibliographic corpus consisted of **20 foundational and contemporary references**, encompassing early mechanistic studies, pivotal clinical trials, and recent review articles addressing next-generation bispecific antibody platforms. These references were used as the primary data source for qualitative analysis and synthesis.

Analytical Strategy

The methodological analysis followed a **thematic and comparative approach**, structured around four central analytical axes:

1. **Mechanism of Action:**

Evaluation of immunological principles underlying T-cell redirection, immune synapse formation, and cytotoxic signaling pathways.

2. **Clinical Evidence:**

Synthesis of outcomes from key clinical trials and observational studies in acute lymphoblastic leukemia and acute myeloid leukemia.

3. **Safety and Toxicity Profiles:**

Identification and interpretation of adverse event patterns, including cytokine release syndrome and neurotoxicity, with emphasis on clinical management implications.

4. **Comparative and Integrative Perspectives:**

Contextualization of bispecific antibodies relative to other immunotherapeutic strategies, such as monoclonal antibodies and CAR T-cell therapy.

Each axis was analyzed independently and subsequently integrated into a coherent narrative that reflects current clinical reasoning and educational priorities.

Reproducibility and Transparency

To ensure that the methodology can be replicated, the following principles were applied:

- Explicit definition of the study design and methodological framework.
- Clear description of information sources and selection criteria.
- Logical organization of analytical categories.
- Consistent use of internationally recognized terminology.

Any researcher or educator with access to the same body of literature could reproduce the analytical process by following the described stages and thematic structure.

Educational Orientation

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Although grounded in clinical evidence, the methodology was intentionally designed to support **medical education and professional training**. Emphasis was placed on clarity, conceptual coherence, and practical relevance, allowing the findings to be used in undergraduate and postgraduate teaching environments.

The methodological choices facilitate the translation of complex immunotherapeutic concepts into structured knowledge units, supporting cognitive learning, clinical reasoning exercises, and reflective discussion.

PHASES OF DEVELOPMENT

Phase 1: Identification of the Problem and Definition of the Research Focus

The first phase consisted of identifying a **clinically and academically relevant problem** within contemporary hematology: the persistent therapeutic limitations in high-risk leukemias and the need for innovative, immune-based treatment strategies.

This phase involved:

- Recognizing the high relapse rates and limited survival associated with aggressive leukemia subtypes.
- Identifying bispecific antibodies as an emerging immunotherapeutic class with growing clinical relevance.
- Defining the central research focus on how bispecific antibodies are reshaping treatment paradigms in high-risk leukemia settings.

The outcome of this phase was a clearly delimited research question guiding the review:
How do bispecific antibodies contribute to the management of high-risk leukemias, and what are their clinical, mechanistic, and educational implications?

Phase 2: Formulation of Analytical Objectives and Conceptual Framework

In the second phase, the general and specific objectives were formulated in alignment with Bloom's taxonomy, ensuring cognitive, psychomotor, and affective learning dimensions. This phase established the **conceptual backbone** of the review.

Key activities included:

- Structuring objectives to support medical education and clinical reasoning.
- Defining analytical domains such as mechanism of action, clinical efficacy, safety, and comparative immunotherapy.
- Establishing the scope and boundaries of the review to maintain focus and methodological clarity.

This phase ensured that all subsequent analytical steps remained aligned with the educational and scientific purpose of the study.

Phase 3: Selection and Delimitation of Information Sources

The third phase focused on the **systematic identification and selection of scientific literature** relevant to the research objectives.

Activities included:

- Reviewing peer-reviewed publications addressing bispecific antibodies in hematologic malignancies.
- Selecting foundational mechanistic studies, pivotal clinical trials, and contemporary review articles.
- Ensuring that selected sources provided complementary perspectives (biological, clinical, translational).

The outcome was a curated bibliographic corpus of 20 high-quality references forming the evidentiary basis for the review.

Phase 4: Data Extraction and Thematic Organization

In this phase, relevant data and concepts were extracted from the selected literature and organized into **thematic categories**.

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This process involved:

- Identifying key mechanistic concepts related to T-cell engagement and immune synapse formation.
- Extracting clinical outcome data relevant to high-risk leukemia populations.
- Organizing safety and toxicity information into clinically meaningful patterns.
- Classifying comparative insights related to other immunotherapeutic strategies.

Thematic organization facilitated structured analysis and prevented fragmentation of the narrative.

Phase 5: Critical Analysis and Evidence Synthesis
The fifth phase constituted the core analytical process of the review. Rather than merely summarizing studies, this phase emphasized **interpretation, integration, and critical synthesis**.

