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Nanotechnology in Hematology: Enhancing Therapeutic Efficacy With Nanoparticles

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ABSTRACT

Background and Aims: Hematological malignancies, such as leukemia, lymphoma, and multiple myeloma, contribute significantly to global cancer diagnoses. Despite progress in conventional therapies, such as chemotherapy and immunotherapy, these treatments face limitations, including nonspecific targeting, side effects, and drug resistance. The aim of this review is to explore the potential of nanotechnology, particularly nanoparticles (NPs), to improve therapeutic outcomes for these cancers by enhancing drug delivery and reducing toxicity.

Methods: This review examines recent advancements in NP-based therapies, focusing on their application in hematological malignancies. We discuss different types of NPs, including liposomes, polymeric, and inorganic NPs, for their potential in targeted drug delivery. The review also evaluates the current state of clinical trials and highlights challenges in the translation of nanomedicines from preclinical research to clinical practice.

Results: Nanoparticles, with their unique properties, offer significant advantages in drug delivery systems, such as enhanced stability, extended circulation time, and targeted tumor delivery. Various NP formulations have shown promise in clinical trials, including liposomal formulations like Vyxeos for acute myeloid leukemia and Marqibo for Ph-negative acute lymphoblastic leukemia. However, challenges in toxicity, regulatory hurdles, and large-scale production still remain.

Conclusion: Nanomedicine holds transformative potential in the treatment of hematological malignancies, offering more effective and specific therapies compared to conventional treatments. Continued research is necessary to overcome the clinical challenges and maximize the benefits of NP-based therapies for patients with blood cancers.

1 | Introduction

Hematological malignancies are cancers of the blood, bone marrow (BM), and lymphatic system, representing 9% of all cancers and ranking fourth in developed regions [1]. These malignancies primarily affect the BM, peripheral blood, spleen, and lymph nodes [2, 3]. In BM, hematopoietic stem cells differentiate into myeloid cells (producing granulocytes, monocytes, mast cells, erythrocytes, and thrombocytes) and lymphoid cells (generating T cells, B cells, Natural Killer cells, and plasma cells). These cancers are categorized as leukemia, lymphoma, or multiple myeloma based on cell origin [4, 5]. While numerous chemotherapeutic and targeted drugs exist for hematological malignancies (HM), complete remission remains limited. This is partly due to poor drug specificity and short biological half-lives [6], resulting in off-target effects on healthy

tissues [7]. Nanotechnology, particularly nanomedicine as defined by the USA National Institutes of Health [8, 9] offers promising solutions in healthcare. Nanoparticles (NPs), measuring 1–100 nm, feature high surface area-to-volume ratios and have significantly advanced medical treatments by improving accuracy and enabling early disease detection [10–12]. Key considerations for nanomaterials in treatment include biodegradability, biocompatibility, size, hydrophilicity, and drug conjugation capacity [13]. NPs as delivery systems offer several advantages: enhanced intracellular drug uptake, improved water solubility in cancer cells, extended circulation time, and targeted delivery that spares healthy cells [14, 15]. These properties result in better drug stability, reduced toxicity, and increased efficacy [16]. Recent decades have seen increased development of nanocarriers, including liposomes and polymeric NPs, for solid tumor treatment, leading to several clinically approved formulations [7, 17]. The purpose of this review is to consolidate and examine recent developments in the field of nanomedicine, specifically focusing on the utilization of NPs in the management of hematologic malignancies.

2 | Hematological Malignancies

2.1 | Hematological Malignancies Classification

2.1.1 | Leukemia

Leukemia, prevalent in both children and adults, results from dysregulated hematopoietic stem cell (HSC) proliferation in BM. Classifications are based on cellular involvement, maturation degree, and lineage, comprising four main types: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML) [18, 19].

ALL is the most common type of children's cancer, with predisposing factors like genetic susceptibility or environmental exposure [20]. AML involves abnormal myeloblast proliferation, causing rapid disease progression with symptoms including fatigue, breathing difficulties, and bleeding tendencies. AML's annual incidence is 4.1 per 100,000, with 2.7 per 100,000 mortality rate [21]. CLL is a prevalent type of leukemia in adults in Western nations, characterized by the gradual growth and accumulation of mature but ineffective lymphocytes [22]. CML, on the other hand, is caused by defects in pluripotent HSCs and is distinguished by the Philadelphia chromosome. The BCR-ABL1 fusion gene on the Ph chromosome activates the BCR-ABL1 tyrosine kinase, leading to leukemic cell proliferation and the progression of the disease. Most CML cases are detected in the chronic phase (CP) 3–5 years after diagnosis [23]. Table 1 illustrates novel NPs for the targeted treatment of leukemia.

2.1.2 | Lymphoma

Lymphoma, which is one of the most common lymphoid cancers globally, is a diverse group of diseases that includes Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). HL constitutes 10%–15% of lymphoma cases and is identified by the presence of Reed–Sternberg cells. NHL makes up 80%–85% of lymphoma cases and encompasses B-cell NHLs expressing CD20 or CD19, T-cell NHLs expressing CD3, CD4, or CD8, and NK/T-cell NHLs expressing CD56 [30].

2.1.3 | Multiple Myeloma (MM)

The most common plasma cell tumor, MM, affects about 30,000 new people in the US each year. Bone pain is the most common presenting symptom in 75% of individuals with MM, and osteolytic lesions are evident at diagnosis. Patients with MM had few treatment choices in the past, and the condition is incurable. However, the development of innovative systemic medications throughout the last 20 years has greatly increased patients' overall survival and quality of life with MM. The International Myeloma Working Group (IMWG) has established diagnostic criteria for MM that include having 10% or more clonal plasma cells in the BM (and/or a biopsy-proven plasmacytoma) in addition to any one or more myeloma-defining events (MDE): end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions) attributable to the underlying plasma-cell disorder, BM clonal plasma cells $\geq 60\%$, serum involved to uninvolved free light chain (FLC) ratio ≥ 100

TABLE 1 | Novel NPs for targeted treatment of leukemia.

