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Next-Generation Nanocarriers for Hematological Malignancies: A Mechanistic Review of Stimuli-Responsive and Targeted Delivery Systems

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ABSTRACT

Leukemia management has improved with the advent of tyrosine kinase inhibitors and immunotherapy; however, long-term remission remains limited due to relapse, systemic toxicity, and the persistence of leukemic stem cells (LSCs) within the bone marrow niche. Conventional therapies often fail to effectively target these protected microenvironments, leading to drug resistance and disease recurrence. This review summarizes recent advances (2010–2025) in nanocarrier-based strategies for leukemia treatment, focusing on organic, inorganic, and hybrid nanoplatforms. Particular emphasis is placed on targeted delivery systems that utilize ligand-mediated recognition of leukemia-associated markers such as CD33, CD123, and CD26, along with microenvironment-responsive drug release mechanisms. Organic nanocarriers, including liposomes, polymeric micelles, and dendrimers, enhance drug solubility, stability, and pharmacokinetics while reducing off-target toxicity. In contrast, inorganic nanomaterials such as gold and iron oxide nanoparticles offer multifunctional capabilities, including imaging and stimulus-responsive therapeutic delivery. Emerging biomimetic systems further improve immune evasion and bone marrow targeting by mimicking natural cellular components. Collectively, these nanotechnology-driven approaches provide a promising platform for improving therapeutic precision and overcoming current limitations in leukemia treatment. Despite challenges related to scalability, regulatory approval, and long-term safety, continued integration of nanotechnology with molecular oncology may facilitate the development of more effective and targeted therapies for hematological malignancies.

Keywords: Chronic Myeloid Leukemia, Nanomedicine, BCR-ABL1, Stimuli-responsive, Targeted Drug Delivery, Leukemic Stem Cells.

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INTRODUCTION

Leukemia encompasses a diverse group of malignant hematological disorders arising from the uncontrolled proliferation and impaired differentiation of hematopoietic stem and progenitor cells. The accumulation of dysfunctional white blood cells in the bone marrow, peripheral blood, and lymphoid tissues disrupts normal hematopoiesis and immune regulation, ultimately leading to organ failure and life-threatening complications. Despite continuous advances in molecular diagnostics and disease classification, leukemia remains a major contributor to global cancer morbidity and mortality. Its clinical heterogeneity reflected in distinct genetic, epigenetic, and phenotypic profiles across acute and chronic subtypes poses substantial challenges to effective and durable treatment [1].

Conventional therapeutic strategies, including chemotherapy, radiotherapy, immunotherapy, and hematopoietic stem cell transplantation, have significantly improved remission rates in selected patient populations. However, these approaches are often limited by poor selectivity, systemic toxicity, therapy-related complications, and a high incidence of relapse driven by minimal residual disease and acquired drug resistance [2]. As leukemia is a systemic malignancy involving circulating and bone marrow–resident cells, achieving sufficient drug exposure at disease sites while minimizing damage to healthy tissues remains a persistent clinical dilemma. These limitations underscore the need for treatment paradigms that move beyond broadly cytotoxic regimens toward more precise and individualized therapeutic interventions. The emergence of precision medicine has reshaped leukemia management by enabling therapies tailored to specific molecular alterations and signaling pathways. Targeted agents, such as tyrosine kinase inhibitors, B-cell receptor pathway inhibitors, and mutation-specific drugs, have demonstrated substantial clinical benefit in defined leukemia subtypes. Nevertheless, precision therapies alone do not fully resolve key challenges, including suboptimal pharmacokinetics, limited intracellular drug delivery, off-target effects, and resistance mediated by the bone marrow microenvironment. Consequently, a critical translational gap persists between the promise of molecularly targeted agents and their sustained clinical efficacy [3].

Advanced nanomaterials have emerged as a powerful platform to bridge this gap between conventional therapy and precision medicine in leukemia. Owing to their tunable physicochemical properties, nanomaterials enable the rational design of drug delivery systems with enhanced stability, prolonged circulation, controlled release, and improved cellular uptake. Both organic nanocarriers such as liposomes, polymeric nanoparticles, protein-based systems, and cell-derived vesicles and inorganic nanomaterials including metal, magnetic, and silica-based nanoparticles