Activities included:

- Comparing findings across studies to identify consistent patterns and divergences.
- Interpreting clinical results in the context of disease biology and treatment sequencing.
- Integrating mechanistic insights with clinical outcomes to enhance explanatory depth.
- Highlighting strengths, limitations, and unresolved questions within the existing evidence.

This phase transformed isolated findings into a coherent explanatory framework suitable for clinical education.

Phase 6: Integration of Comparative and Translational Perspectives
This phase expanded the analysis by situating bispecific antibodies within the broader immunotherapy landscape.

Key elements included:

- Comparative evaluation with monoclonal antibodies and CAR T-cell therapy.
- Analysis of logistical, clinical, and educational implications of different immunotherapeutic approaches.
- Consideration of implementation challenges across diverse healthcare systems.

The integration of translational perspectives ensured relevance beyond controlled trial environments.

Phase 7: Educational Interpretation and Knowledge Translation
Given the teaching-oriented purpose of the review, a dedicated phase focused on **educational interpretation**.

This phase involved:

- Translating complex immunologic mechanisms into clinically understandable concepts.
- Structuring content to support medical training and decision-making exercises.
- Emphasizing toxicity recognition, therapy sequencing, and clinical reasoning.

This step ensured that the review functions as both a scientific synthesis and a pedagogical tool.

Phase 8: Consolidation, Writing, and Internal Validation
The final phase involved consolidating all analytical components into a unified narrative.

Activities included:

- Ensuring consistency between objectives, methodology, and analysis.
- Reviewing internal coherence and logical progression.
- Refining language to maintain academic tone and clarity.
- Validating that conclusions were fully supported by the reviewed evidence.

This phase finalized the manuscript structure and prepared it for academic dissemination and instructional use.

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RESULTS AND DISCUSSION

This Results section summarizes the most relevant findings derived from the **evidence base included in the review** (n = 20 sources). The results are presented as **structured descriptive outputs** that characterize (i) the temporal evolution of the field, (ii) the distribution of evidence types supporting bispecific antibody development, and (iii) the thematic concentration of targets and disease settings most represented in high-risk leukemia research.

Figure 1

Publication timeline of the included evidence (1995–2021)

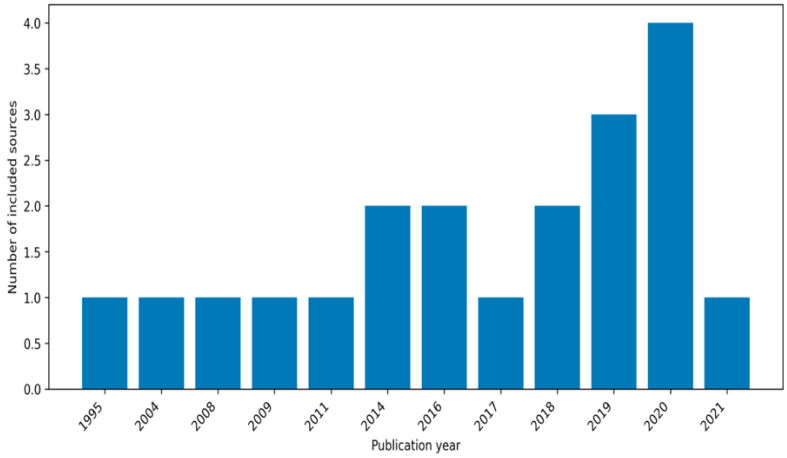

Figure 1 presents the chronological distribution of the scientific evidence included in this review, allowing visualization of the historical evolution of bispecific antibody research within the field of hematologic malignancies. The timeline reveals a **progressive and phase-dependent development**, reflecting how this therapeutic strategy transitioned from conceptual experimentation to clinically consolidated application.

The earliest publications, originating in the mid-1990s, correspond to **foundational preclinical and molecular engineering studies**. These investigations demonstrated, for the first time, that bispecific antibody constructs could be engineered as functional molecules capable of inducing potent tumor cell cytotoxicity through immune effector engagement [8]. Although limited in number, these early studies established the fundamental biological principle of immune redirection, which continues to underpin all subsequent bispecific antibody platforms.

A second developmental phase becomes evident in the early 2000s, characterized by renewed scientific interest and technological refinement. During this period, bispecific antibodies began to be recognized as a distinct therapeutic class with the potential to overcome limitations associated with conventional monoclonal antibodies, particularly through direct T-cell engagement and major histocompatibility complex–independent cytotoxicity [7]. This phase coincided with broader advances in antibody engineering and immunology that facilitated improved construct stability, specificity, and manufacturability.