Type of NPs	Targeting mechanism	Refs.
Curcumin-loaded hyaluronic acid–liposomes	Targeting of the CD44 receptor thereby targeting curcumin to these cells with high stability.	[24]
Arsenic trioxide loaded double oligopeptide coupled NPs	Enhanced stability and loading efficiency of Arsenic trioxide as well as targeting in the lesions.	[25]
Aptamer–methotrexate conjugate	Targeting the biomarker CD117, which is overexpressed on AML cells with no effect on the background marrow cells.	[26]
Gemcitabine-loaded Mesoporous silicon NPs coated with lipid bilayer	Coating with biotinylated EGFR antibody achieved leukemia cell targeting as well as offering a targeted release of gemcitabine.	[27]
Silver NPs loaded on multi-walled carbon nanotubes	Increased antioxidant activity against leukemia cells in a dose-dependent manner.	[28]
siRNA loaded folate–PEG oligoaminoamide	Targeted delivery as folic acid receptor is overexpressed in leukemia cells.	[29]

(as long as involved FLC level is ≥ 100 mg/L), or more than one focal lesion (5 mm or more in size) on magnetic resonance imaging [31, 32].

2.2 | Conventional Treatment Approaches

2.2.1 | Chemotherapy

The World Cancer Report states that cancer is a leading cause of premature death in many countries and is a significant issue in clinical management. The primary treatment for solid tumors includes surgery, radiotherapy, and chemotherapy. Chemotherapy is often used for metastasized tumors or those that cannot be surgically removed. However, a challenge with systemic chemotherapy is its lack of specificity in targeting tumors and difficulty in achieving therapeutic drug levels [33]. In 2018 [34], Sherief et al. conducted a study on the long-term neurocognitive effects of two chemotherapy protocols in Egyptian children who survived ALL.

2.2.2 | Radiation Therapy

Radiation therapy (radiotherapy) has evolved into a vital cancer treatment modality alongside surgery and chemotherapy. As a cost-effective single-modality treatment, it comprises only 5% of total cancer care costs while being utilized in 50% of cancer patients and contributing to 40% of curative treatment expenditure. The field continues to advance through improved X-ray production, treatment delivery systems, computerized planning, imaging techniques, and enhanced radiobiological understanding. Radiation functions as an ionizing agent, depositing energy in tissue cells to either destroy cancer cells or modify their genetic structure. Since 1931, radiation therapy has proven effective for multiple myeloma (MM), particularly in managing symptoms and achieving long-term disease control. It is especially valuable in treating extramedullary and solitary bone plasmacytomas, which are highly radiosensitive neoplasms [35–37].

2.2.3 | Immunotherapy

Immunotherapy for leukemia involves the use of specific medications to help the immune system combat the disease. While the immune system can naturally defend against harmful invaders like bacteria and fungi, it may not always recognize cancer cells as threats. Immunotherapy works by training the immune system to target cancer cells, often through the introduction of lab-produced or modified cancer-fighting cells. This approach shows potential in eliminating chemotherapy-resistant clones and providing long-term disease management. AML has historically shown responsiveness to immunotherapy and remains a common reason for patients to undergo allogeneic hematopoietic stem cell transplantation (alloHSCT). However, the limited effectiveness of alloreactive T cells in preventing AML relapse after transplantation underscores the need for more potent and targeted treatments for this disease [38].

2.2.4 | Targeted Therapy

One type of cancer treatment, considered targeted therapy, focuses on targeting the proteins that regulate the growth, division, and metastasis of cancer cells. It serves as the foundation of precision medicine. Researchers are becoming more adept at creating drugs that specifically target the proteins and changes in DNA that lead to cancer. The majority of targeted treatments consist of monoclonal antibodies or small-molecule medications. Small-molecule drugs, which can readily penetrate cells, are used to treat targets found inside cells. Therapeutic antibodies, or monoclonal antibodies, are laboratory-produced proteins designed to attach to specific regions of cancer cells. Certain monoclonal antibodies label cancer cells to assist the immune system in recognizing and eliminating them more easily. Various monoclonal antibodies work by directly halting the growth of cancer cells or triggering their self-destruction, while some deliver toxins specifically to cancer cells. Explore more about monoclonal antibodies. The range of targeted therapies available for treating AML is continuously increasing. The introduction of imatinib for CML and its impressive outcomes have instilled hope for similar benefits from targeted therapies in AML. After more than 20 years of clinical research, eight targeted medications have received FDA approval, representing a crucial initial advancement in enhancing the clinical outcomes for AML patients. Ofatumumab, a fully humanized second-generation CD20 antibody, demonstrates more potent CDC (complement-dependent cytotoxicity) in lab settings than rituximab. Ofatumumab is endorsed for use in combination with chlorambucil for CLL [39–41].