have demonstrated significant potential for targeted leukemia therapy [4]. Unlike solid tumors, leukemia lacks a well-defined enhanced permeability and retention effect, necessitating the development of actively targeted nanoplatforms capable of recognizing leukemia-specific surface markers or microenvironmental cues to selectively engage circulating and bone marrow–localized malignant cells [5]. Beyond drug delivery, nanomaterials play an increasingly important role in enabling multifunctional precision medicine strategies for leukemia. Nanoplatforms have been employed for gene therapy to modulate oncogenic signaling, overcome multidrug resistance, and induce apoptosis in leukemic cells. Additionally, nanomaterial-assisted immunotherapy has gained attention for its ability to enhance immune activation, improve antigen presentation, and synergize with antibody- and cell-based therapies [6]. The integration of diagnostic and therapeutic functions within a single nanosystem further supports real-time disease monitoring and treatment optimization, aligning with the principles of personalized medicine. Despite their promise, the clinical translation of nanomaterial-based leukemia therapies faces several challenges, including biosafety concerns, immunogenicity, long-term toxicity, and scalable manufacturing [7]. A deeper understanding of nanoparticle–biological interactions and standardized evaluation frameworks is essential to ensure safety and reproducibility. Addressing these challenges will be critical for advancing nanotechnology-enabled platforms from experimental systems to clinically viable therapies.

In this review, we comprehensively examine recent advances in nanomaterials for targeted leukemia management, with a focus on how these systems bridge conventional treatment modalities and precision medicine. We discuss the design principles, targeting mechanisms, and therapeutic applications of advanced nanomaterials across drug delivery, gene regulation, immunotherapy, and diagnostic integration. Furthermore, we highlight current limitations and future directions, aiming to provide a critical framework for the development of next-generation nanotechnology-based strategies for precision leukemia therapy (Figure 1).

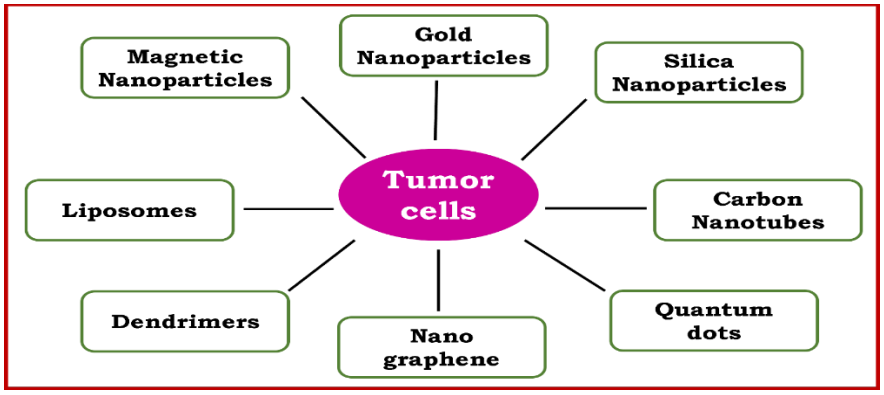

Figure 1: Nanomaterials for cancer diagnosis and therapy

MATERIALS AND METHOD

This study was conducted as a narrative review aimed at summarizing recent advances in nanocarrier-based therapeutic strategies for leukemia. The review focuses on the mechanistic aspects of organic, inorganic, and hybrid nanomaterials, with particular emphasis on targeted drug delivery and microenvironment-responsive systems. Relevant literature was collected from major scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. These sources were selected to ensure comprehensive coverage of peer-reviewed publications in the fields of nanotechnology and hematological malignancies. A systematic keyword-based search was performed for articles published between 2010 and 2025. Keywords included "leukemia," "nanocarriers," "nanoparticles," "targeted drug delivery," "stimuli-responsive systems," and "leukemic stem cells." Boolean operators (AND, OR) were used to refine the search. Additionally, reference lists of selected articles were manually screened to identify further relevant studies. Studies were included if they focused on nanomaterial-based approaches for leukemia treatment, particularly those addressing mechanisms of action, targeting strategies, and therapeutic outcomes. Peer-reviewed research articles and review papers were considered. Articles were excluded if they were not in English, lacked sufficient scientific detail, or were not directly relevant to the scope of this review. Priority was given to recent and high-impact studies to ensure the inclusion of up-to-date information. The selected studies were critically analyzed and categorized based on the type of nanocarrier (organic, inorganic, or hybrid) and their functional mechanisms. Key findings were synthesized to highlight advances in targeted delivery, therapeutic efficiency, and challenges associated with clinical translation.