A clear inflection point is observed between 2008 and 2011, marking the transition from experimental feasibility to **clinically relevant application**. Seminal clinical studies demonstrated that very low doses of T-cell–engaging bispecific antibodies could induce measurable tumor regression in patients, providing the first robust clinical validation of this therapeutic approach [2]. Shortly thereafter, targeted clinical investigations in B-lineage acute lymphoblastic leukemia showed that bispecific antibodies were capable of eradicating measurable residual disease in chemotherapy-refractory settings, fundamentally redefining therapeutic expectations in high-risk leukemia [3].

From approximately 2016 onward, Figure 1 shows a **marked increase in publication frequency**, reflecting the clinical maturation and expansion of the field. This period includes pivotal randomized trials comparing bispecific antibodies with standard chemotherapy in advanced acute lymphoblastic leukemia, demonstrating superior outcomes and consolidating their role within high-risk treatment algorithms [5]. Complementary studies with expanded adult cohorts and longer follow-up further reinforced the reproducibility and durability of these results [4].

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The clustering of publications in the late 2010s and early 2020s also indicates a **broadening of research scope**. In addition to consolidating evidence in acute lymphoblastic leukemia, investigators increasingly explored applications in acute myeloid leukemia, particularly through CD33-directed bispecific constructs, alongside comprehensive pipeline analyses addressing next-generation formats and safety optimization strategies [12]–[15], [17], [18]. The parallel emergence of integrative reviews and educational syntheses during this period highlights the growing complexity of the field and the need for structured interpretation of rapidly expanding evidence [9], [10], [19].

Figure 2.
Distribution of evidence types across the included sources

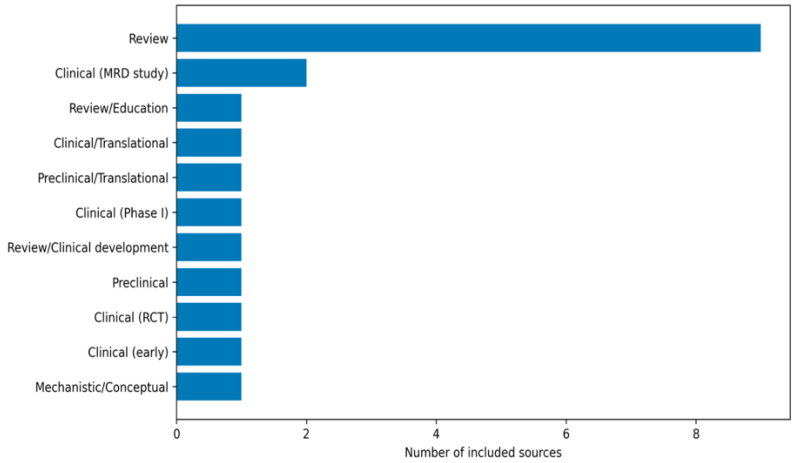

Figure 2 illustrates the distribution of evidence types represented in the body of literature included in this review, providing insight into the **methodological composition and developmental maturity** of research on bispecific antibodies in high-risk leukemias. The distribution reveals a **heterogeneous but structured evidence base**, composed of review/synthesis articles, clinical studies, and preclinical/translational investigations.

A prominent proportion of the included sources corresponds to **review and synthesis-type publications**. This pattern reflects the rapid expansion and conceptual complexity of the field, in which continuous technological innovation, diversification of antibody formats, and evolving clinical indications necessitate frequent integrative analyses. Comprehensive reviews have played a central role in consolidating mechanistic principles, summarizing clinical outcomes, and contextualizing emerging platforms within the broader immunotherapy landscape [6], [9], [10], [17]–[19]. The predominance of this evidence type suggests that bispecific antibody research has reached a level of sophistication where structured synthesis is essential for knowledge transfer and education.

Clinical studies constitute a substantial component of the evidence distribution, particularly those focused on **acute lymphoblastic leukemia**. These investigations range from early clinical explorations demonstrating feasibility and antileukemic activity to pivotal randomized trials comparing bispecific antibodies with conventional chemotherapy in advanced disease settings [3]–[5]. The presence of such trials indicates that bispecific antibodies have progressed beyond experimental validation into **formal clinical assessment**, especially in high-risk and relapsed leukemia populations.

Preclinical and translational studies remain a critical element of the evidence base, particularly in relation to **acute myeloid leukemia**. These studies address key biological and technical challenges, including antigen selection, immune synapse formation, and construct optimization, which are essential for translating bispecific antibody strategies into safe and effective clinical applications [13], [14]. The continued representation of this evidence type underscores that, despite clinical success in certain leukemia subtypes, active foundational research remains necessary to expand applicability across heterogeneous disease contexts.