2.2.5 | Hematopoietic Stem Cell Transplantation (HSCT)

Stem cell transplants are procedures that replenish blood-forming stem cells in individuals who have been destroyed by high doses of chemotherapy or radiation therapy for specific cancers, blood disorders, and autoimmune diseases. HSCT, including BM, peripheral blood, cord blood, autologous, allogeneic, related, or unrelated transplants, plays a crucial role in cancer treatment by providing supportive care for BM issues and using immunotherapy against cancer cells. However, HSCT may lead to severe side effects like infections or graft-versus-host disease. Autologous hematopoietic stem cell transplantation (AHSCT) aims to prevent severe BM issues, allowing the administration of high doses of anticancer drugs. AlloHSCT combines supporting BM function and immunotherapy, potentially resulting in immunological complications. Mini-transplants or reduced-intensity allogeneic transplants primarily focus on immunotherapy. AHSCT serves as a crucial post-remission treatment for acute leukemia (AL), with favorable overall survival and leukemia-free survival outcomes in adult AL patients. High-dose chemotherapy followed by AHSCT is the standard treatment approach in first-line therapy for eligible patients with mantle cell lymphoma and most T cell non-Hodgkin lymphoma cases [42, 43].

3 | Nanoparticles

Traditional chemotherapy, while effective against leukemia, faces challenges including chemoresistance and adverse effects.

Despite eliminating many diseased cells, resistant cells and leukemic stem cells often persist due to chemotherapy's limited targeting ability [44–47]. Conventional cancer treatments rely on complex, generalized diagnostic systems that are time-consuming and broad-spectrum [48]. Nanotechnology, particularly nanomedicine, offers promising alternatives for cancer treatment. The National Nanotechnology Initiative (NNI) defines nanotechnology as the study of 1–100 nm materials [49, 50]. While NIH expands this definition to include biological research tools, engineered biomolecules, and precise biological system manipulation [51–53]. The field has grown significantly since the 1990s, reaching $10.5 billion in US market value by 2008 [54, 55]. Excel in medical applications due to their size, high surface area-to-volume ratio, and functionalization capability [56]. While most FDA-approved nano-therapeutics are parenteral, with AmBisome being the first approved nanosystem [57]. NPs offer advantages including deep tissue penetration and enhanced permeability and retention (EPR) [58]. Key requirements for in vivo applications include biocompatibility, non-toxicity, biodegradability, and stability [59, 60]. NPs improve drug solubility, stability, and cellular delivery while enabling controlled release at target sites, reducing side effects, and improving patient compliance [61–65]. Unlike solid tumors, blood cancers require different NP approaches due to the absence of the EPR effect [66, 67]. Challenges include blood protein opsonization and mononuclear phagocyte system recognition [68]. Market transition faces obstacles in characterization, toxicity assessment, and regulatory compliance [69, 70]. NPs are categorized as:

1. Organic NPs (dendrimers, lipid-based, polymeric)—superior biocompatibility
2. Inorganic NPs (quantum dots, silica, gold, magnetic materials)—unique functional properties
3. Hybrid NPs—combining organic and inorganic materials for enhanced capabilities [71, 72]

Figure 1 demonstrates mechanisms of cell death in cancer induced by nanoparticles. Also, Table 2 gives a brief summary of NP types.

3.1 | Organic NPs

3.1.1 | Liposome

Liposomes represent a leading nano-formulation for drug delivery, featuring vesicles with bilayer structures composed of phospholipids surrounding an aqueous core [73]. Their ability to carry both hydrophilic and hydrophobic molecules makes them versatile nanocarriers [74]. Key advantages include protection against enzymatic degradation, reduced immune response, minimal healthy tissue exposure, and extended circulation time [75–77]. Liposome stability and effectiveness are enhanced through cholesterol incorporation in the phospholipid bilayer [78] and pegylation with polyethylene glycol (PEG), which shields drugs from immune detection [79, 80]. Notable FDA-approved liposomal formulations include:

- Marqibo (vincristine sulfate, 2012) for relapsed Ph-ALL treatment [81, 82].
- CPX-351 (Vyxeos, 2017) for adult AML, delivering cytarabine and daunorubicin in a 5:1 molar ratio [83].
- Other approved formulations: Depocyt, OnivydeTM, Visudyne, and Doxil [84, 85].

3.1.2 | Micelles

Micelles represent a distinct category of biocompatible nanosystems, characterized by their size ranging from 5 to 100 nm. These nanosystems consist of a single layer of amphiphilic molecules that possess a natural tendency to self-assemble in aqueous surroundings at a specific concentration called the critical micelle concentration (CMC) [86]. Micelles can exist in two different forms: one with a hydrophobic core and hydrophilic polar heads on the outside, and another with a hydrophilic core and hydrophobic tails on the outside [87]. The initial technique of encapsulation is often characterized by limited stability, as these formations may swiftly disassemble following intravenous administration. This phenomenon is attributed to a combination of dilution effects and interactions with surfactant proteins [88]. Hydrophobic drugs are typically enclosed within the hydrophobic core, while hydrophilic drugs can either be adsorbed or chemically attached to the outer shell [89]. The administration of anticancer drugs through biocompatible micelles, as opposed to free drug delivery, led to a decrease in systemic toxicity and an enhancement in drug solubility. Additionally, this approach facilitated the targeted accumulation of the drug at specific tumor sites [90].