Pathophysiology of Chronic Myeloid Leukemia and the Current Therapeutic Landscape

Molecular Basis of CML: BCR–ABL1–Driven Signaling

Chronic myeloid leukemia (CML) is a paradigmatic example of a molecularly defined malignancy, primarily driven by the Philadelphia (Ph) chromosome resulting from the reciprocal translocation *t*(9;22)(q34;q11). This chromosomal rearrangement generates the BCR–ABL1 fusion gene, which encodes a constitutively active tyrosine kinase that plays a central role in CML initiation and progression. Unlike its physiological counterpart, the BCR–ABL1 oncoprotein exhibits deregulated kinase activity, leading to persistent activation of multiple downstream signaling cascades, including the RAS/MAPK, PI3K/Akt, and JAK/STAT pathways. Collectively, these pathways promote uncontrolled myeloid proliferation, enhanced survival, genomic instability, and resistance to apoptosis, thereby establishing and sustaining the leukemic phenotype [8]. The oncogenic addiction of CML cells to BCR–ABL1 signaling has positioned this fusion protein as an

ideal therapeutic target and has fundamentally shaped the development of precision therapies in hematologic malignancies.

Evolution of Tyrosine Kinase Inhibitor Therapy in CML

The clinical management of CML has undergone a transformative shift from non-specific cytotoxic chemotherapy to targeted inhibition of BCR–ABL1 kinase activity. Tyrosine kinase inhibitors (TKIs) now constitute the cornerstone of CML therapy and are broadly classified into three generations based on their molecular design and resistance profiles. The first-generation TKI, imatinib, was the pioneering ATP-competitive inhibitor targeting the ABL1 kinase domain and remains the standard frontline therapy for patients in the chronic phase of CML [9]. While imatinib induces durable cytogenetic and molecular responses in a substantial proportion of patients, its clinical efficacy is limited by suboptimal pharmacokinetics, incomplete target inhibition, and the emergence of resistance. Second-generation TKIs, including nilotinib, dasatinib, and bosutinib, were developed to enhance binding affinity and overcome imatinib-resistant BCR–ABL1 mutations [10]. These agents exhibit improved potency and faster molecular responses; however, their clinical use is often constrained by off-target toxicities [11]. Third-generation TKIs, exemplified by ponatinib, were rationally designed to inhibit the BCR–ABL1 T315I “gatekeeper” mutation, which confers resistance to earlier TKIs. Despite its efficacy against refractory disease, ponatinib use is restricted by severe vascular toxicities, including arterial occlusive events, necessitating careful patient selection and dose optimization [12].

Therapeutic Barriers: Drug Resistance and Leukemic Stem Cell Persistence

Although TKI therapy has dramatically improved survival outcomes for patients with CML, it rarely achieves complete disease eradication. Two interrelated challenges continue to limit curative potential [13]. First, acquired drug resistance arises through both BCR–ABL1–dependent mechanisms such as kinase domain point mutations and BCR–ABL1–independent mechanisms, including activation of compensatory signaling pathways and overexpression of drug efflux transporters such as P-glycoprotein [14]. These adaptive responses reduce intracellular drug accumulation and compromise sustained target inhibition. Leukemic stem cells (LSCs) residing within the bone marrow niche represent a critical reservoir of minimal residual disease. These cells are typically quiescent, exhibit low levels of BCR–ABL1 expression, and are intrinsically insensitive to TKI-mediated cytotoxicity [15]. Furthermore, interactions with the bone marrow microenvironment provide biochemical and physical protection that shields LSCs from systemic drug exposure, facilitating disease persistence and relapse following treatment discontinuation.

Rationale for Nanotechnology-Enabled Therapeutic Strategies

The clinical limitations of conventional TKI therapy are closely linked to unfavorable pharmacokinetic properties, including poor aqueous solubility, rapid systemic clearance, and non-specific biodistribution. These shortcomings necessitate prolonged and high-dose administration, thereby increasing cumulative toxicity and diminishing patient adherence. Nanotechnology-based drug delivery systems offer a compelling strategy to address these challenges by enabling site-specific drug accumulation, controlled release, and microenvironment-responsive targeting. Advanced nanomaterials can be engineered to improve TKI solubility, prolong circulation time, enhance intracellular delivery, and selectively target leukemic cells or bone marrow niches (Figure 2) [16-17].