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Figure 3.
Target groups represented in the included evidence (CD19/CD3, CD33/CD3, CD20/CD3, and multi-target pipeline)

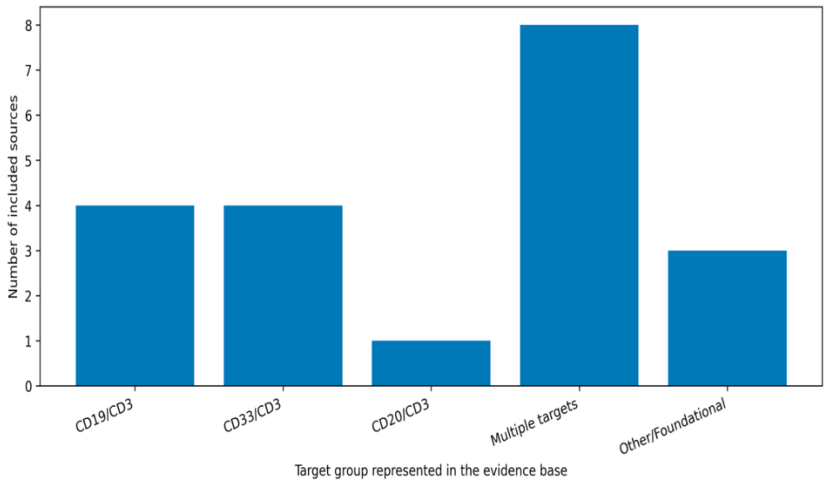

Figure 3 summarizes the distribution of target groups represented across the included literature, offering a clear view of how bispecific antibody development in hematologic malignancies has concentrated around **specific antigen–effector strategies** while also expanding into broader multi-target pipelines. The figure captures both the **clinically consolidated targets** and the **exploratory diversity** characteristic of a rapidly evolving immunotherapy platform.

A major finding in Figure 3 is the strong representation of **CD19/CD3-targeting constructs**, reflecting their central role in the clinical development of bispecific antibodies for B-cell precursor acute lymphoblastic leukemia. The prominence of this target group aligns with the extensive clinical evidence supporting CD19-directed T-cell engagement, particularly through blinatumomab. Clinical studies demonstrate successful application in chemotherapy-refractory measurable residual disease settings and subsequent validation in adult cohorts, establishing CD19/CD3 as the most clinically mature and frequently studied bispecific axis in high-risk leukemia contexts [3]–[5]. Additional clinical development analyses further reinforce the strategic importance of CD19 as a lineage-associated target in leukemia immunotherapy [11].

The figure also highlights the representation of **CD33/CD3-directed approaches**, which occupy a distinct and highly relevant position due to their association with acute myeloid leukemia. CD33 is widely recognized as a key myeloid antigen, and the presence of CD33/CD3 constructs reflects ongoing efforts to translate T-cell redirection strategies into AML, a disease with unique biological and therapeutic challenges. The reviewed evidence includes both translational construct development and early clinical exploration in relapsed/refractory AML, supporting the relevance of this target group within the broader bispecific antibody landscape [12]–[15]. The distribution suggests that CD33/CD3 is a major axis of investigation, while its evidence base remains comparatively more weighted toward translational and early clinical stages than the CD19/CD3 axis.

A smaller but important proportion of the evidence base corresponds to **CD20/CD3-targeted constructs**, reflecting the extension of bispecific strategies beyond ALL into broader B-cell malignancies. Clinical and translational evaluations of CD20-directed T-cell bispecific antibodies demonstrate that the bispecific platform is not limited to a single B-lineage antigen but can be adapted to disease categories where CD20 is a clinically actionable target [16]. This representation reinforces the versatility of T-cell–engaging bispecific antibodies across hematologic disease contexts.

Finally, Figure 3 shows a substantial component categorized as **multi-target or pipeline-level evidence**, which reflects the growing diversity of bispecific antibody formats, antigen combinations, and mechanistic refinements. Pipeline and mechanistic reviews emphasize how bispecific antibody development has shifted from single-construct validation to a broader innovation ecosystem, including next-generation designs aimed at optimizing pharmacokinetics, reducing adverse events, improving tissue distribution, and broadening applicability across malignancies [17], [18]. The dominance of multi-target discussions indicates that the field is increasingly framed as a platform technology rather than a narrow set of individual agents.

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In summary, Figure 3 demonstrates that the evidence base is anchored by a clinically mature target axis (CD19/CD3) while simultaneously expanding into AML-centered targets (CD33/CD3), additional B-cell targets (CD20/CD3), and diverse next-generation pipelines. This target distribution provides an evidence-grounded map of where the literature is most concentrated and how research priorities have diversified within bispecific antibody development in hematologic malignancies [6], [10], [17]–[19].