3.1.3 | Polymeric NPs

Polymeric NPs (PNPs) are preferred for their biocompatibility, biodegradability, and established safety data [91–93]. They exist as nanospheres or nanocapsules (1–1000 nm) and can be synthesized from [94]:

1. Synthetic polymers:

- Poly lactide
- Poly lactide-co-glycolide
- Poly(ε-caprolactone)

2. Natural polymers:

- Chitosan
- Alginate
- Gelatin
- Albumin

Synthetic polymers enable extended drug release (days to weeks), while natural polymers degrade faster. Poly(lactic-co-glycolic acid) (PLGA), an FDA-approved copolymer, is the most common biodegradable polymer, offering variable erosion times and mechanical properties [95, 96]. Despite extensive preclinical research, no anticancer PLGA formulations have received FDA approval [97]. FDA-approved Poly(ε-caprolactone), derived from ε-caprolactone, offers slower degradation than PLGA, making it ideal for sustained-

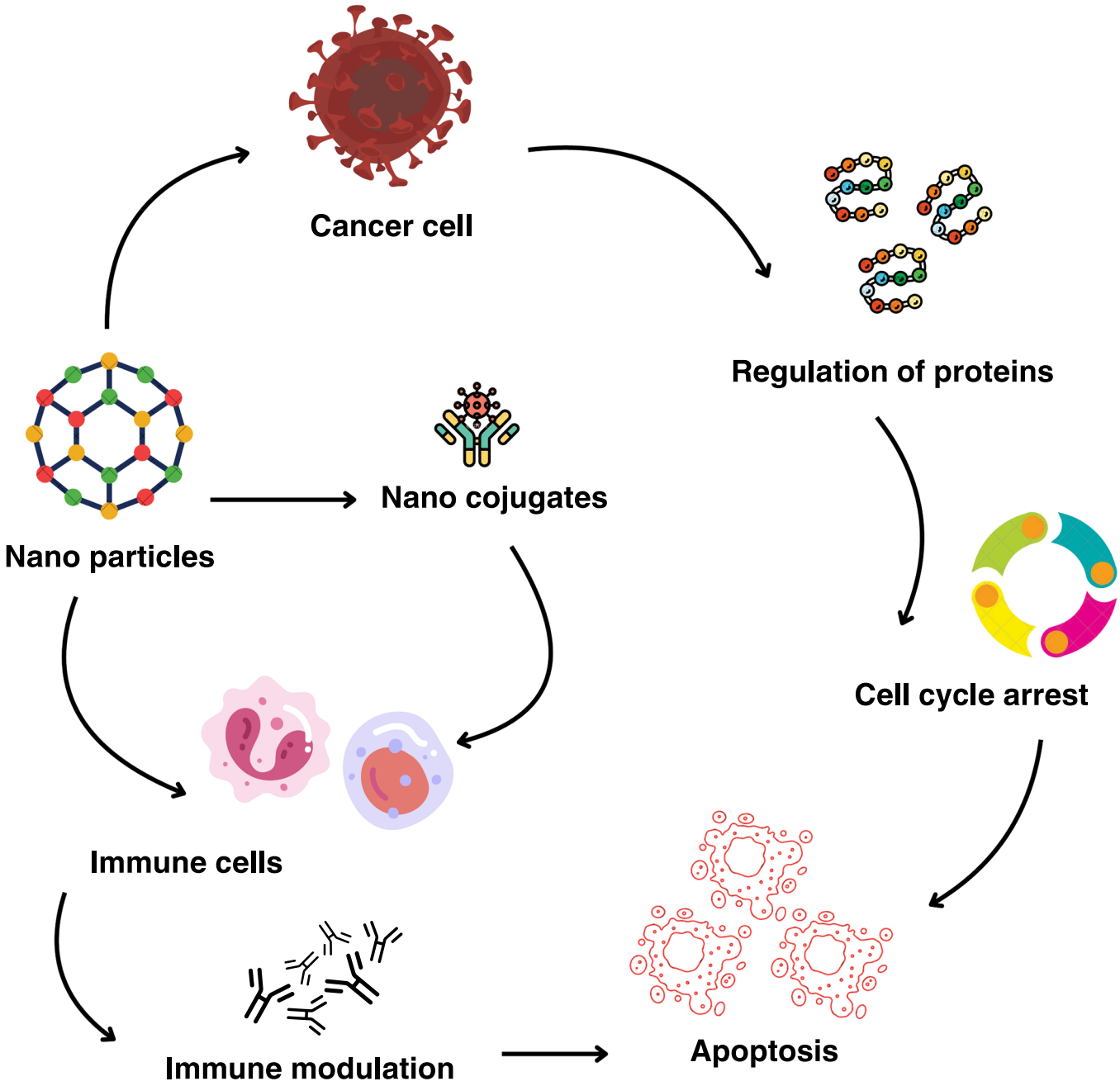

FIGURE 1 | Mechanisms of cell death in cancer induced by nanoparticles.

release systems. It demonstrates high encapsulation efficiency in cancer therapy applications [98, 99].

3.1.3.1 | Dendrimers. Dendrimers exhibit a distinctive hyper-branched structure, characterized by their highly branched and flexible surfaces. These molecules vary in size, usually falling within the range of 1–10 nm. Nevertheless, through tailored synthesis techniques, it is feasible to produce larger dendrimers that may extend to several nanometers in width [100, 101]. Dendrimer molecules consist of three primary structural components: the central core, which contains theragnostic agents that are enclosed through noncovalent interactions; the interior dendritic structure, also referred to as branches; and the outer surface, which is conjugated with functional groups [102]. Dendrimers stand out among other nanomaterials for their distinctive features, such as exceptional solubility, precise molecular weight, capability to enhance the bioavailability of hydrophobic medications, flexible branches, and a narrow polydispersity index. Studies have demonstrated that the incorporation of ruthenium into dendrimer structures amplifies their efficacy in the field of anticancer treatment [103].

3.1.4 | Solid Lipid NPs (SLNs)

SLNs offer a unique combination of benefits from emulsions and liposomes, as well as polymeric NPs. These advantages include safeguarding the encapsulated drugs from degradation, precise control over drug release, and high tolerability. Furthermore, SLNs manage to circumvent certain drawbacks

TABLE 2 | Summary of nanoparticle types and their applications in hematological malignancies.