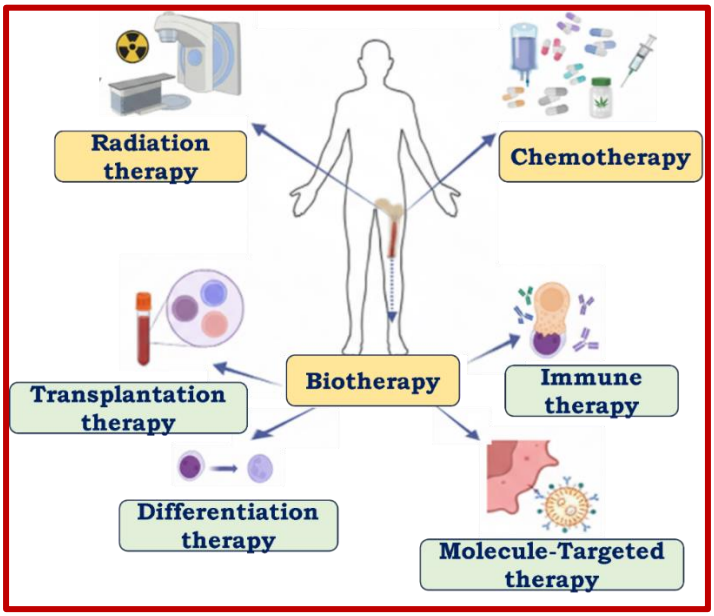

Figure 2: The different treatment approaches for chronic myelogenous leukemia.

Nanomaterials for Leukemia Targeted Treatment

Nanomaterials generally refer to engineered materials with characteristic dimensions at the nanoscale, typically below 100 nm, that exhibit physicochemical and biological properties distinct from their bulk counterparts. These properties include a high surface area-to-volume ratio, tunable surface chemistry, enhanced reactivity, and improved cellular internalization, all of which make nanomaterials highly attractive for biomedical applications. In oncology, and particularly in leukemia, nanomaterials offer unique opportunities to improve therapeutic precision, drug bioavailability, and treatment safety [18]. One of the most significant advantages of nanomaterials in leukemia therapy is their ability to enable targeted drug delivery. By functionalizing nanoparticle surfaces with antibodies, peptides, or small-molecule ligands that recognize leukemia-associated receptors, therapeutic agents can be selectively delivered to malignant cells while sparing normal tissues [19]. This targeted approach reduces systemic exposure to cytotoxic drugs

and mitigates adverse effects commonly associated with conventional chemotherapy, such as myelosuppression, gastrointestinal toxicity, and organ damage. In addition, targeted nanocarriers enhance drug accumulation at disease sites, thereby improving therapeutic efficacy. Several studies have demonstrated that ligand-modified polymeric nanoparticles can achieve favorable biodistribution profiles, prolonged circulation, and enhanced antileukemic activity in both cellular and animal models [20]. Nanomaterials also allow precise control over drug release kinetics. Controlled and stimuli-responsive release systems can be engineered to respond to specific internal or external triggers, such as temperature, pH, redox conditions, or light irradiation [21]. These systems prolong drug retention at the target site, reduce dosing frequency, and minimize premature drug leakage. For example, thermoresponsive nanoparticle systems have been shown to release chemotherapeutic agents in response to localized hyperthermia, leading to enhanced intracellular drug accumulation and increased cytotoxicity in leukemia cells while minimizing damage to surrounding healthy tissues [22]. In addition to therapeutic delivery, nanomaterials play an increasingly important role in leukemia imaging and diagnosis. Nanoparticles possessing magnetic, optical, or fluorescent properties can serve as contrast agents for imaging modalities such as magnetic resonance imaging and computed tomography. When conjugated with leukemia-specific targeting moieties, these nanomaterials improve detection sensitivity and enable more accurate identification of malignant cells. Such imaging capabilities facilitate early diagnosis, real-time monitoring of treatment response, and improved assessment of disease progression [23]. Multidrug resistance remains a major obstacle in leukemia treatment, often resulting from reduced intracellular drug accumulation and enhanced efflux mediated by membrane transporters. Nanomaterial-based delivery systems offer effective strategies to overcome these resistance mechanisms. By bypassing conventional drug transport pathways and inhibiting efflux pumps, nanoparticles can significantly increase intracellular drug concentrations in resistant leukemia cells [24]. Moreover, co-delivery systems that combine chemotherapeutic agents with resistance-modulating molecules have shown promising results in restoring drug sensitivity and inducing apoptosis in multidrug-resistant leukemia models. From a materials perspective, nanomaterials used in leukemia therapy are broadly classified into organic and inorganic systems. Organic nanomaterials include lipid-based carriers, polymeric nanoparticles, protein-based systems, and carbon-derived materials, which generally exhibit favorable biocompatibility and biodegradability [25]. Inorganic nanomaterials, such as metal nanoparticles, magnetic nanoparticles, and mesoporous silica structures, possess unique optical, magnetic, and catalytic properties that expand their functionality beyond conventional drug carriers [26]. Through rational design and surface