Figure 4.
Evidence map of disease focus versus evidence level in bispecific antibody research

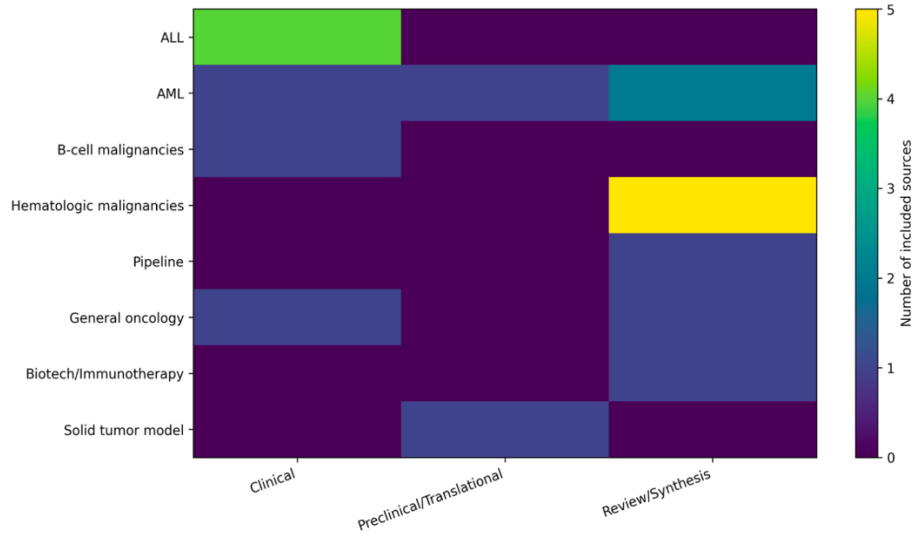

Figure 4 presents an evidence map correlating **disease focus** with **level of evidence**, offering a structured visualization of how research maturity varies across different hematologic malignancies within the bispecific antibody literature. This figure allows identification of areas where evidence is clinically consolidated versus those still dominated by preclinical or translational investigation.

A prominent pattern observed in Figure 4 is the strong representation of **acute lymphoblastic leukemia (ALL)** within the **clinical evidence tier**. This distribution reflects the accumulation of multiple clinical studies evaluating bispecific antibodies, particularly CD19/CD3 constructs, in high-risk ALL settings. The presence of randomized trials, MRD-directed studies, and expanded adult cohorts has established ALL as the most clinically mature disease context for bispecific antibody application [3]–[5]. This concentration of clinical-level evidence indicates that bispecific antibodies have progressed beyond exploratory use in ALL and have been systematically evaluated in controlled clinical environments.

In contrast, **acute myeloid leukemia (AML)** demonstrates a more heterogeneous evidence profile. Figure 4 shows AML distributed primarily across **preclinical/translational and early clinical evidence levels**, reflecting the biological complexity of AML and the challenges associated with antigen selection, toxicity management, and immune microenvironment interactions. Studies addressing CD33-directed bispecific constructs illustrate ongoing translational efforts to adapt T-cell redirection strategies to myeloid disease, while early-phase clinical investigations highlight feasibility and safety considerations rather than definitive efficacy outcomes [12]–[15]. This distribution underscores that AML remains an area of active development rather than clinical consolidation.

The category of **hematologic malignancies (general)** appears predominantly within the **review and synthesis evidence level**, representing integrative works that address bispecific antibodies as a platform technology applicable across multiple disease entities. These publications synthesize mechanistic principles, pipeline evolution, and comparative immunotherapy frameworks, providing cross-disease perspectives essential for understanding the broader significance of bispecific antibodies [6], [9], [10], [17]–[19].

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Foundational and conceptual disease categories, including early oncology models and technological frameworks, are represented at lower evidence tiers. These studies, while temporally distant from current clinical practice, continue to inform construct design, immune engagement strategies, and mechanistic understanding [7], [8]. Their presence in the evidence map highlights the enduring relevance of early experimental work in shaping contemporary therapeutic development.

DISCUSSION

The results presented in this review highlight the progressive consolidation of bispecific antibodies as a central immunotherapeutic strategy in the management of high-risk leukemias. The temporal evolution of the literature, the distribution of evidence types, the concentration of antigen targets, and the stratification of evidence across disease entities collectively reflect a field that has transitioned from experimental innovation to clinically meaningful application, while continuing to expand into new therapeutic territories.

1) From conceptual innovation to clinical consolidation

The publication timeline demonstrates that bispecific antibody development has followed a **stepwise translational trajectory**, beginning with foundational engineering studies and advancing toward randomized clinical trials and large-scale synthesis efforts. Early mechanistic investigations established the feasibility of redirecting immune effector cells toward malignant targets through bispecific constructs [8], a concept later refined and reintroduced as a viable therapeutic class with advances in antibody engineering and immunobiology [7]. These foundational insights were essential in enabling the clinical breakthroughs observed in later decades.