Type of nanoparticle	Properties	Advantages	Applications/examples
Liposomes	Bilayer structure can encapsulate hydrophilic and hydrophobic drugs	High biocompatibility, prolonged circulation time, reduced toxicity	Doxil (doxorubicin liposome), Marqibo (vincristine sulfate liposome)
Polymeric nanoparticles	Biodegradable, can be synthesized in various shapes and sizes	Controlled drug release, high drug loading capacity	PLGA-based nanoparticles for AML, Bendamustine-loaded PLGA NPs
Micelles	Self-assembling, size range 5–100 nm	Improved drug solubility, reduced systemic toxicity	Polymeric micelles for paclitaxel delivery
Solid lipid nanoparticles	Stable lipid matrix, biocompatible	Protects encapsulated drugs, controlled release	SLNs for curcumin delivery
Iron oxide nanoparticles	Magnetic properties, biocompatible, biodegradable	Targeted drug delivery, enhanced imaging capabilities	Iron oxide NPs for MRI and hyperthermia
Silica nanoparticles	Mesoporous structure, adjustable pore sizes	High surface area, uniform drug distribution	Mesoporous silica NPs for harmine delivery in lymphoma
Gold nanoparticles	Unique optical and electrical properties, nontoxic	Easy surface modification, stable	Gold NPs for BCR-ABL gene targeting in CML
Dendrimers	Highly branched, controlled structure	High solubility, customizable surface functionality	Dendrimer-based delivery of anticancer agents
Hybrid nanoparticles	Combination of organic and inorganic materials	Combines the benefits of both types, versatile	Hybrid NPs for multi-modal cancer therapy

associated with emulsions, liposomes, and polymeric NPs, particularly issues related to in vivo stability [104]. SLNs can overcome physiological barriers that impede the transportation of drugs to tumors and bypass multidrug resistance mechanisms in cancer cells [105]. One potential drawback of SLNs is their limited drug loading capacity, which is typically around 25%–50% compared to the lipid matrix. Additionally, there is a risk of accidental drug expulsion during long-term storage [106].

3.2 | Inorganic NPs

3.2.1 | Iron Oxide

Iron oxide NPs are recognized as biocompatible, stable, and biodegradable platforms. Their application in drug delivery has only been explored in the past few years. Typically, these NPs consist of an inorganic core composed of magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3) encapsulated by an (in)organic coating that is essential for maintaining stability and stealthiness in biological environments [107]. Iron oxide NPs have varying dimensions, from nanometers to microns. They have been extensively researched for MRI and anemia treatment, gaining FDA approval. They can also be used for hyperthermia, selectively eliminating cancer cells with an alternative magnetic field [108]. Iron oxide NPs offer a significant advantage over other nanocarriers due to their unique ability to facilitate magnetic drug release.

3.2.2 | Silica NPs

Silica NPs exhibit exceptional biocompatibility, biodegradability, and chemical stability as nanosystems with sizes ranging from 10 to 10,000 nm. These NPs possess a mesoporous structure that can be easily adjusted, with pore sizes ranging from 2 to 50 nm. The solid framework of silica NPs, which is made up of Si-O bonds, is highly resistant to degradation and external pressures. Due to their high surface area to volume ratio, they have a high drug loading capacity and provide uniform drug distribution [109]. The uniform pore sizes in MSNs result from the precise pore network arrangement, enabling efficient loading of hydrophilic and hydrophobic therapeutic agents. The ordered pore structure of MSNs aids in the controlled release of the loaded drugs [110]. Numerous silica NPs have been developed for the delivery of cancer drugs since they were first introduced by Vallet-Regi and colleagues [111] in the early 2000s [112]. The main constraint associated with these systems stems from their hemolytic effect, which results from the interaction between their silanol groups and the phospholipid surface of red blood cell membranes [113]. Zhao et al. conducted research on the development of harmine-loaded MSNs (H@MSNs) as a potential treatment for lymphoma [114].

3.2.3 | Gold NPs

Gold NPs have unique properties that make them ideal for treating tumors. They are nontoxic, have distinct optical and electrical properties, and can biodegrade. Their surface can also be easily modified, making them even more useful in tumor therapy. With these advantages, gold NPs show promise for developing effective cancer treatments [115]. Gold NPs (AuNPs) have gained significant interest in various scientific fields for their diverse applications. These include drug and gene delivery, thermal ablation, radiotherapy enhancement, diagnostics, optics, sensing, biochemistry, electronics, and bioremediation. Their exceptional sensitivity makes

them valuable tools in diagnostic applications, while their versatility allows for use in a wide range of other areas such as drug delivery and biochemistry [67].

3.3 | Aptamers

NP multifunctionality addresses chemoresistance through enhanced molecular targeting and localized drug accumulation, offering solutions to conventional chemotherapy limitations [116]. Chemoresistance, the ability of tumor cells to resist drugs, remains a significant challenge in cancer treatment, leading to reduced survival rates and increased recurrence [117]. Chemoresistance, the ability of tumor cells to resist drugs, remains a significant challenge in cancer treatment, leading to reduced survival rates and increased recurrence [118]. These engineered oligonucleotides can trigger various biochemical responses and are produced using systematic evolution of ligands by exponential enrichment (SELEX) [119]. They offer numerous benefits compared to commonly employed small-molecule ligands. Their advantages include:

(i) enhanced tissue permeability, (ii) multiple available targets, (iii) robust stability, and (iiii) modification capability [120–122]. Aptamers possess the unique ability to selectively identify molecular targets and regulate their biological functions, thereby enabling their application in therapeutic and diagnostic contexts [123]. Aptamers are commonly linked to NPs to facilitate detection for diagnostic applications. Zhao et al. created aptamer-modified fluorescent silica NPs (FSNPs) by attaching amine-labeled Sgc8 aptamer to carboxyl-modified FSNPs through amide coupling for the purpose of identifying leukemia cells [124]. A different investigation documented the creation of aptamer-linked gold-coated magnetic NPs for the smart identification of leukemia cancer cells [125]. Targeted drug delivery systems (TDDS) are a highly effective method for delivering drugs to specific tissues in the body, particularly in the context of treating cancer. TDDS utilize nanocarriers and ligands, such as aptamers, to precisely deliver drugs to desired sites within the body. Aptamers are favored for their ease of synthesis and high specificity, making them a popular choice for customization of both organic and inorganic nanocarriers. By directing these nanocarriers to tumors, drugs can be efficiently delivered to tumor cells, facilitating cell death. A key focus in the development of aptamer-based drug delivery systems is enhancing drug concentration at the tumor site and overcoming drug resistance mechanisms, offering a promising strategy for improved cancer treatment outcomes. Despite the abundance of resources available for aptamers, certain aspects remain that require improvement in their utilization. The advancement of synthetic technology for oligonucleotides is necessary to enhance the production of aptamers. Additionally, it is crucial to carefully consider the biological stability of aptamers in vivo, as it serves as a prerequisite for their practical application [123]. Figure 2 visually represents the classification of nanoparticles used in cancer therapy.

3.3.1 | Development of Different Nanoconjugates for the Management of Blood Cancer

Nanoconjugates represent an advanced drug delivery system in cancer therapy, offering improved targeting, enhanced drug stability, and better therapeutic outcomes. In blood cancers, including leukemia, lymphoma, multiple myeloma, and myelodysplastic syndromes, nanoconjugates play a crucial role in enhancing drug bioavailability, reducing systemic toxicity, and overcoming drug resistance [126]. These conjugates involve nanoparticles functionalized with therapeutic agents, monoclonal antibodies, peptides, or ligands, allowing precise delivery to malignant cells while minimizing damage to healthy tissues [127].

One of the most significant applications of nanoconjugates in blood cancer therapy is targeted drug delivery [127]. Conventional chemotherapy often lacks specificity, leading to adverse effects on normal hematopoietic cells. However, nanoconjugates improve therapeutic selectivity by incorporating targeting ligands such as monoclonal antibodies [128]. For instance, liposome-based drug delivery systems have been developed, including CPX-351, which encapsulates cytarabine and daunorubicin for AML treatment. This formulation enhances drug retention, ensuring a controlled release at the tumor site. Similarly, doxorubicin-loaded liposomes conjugated with CD19 antibodies have shown remarkable improvements in B-cell leukemia, ensuring selective binding to CD19-expressing cells [129]. Polymeric nanoparticles, particularly those made from PLGA, have also demonstrated selective targeting capabilities when conjugated with anti-CD123 antibodies. These nanoparticles show strong efficacy in targeting leukemia stem cells in AML, an important feature in preventing relapse. Gold and silver nanoparticles further expand this approach, with gold nanoparticles conjugated with rituximab (anti-CD20) proving effective against NHL and silver nanoparticles functionalized with transferrin demonstrating promise in leukemia drug delivery.

Overcoming drug resistance remains a critical challenge in blood cancer management, and nanoconjugates have been instrumental in addressing this issue. Many hematologic malignancies develop resistance to standard chemotherapy due to mechanisms such as increased drug efflux and intracellular drug degradation Janani et al. 2023). To counteract these effects, P-glycoprotein (P-gp) targeted nanoconjugates have been designed. Carbon nanotube-based nanoconjugates that target P-gp-overexpressing leukemia cells have demonstrated increased intracellular drug accumulation and cytotoxicity, overcoming resistance mechanisms. In multiple myeloma, nanoconjugates that co-load bortezomib (a proteasome inhibitor) and azacitidine (an epigenetic modulator) have significantly enhanced therapeutic synergy, reducing the likelihood of resistance. Similarly, mesoporous silica nanoparticles conjugated with daunorubicin and a hypoxia-responsive ligand have proven effective in reversing hypoxia-induced drug resistance in AML, ensuring better therapeutic outcomes.

In addition to targeted drug delivery and resistance reversal, nanoconjugates play an essential role in immunotherapy for blood cancer. Cancer cells often evade immune surveillance, making immunotherapy an attractive approach. However, the efficacy of immune-based treatments can be limited due to tumor-induced immunosuppression. Nanoconjugates have been employed to enhance the persistence and function of immunotherapeutic agents. One of the most promising areas is CAR-T cell therapy, where nanoparticles conjugated with