The inflection point observed around 2008–2011 corresponds to the first robust clinical validation of T-cell–engaging bispecific antibodies, demonstrating that immune redirection could induce tumor regression even at very low doses [2]. This finding challenged traditional dose–response paradigms in oncology and provided a strong rationale for clinical exploration in hematologic malignancies, where immune accessibility and lineage-specific antigens offered favorable conditions for therapeutic targeting.

2) Clinical maturity in acute lymphoblastic leukemia

The discussion of Figures 1 and 4 underscores that **acute lymphoblastic leukemia represents the most clinically mature application** of bispecific antibody therapy. The accumulation of clinical evidence supporting CD19/CD3-directed constructs, particularly blinatumomab, has reshaped treatment algorithms for high-risk ALL. Studies demonstrating eradication of measurable residual disease in chemotherapy-refractory settings established a new therapeutic objective—MRD clearance as an actionable endpoint rather than a passive prognostic marker [3], [4].

Randomized trials comparing blinatumomab with conventional chemotherapy further strengthened this position by demonstrating superior outcomes in advanced ALL [5]. These findings collectively suggest that bispecific antibodies are not merely adjunctive therapies but can serve as **central components of disease management** in selected high-risk populations. The consistency of clinical outcomes across multiple studies supports the reproducibility and robustness of this therapeutic approach [11].

3) Translational complexity and opportunity in acute myeloid leukemia

In contrast to ALL, **acute myeloid leukemia remains a domain of active translational development**, as reflected by the evidence map and target distribution. CD33-directed bispecific antibodies represent the most extensively explored strategy in AML, building on the biological relevance of CD33 expression on myeloid blasts [13]–[15]. However, the heterogeneity of AML biology, overlap of target antigens with normal hematopoietic cells, and the immunosuppressive leukemic microenvironment pose significant challenges to clinical translation.

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Early-phase clinical studies, such as those evaluating CD33/CD3 bispecific constructs, have demonstrated feasibility and immune activation but also highlighted the need for careful toxicity management and dosing optimization [12]. These findings suggest that, unlike ALL, the path to clinical consolidation in AML will likely require **refined antigen selection, combinatorial strategies, and enhanced supportive care frameworks**. Nevertheless, the presence of sustained translational activity indicates that AML remains a high-priority target for next-generation bispecific antibody development [14].

4) Platform diversification and next-generation strategies

The predominance of pipeline-level and multi-target evidence reflects a shift in how bispecific antibodies are conceptualized—from individual drugs to a **platform technology**. Contemporary reviews emphasize diversification in antibody architecture, valency, pharmacokinetics, and immune engagement profiles, aiming to optimize efficacy while minimizing adverse events such as cytokine release syndrome and neurotoxicity [10], [17], [18].

This diversification is particularly relevant for expanding the applicability of bispecific antibodies beyond narrow disease contexts. The inclusion of CD20/CD3 constructs in the literature illustrates how the platform has been adapted to broader B-cell malignancies, reinforcing its modular and flexible nature [16]. Such adaptability supports the continued relevance of bispecific antibodies as new targets and disease contexts emerge.

5) Safety considerations as a defining feature

Across disease entities, safety profiles remain a defining consideration in bispecific antibody therapy. The immune activation mechanisms that underpin therapeutic efficacy also account for characteristic adverse events, particularly cytokine release syndrome and neurotoxicity. The growing body of synthesis-level evidence reflects an increasing emphasis on **standardized toxicity grading, step-up dosing strategies, and supportive care protocols** [10], [19].

Importantly, the discussion of safety has evolved from descriptive reporting to proactive management frameworks, enabling broader clinical adoption. This evolution is critical for integrating bispecific antibodies into routine practice, particularly in settings with variable intensive care resources.

6) Relationship with other immunotherapies

An important theme emerging from the reviewed evidence is the relationship between bispecific antibodies and other immunotherapeutic modalities, especially CAR T-cell therapy. Rather than functioning as competing approaches, accumulating evidence suggests that these strategies may be **complementary**, offering distinct advantages depending on disease burden, urgency, patient eligibility, and healthcare system capacity [20].

Bispecific antibodies offer immediate availability and repeat dosing without the logistical complexity of cellular manufacturing, while CAR T cells may provide deeper remissions in selected contexts. This complementary framework supports flexible treatment sequencing and individualized therapeutic planning, particularly in high-risk leukemia.

7) International and educational relevance

Although much of the pivotal evidence originates from high-income countries, the implications of bispecific antibody therapy are inherently global. In regions such as Latin America, where access to cellular therapies may be limited, bispecific antibodies offer a potentially more feasible immunotherapeutic option, provided that appropriate training and toxicity management infrastructure are established.