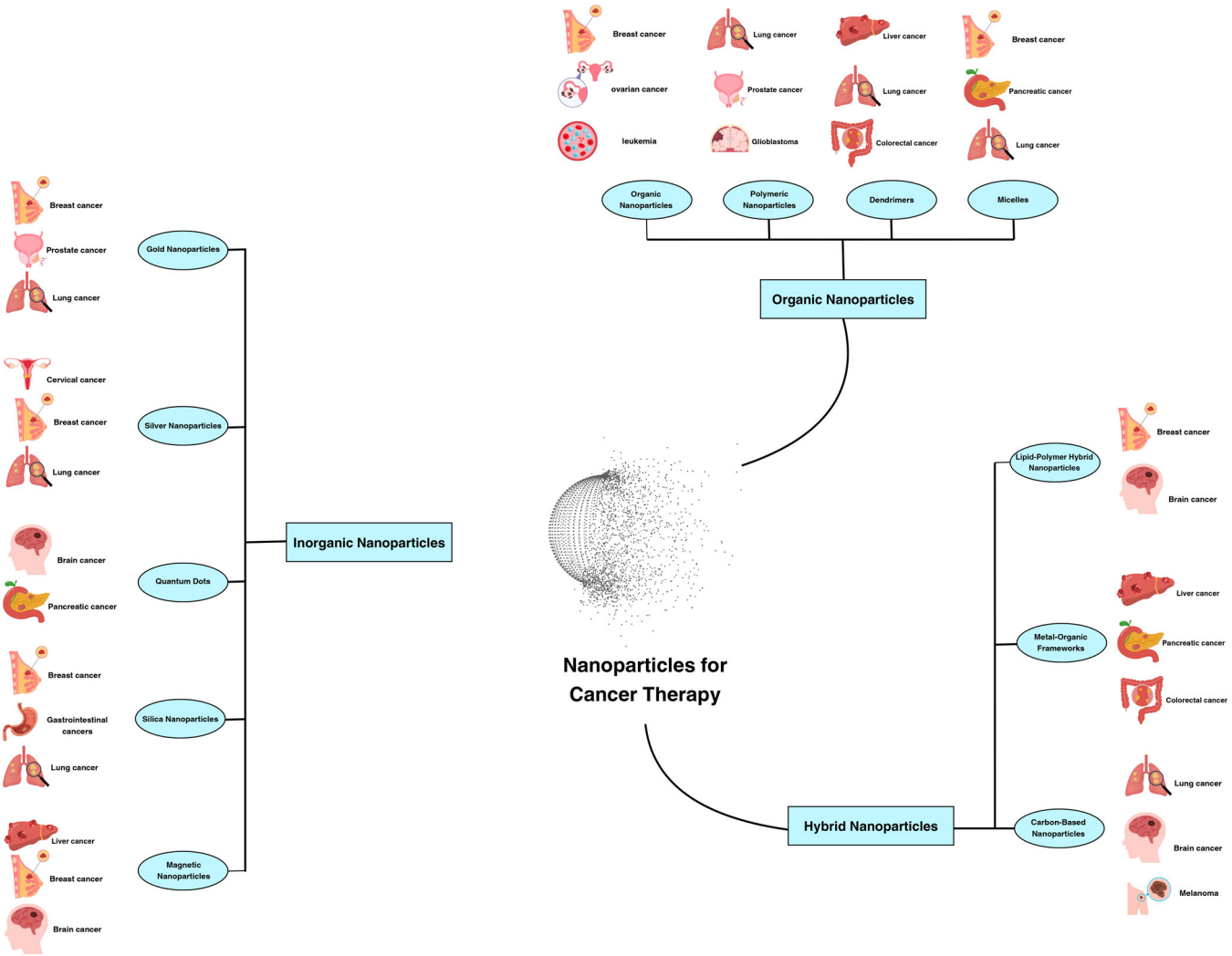

FIGURE 2 | The diagram visually represents the classification of nanoparticles used in cancer therapy, with a central node labeled "Nanoparticles for Cancer Therapy" connecting to three major categories: Organic Nanoparticles, Inorganic Nanoparticles, and Hybrid Nanoparticles. Each category further branches out to specific nanoparticle types that are actively researched for their applications in cancer treatment. The first group categorizes Organic Nanoparticles, which include liposomes, polymeric nanoparticles, dendrimers, and micelles. These nanoparticles are biodegradable and commonly used for drug delivery, helping to target specific cancer cells while reducing systemic toxicity. They are primarily researched for breast cancer, lung cancer, liver cancer, and glioblastoma, among others. The second group focuses on Inorganic Nanoparticles, including gold, silver, quantum dots, silica, and magnetic nanoparticles. These nanoparticles have unique optical, magnetic, and cytotoxic properties, making them useful for both imaging and treatment. They are particularly applied in brain cancer, breast cancer, prostate cancer, and gastrointestinal cancers, where precise imaging and targeted therapy are crucial. The third group highlights Hybrid Nanoparticles, which combine organic and inorganic components for enhanced effectiveness. These include lipid–polymer hybrid nanoparticles, metal-organicframeworks (MOFs), and carbon-based nanoparticles such as graphene and carbon nanotubes. They are being researched for pancreatic cancer, liver cancer, lung cancer, and melanoma, offering improved drug stability, high drug-loading capacity, and advanced photothermal therapy.

cytokines and immune checkpoint inhibitors have been developed to improve CAR-T cell survival and function in B-cell leukemia and lymphoma. Moreover, polymeric nanoconjugates loaded with PD-1 inhibitors have been investigated to counteract immune evasion in blood cancers, showing promising preclinical results. Additionally, vaccine-based nanoconjugates are emerging as a novel strategy for stimulating an anti-leukemia immune response. Hydrogel-based vaccine formulations containing AML-specific antigens, such as Wilms tumor protein 1 (WT1), have shown potential in triggering a long-lasting immune response, reducing the risk of relapse. Similarly, nanoparticle formulations loaded with leukemia antigens have demonstrated significant improvements in immune activation compared to conventional vaccine strategies.

Looking ahead, the future of nanoconjugates in blood cancer therapy lies in the development of stimuli-responsive, personalized nanomedicine that can adapt to tumor microenvironments. Emerging research is exploring the potential of gene therapy nanoconjugates, delivering CRISPR/Cas9-based gene editing systems to specifically target genetic mutations in leukemia cells [130]. Additionally, hybrid nanoconjugates that integrate organic and inorganic nanoparticles are being investigated for multimodal therapy, combining chemotherapy,

TABLE 3 | Clinical trials involving nanoparticle-based therapies for hematological malignancies.

Nanoparticle type	Drug/compound	Targeted malignancy	Clinical trial phase	Outcome
Liposomes	Vyxeos (daunorubicin and cytarabine)	Acute myeloid leukemia	FDA approved	Improved survival rates compared to traditional therapies
Liposomes	Marqibo (vincristine)	Ph-ALL	FDA Approved	20% complete remission rate, 35% overall response rate
Polymeric NPs	AZD2811	Relapsed/refractory AML	Phase 1/2	Ongoing trial by AstraZeneca for safety and efficacy
PLGA NPs	ATRA	APL	Preclinical	Improved IV administration
PLGA NPs	Imatinib mesylate	Leukemia	Preclinical	86% encapsulation efficiency
Magnetic NPs	VCR-SANs	Leukemia	Preclinical	Enhanced anti-leukemic activity
Gold NPs	AuNP@PEG@e14a2	Chronic myeloid leukemia	Preclinical	Effective BCR-ABL gene silencing
Iron oxide NPs	EpCAM-antibody-coated NPs	Leukemia diagnosis	Phase 1	Ongoing trial at University Hospital Zurich
Radio-immunotherapy NPs	Actinium-225-Labeled HuM195	AML	Phase 1	Ongoing trial at Memorial Sloan Kettering
Albumin NPs	Nab-paclitaxel with rituximab	Non-Hodgkin lymphoma	Phase 1	Ongoing trial at Mayo clinic
Gold NPs	PEG-glucosamine modified	K562 leukemia	Preclinical	Enhanced NK cell targeting
Peptide NPs	BCMA-targeting	Multiple myeloma	Preclinical	Enhanced T cell function
Micelles	Paclitaxel-loaded micelles	Non-Hodgkin lymphoma	Phase 1/2	Reduced systemic toxicity and enhanced tumor targeting

photothermal therapy, and immunotherapy in a single platform. Another key advancement involves biodegradable nanoconjugates, ensuring safe elimination from the body to minimize potential toxicity associated with long-term nanoparticle retention [131].

In conclusion, nanoconjugates offer a transformative approach to blood cancer therapy by enabling targeted drug delivery, overcoming drug resistance, and enhancing immunotherapy. Their ability to improve therapeutic efficacy while minimizing systemic toxicity makes them a powerful tool in cancer management. Continued research efforts should focus on optimizing their clinical translation, improving biocompatibility, and tailoring nanoconjugates for personalized medicine approaches. As the field progresses, these advanced nanosystems hold the potential to significantly improve patient outcomes and redefine the treatment landscape for hematologic malignancies.

4 | Clinical Trials

Nanotechnology has revolutionized cancer treatment through enhanced diagnosis and targeted drug delivery systems [132]. The major nanoparticle systems in clinical development include:

Liposomal formulations lead the field with two FDA-approved products: Vyxeos, combining daunorubicin and cytarabine for AML treatment with improved survival rates, and Marqibo (vincristine) for Ph-ALL, achieving 20% complete remission and 35% overall response rates [133–137]. Polymeric nanoparticles show promising developments, with AZD2811 currently in Phase I/II trials for refractory AML. PLGA-based formulations have demonstrated success in preclinical studies, including ATRA for APL with improved IV administration, and imatinib mesylate achieving 86% encapsulation efficiency [138–142]. Magnetic nanoparticles, particularly VCR-SANs, have shown enhanced anti-leukemic activity in preclinical studies. Gold nanoparticles have proven effective in multiple applications, from FLT3 inhibitor delivery for AML to PEG-glucosamine modifications for enhanced NK cell targeting against K562 leukemia [143–146].

Novel approaches include radio-immunotherapy with Actinium-225-HuM195 (Phase I for AML), and combination therapies like nab-paclitaxel with rituximab for B-cell NHL (Phase I). Diagnostic applications are advancing with EpCAM-antibody coated iron oxide nanoparticles for improved circulating tumor cell detection [147–149]. Peptide nanoparticles targeting BCMA for multiple myeloma have shown promise in preclinical studies by enhancing T cell function, representing an emerging direction in immunotherapy approaches [150–153]. Table 3 summarizes clinical trials involving NP-based therapies for hematological malignancies.

5 | Conclusion

Nanotechnology has emerged as a transformative approach in the treatment of hematological malignancies, offering solutions to many limitations of conventional therapies. Through the development of various nanoparticle systems, including liposomes, polymeric nanoparticles, and inorganic nanoparticles, significant advances have been made in drug delivery, targeting efficiency, and therapeutic outcomes. FDA-approved formulations like Vyxeos and Marqibo demonstrate the clinical viability of nanomedicine approaches, while numerous promising candidates are advancing through clinical trials [154–157].

The success of nanoparticle-based therapies in hematological cancers can be attributed to their unique properties, including enhanced drug solubility, controlled release mechanisms, and the ability to overcome biological barriers. Their capacity to specifically target cancer cells while sparing healthy tissues represents a significant advancement over conventional treatments [158]. However, challenges remain regarding toxicity assessment, regulatory compliance, and scale-up production.

Looking ahead, the field of nanomedicine in hematological malignancies continues to evolve, with emerging technologies like aptamer-based targeting and hybrid nanoparticles showing promise. While obstacles exist in translating these innovations to clinical practice, the growing body of successful applications and ongoing research suggests a bright future for nanoparticle-based therapies in treating blood cancers.

Author Contributions

Nima Torabi Fard: conceptualization and writing – original draft. **Melika Khademi:** conceptualization and writing – original draft. **Aryan Salahi-Niri:** conceptualization, investigation, visualization, writing – review and editing. **Shadi Esmaeili:** conceptualization, methodology, project administration, validation, investigation, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data and summarization are available within the manuscript.

Transparency Statement

The corresponding author Shadi Esmaeili affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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