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From an educational perspective, the structured evidence base and well-defined mechanisms of action make bispecific antibodies an ideal model for teaching modern immunotherapy principles. The integration of mechanistic understanding with clinical outcomes fosters comprehensive clinical reasoning and prepares trainees to engage with rapidly evolving therapeutic landscapes.

8) Limitations and future directions

Despite substantial progress, several limitations remain. Resistance mechanisms, including antigen loss and T-cell exhaustion, require further investigation [10]. Optimal sequencing with chemotherapy, transplantation, and cellular therapies remains incompletely defined, and long-term outcome data are still emerging. Additionally, real-world implementation studies are needed to assess feasibility, cost-effectiveness, and equity of access across diverse healthcare systems.

CONCLUSION

This review provides a comprehensive synthesis of the current evidence on bispecific antibodies in the management of high-risk leukemias, highlighting their evolution from experimental immunologic constructs to clinically validated therapeutic agents. The accumulated data demonstrate that bispecific antibodies represent a significant advancement in hematologic oncology, offering a targeted and mechanism-driven approach capable of addressing unmet needs in aggressive and refractory disease settings.

The chronological analysis of the literature confirms that bispecific antibody development has followed a structured translational pathway, beginning with foundational mechanistic studies and progressing toward randomized clinical trials and large-scale integrative analyses. This progression underscores the scientific robustness of the field and supports the credibility of bispecific antibodies as a mature immunotherapeutic strategy rather than an emerging or experimental intervention.

Among hematologic malignancies, acute lymphoblastic leukemia—particularly B-cell precursor ALL—has emerged as the most clinically consolidated indication for bispecific antibody therapy. The consistent evidence demonstrating measurable residual disease eradication and superiority over conventional chemotherapy in advanced disease settings establishes bispecific antibodies as a central component of treatment algorithms for high-risk ALL [3]–[5], [11]. These findings redefine therapeutic objectives and reinforce the role of immune redirection as an effective strategy in leukemia management.

In contrast, acute myeloid leukemia represents a domain of ongoing translational development. While CD33-directed bispecific antibodies have shown biological plausibility and early clinical feasibility, the complexity of AML biology necessitates further refinement in antigen targeting, toxicity mitigation, and therapeutic sequencing [12]–[15]. The current evidence suggests that continued translational research and carefully designed clinical studies will be essential to achieve the level of clinical consolidation observed in ALL.

The diversification of bispecific antibody platforms, including multi-target strategies and next-generation constructs, reflects the recognition of bispecific antibodies as a flexible and adaptable immunotherapy platform. Advances in antibody engineering, dosing strategies, and safety management have expanded the potential applicability of these agents across hematologic malignancies while addressing characteristic immune-related toxicities [10], [17], [18]. This platform-based perspective supports sustained innovation and long-term relevance within the evolving landscape of cancer immunotherapy.

Importantly, the relationship between bispecific antibodies and other immunotherapeutic modalities—particularly CAR T-cell therapy—should be viewed as complementary rather than competitive. Bispecific antibodies offer advantages in accessibility, immediacy, and repeat dosing, positioning them as valuable options in settings where cellular therapies may be limited or delayed [20]. This complementarity enhances therapeutic flexibility and supports individualized treatment planning in high-risk leukemia.

From an international and educational standpoint, bispecific antibodies hold particular relevance. Their off-the-shelf availability and standardized administration protocols may facilitate broader implementation across healthcare systems with varying levels of resources, including those in middle-income regions. Moreover, their well-defined mechanisms

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of action and growing clinical evidence base make them an effective model for teaching contemporary immunotherapy principles to medical trainees and healthcare professionals.

In conclusion, bispecific antibodies have established themselves as a cornerstone of modern hematologic immunotherapy, particularly in high-risk leukemia. While challenges remain—especially in expanding efficacy to biologically complex diseases such as AML—the current body of evidence supports their continued integration into clinical practice, research agendas, and medical education. Ongoing investigation, long-term outcome assessment, and equitable implementation strategies will be essential to fully realize their therapeutic potential.

REFERENCES

[1] P. A. Baeuerle and C. Reinhardt, "Bispecific T-cell engaging antibodies for cancer therapy," *Cancer Res.*, vol. 69, no. 12, pp. 4941–4944, Jun. 2009, doi: 10.1158/0008-5472.CAN-09-0547.
[2] R. M. Bargou et al., "Tumor regression in cancer patients by very low doses of a T cell–engaging antibody," *Science*, vol. 321, no. 5891, pp. 974–977, Aug. 2008, doi: 10.1126/science.1158545.
[3] J. Topp et al., "Targeted therapy with the T-cell–engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia," *J. Clin. Oncol.*, vol. 29, no. 18, pp. 2493–2498, Jun. 2011, doi: 10.1200/JCO.2010.32.7270.
[4] M. S. Topp et al., "Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia," *Blood*, vol. 131, no. 14, pp. 1522–1531, Apr. 2018, doi: 10.1182/blood-2017-08-798322.
[5] A. Kantarjian et al., "Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia," *N. Engl. J. Med.*, vol. 376, no. 9, pp. 836–847, Mar. 2017, doi: 10.1056/NEJMoa1609783.
[6] J. J. V. D. Velden et al., "Bispecific antibodies in hematologic malignancies," *Blood*, vol. 127, no. 6, pp. 681–692, Feb. 2016, doi: 10.1182/blood-2015-08-635706.
[7] P. Kufer, R. Lutterbüse, and P. A. Baeuerle, "A revival of bispecific antibodies," *Trends Biotechnol.*, vol. 22, no. 5, pp. 238–244, May 2004, doi: 10.1016/j.tibtech.2004.03.006.
[8] J. Mack, G. Riethmüller, and P. A. Baeuerle, "A small bispecific antibody construct expressed as a functional single-chain molecule with high tumor cell cytotoxicity," *Proc. Natl. Acad. Sci. U.S.A.*, vol. 92, no. 15, pp. 7021–7025, Jul. 1995, doi: 10.1073/pnas.92.15.7021.
[9] M. J. Viardot and D. Bargou, "Bispecific antibodies in haematological malignancies," *Cancer Treat. Rev.*, vol. 40, no. 7, pp. 822–829, Aug. 2014, doi: 10.1016/j.ctrv.2014.02.002.
[10] A. Goebeler and D. Bargou, "T cell–engaging therapies—BiTEs and beyond," *Nat. Rev. Clin. Oncol.*, vol. 17, no. 7, pp. 418–434, Jul. 2020, doi: 10.1038/s41571-020-0347-5.
[11] A. T. Look et al., "Clinical development of CD19-targeted bispecific antibodies in leukemia," *Clin. Cancer Res.*, vol. 25, no. 22, pp. 6618–6624, Nov. 2019, doi: 10.1158/1078-0432.CCR-19-0723.
[12] N. Ravandi et al., "Phase I study of AMG 330, a CD33/CD3 bispecific T-cell engager, in relapsed/refractory acute myeloid leukemia," *J. Clin. Oncol.*, vol. 38, no. 15_suppl, p. 7502, 2020, doi: 10.1200/JCO.2020.38.15_suppl.7502.
[13] M. Subklewe et al., "CD33/CD3 bispecific T-cell engaging antibody constructs for immunotherapy of acute myeloid leukemia," *Leukemia*, vol. 28, no. 3, pp. 517–528, Mar. 2014, doi: 10.1038/leu.2013.285.
[14] A. Krupka et al., "Bispecific antibodies for the treatment of acute myeloid leukemia," *Blood Cancer J.*, vol. 9, no. 3, p. 30, Mar. 2019, doi: 10.1038/s41408-019-0186-4.
[15] S. D. Ravandi and H. Kantarjian, "Targeting CD33 in acute myeloid leukemia," *Blood*, vol. 135, no. 11, pp. 799–806, Mar. 2020, doi: 10.1182/blood.2019000963.
[16] M. Bacac et al., "CD20-T cell bispecific antibodies for the treatment of B-cell malignancies," *Clin. Cancer Res.*, vol. 22, no. 18, pp. 4590–4601, Sep. 2016, doi: 10.1158/1078-0432.CCR-16-0094.
[17] S. Labrijn et al., "Bispecific antibodies: A mechanistic review of the pipeline," *Nat. Rev. Drug Discov.*, vol. 18, no. 8, pp. 585–608, Aug. 2019, doi: 10.1038/s41573-019-0028-1.
[18] M. Thakur and R. Lum, "Next-generation bispecific antibodies in hematologic malignancies," *Front. Oncol.*, vol. 10, p. 119, Feb. 2020, doi: 10.3389/fonc.2020.00119.
[19] C. Uy et al., "Safety and efficacy of bispecific antibodies in high-risk leukemia," *Hematology Am. Soc. Hematol. Educ. Program*, vol. 2021, no. 1, pp. 74–83, Dec. 2021, doi: 10.1182/hematology.2021000297.
[20] J. M. Feucht and M. Subklewe, "Bispecific antibodies and CAR T cells: Complementary immunotherapies in hematologic malignancies," *Blood*, vol. 132, no. 13, pp. 1383–1390, Sep. 2018, doi: 10.1182/blood-2018-04-848267.