modification, the composition, size, and structure of nanomaterials can be precisely tuned to meet specific therapeutic requirements. Hybrid and multifunctional nanoplatforms that integrate organic and inorganic components have attracted considerable attention in recent years. These systems combine the biocompatibility of organic materials with the functional versatility of inorganic cores, enabling simultaneous therapeutic delivery, diagnostic imaging, and combination treatment strategies. Such mixed nanostructures have been successfully applied in multimodal therapies, including drug delivery combined with gene regulation, photothermal therapy, photodynamic therapy, or sequential release of multiple therapeutic agents [27]. Although inorganic nanocarriers offer exceptional functional properties, their limited biodegradability and relatively low drug-loading capacity necessitate their incorporation into composite systems with organic materials [28]. Consequently, hybrid nanomaterials represent a balanced approach that maximizes therapeutic performance while addressing safety and translational concerns. Collectively, these advances highlight the growing potential of nanomaterials as adaptable and powerful tools for targeted leukemia therapy.

Organic Nanotechnology Platforms for Leukemia Therapy

Organic nanoparticles, including lipid-based, polymer-based, and dendrimer-based systems, have shown great potential in chronic myeloid leukemia (CML) therapy. Liposomes offer advantages over free drug formulations due to their lower toxicity, ability to be conjugated with antibodies or signaling molecules for targeted delivery, and improved pharmacokinetics and bioavailability [29]. Polylactic-co-glycolic acid (PLGA) nanoparticles provide sustained drug release, enzymatic degradation resistance, and reduced toxicity to healthy cells, making them effective carriers for therapeutic agents [30]. Polymer micelles, constructed using polyethylene glycol (PEG), enhance biocompatibility and improve drug bioavailability. Additionally, dendrimers—small, radially symmetrical nanoparticles-serve as efficient drug delivery systems. Given these benefits, organic nanoparticles play a crucial role in disease treatment, including CML [31]. Several organic nanoparticle formulations have been developed to target CML [32]. To address the overexpression of somatostatin receptor type 2 in CML cells, amino-PEGylated quantum dot nanoparticles were succinylated and coated with the ligand octreotide [33]. The different organic nanomaterials used in CML therapy are summarized in Table 1.

Table 1: Summary of various organic nanoparticles used in CML therapy

S. No	Nanoparticles type	Mechanism of action	Ref.
1	Polylactic acid nanoparticle	Induced apoptosis in K562 cells via daunorubicin and glycyrrhizic acid.	[34]
2	Lipid-polymer hybrid	Reduced tumor growth in K562 cells from 956 mm^3 to 213 mm^3 using doxorubicin and gallic acid.	[35]
3	Ferritin dendrimer	Leukemia cells internalize pre-miRNA via the CD71 receptor, leading to maturation of pre-miRNA and morphological changes.	[36]
4	Protein scaffold	A dodecameric peptide antagonist inhibits MDM2/MDMX and activates the p53 pathway, targeting the C-terminus of Bcr-Abl.	[37]
5	Lipid nanoparticle	Targets the Bcr-Abl fusion oncogene in a mouse myeloid leukemia model using lipid-loaded nanoparticles containing Bcr-Abl siRNA.	[38]
6	Polyethylenimine-Cholesterol	PEI-Chol-mediated delivery of Bcr-Abl siRNA increases apoptosis in K562 cells.	[39]
7	Co-polymer (poly oligo (ethylene glycol) methacrylate-b-poly (styrene–co-4-formylphenyl methacrylate))	Enables controlled drug release and prolonged circulation at high doses, making it a potential CML drug candidate.	[40]

Nanocarriers of Polymers

Polymeric micelles have emerged as a cornerstone of organic nanomedicine due to their unique core-shell architecture, typically ranging from 10 to 100 nm. These structures self-assemble from amphiphilic copolymers, featuring a hydrophobic core for the encapsulation of poorly water-soluble therapeutics and a hydrophilic corona—most commonly composed of polyethylene glycol (PEG). The PEGylated surface provides a critical steric barrier that minimizes protein adsorption and immune-mediated clearance, thereby extending systemic circulation and enhancing drug accumulation within the leukemic niche [41]. The clinical utility of these platforms is further amplified by their capacity for active molecular targeting. By functionalizing the polymer surface with ligands such as folic acid or monoclonal antibodies (e.g., anti-CD33 for AML or anti-CD123 for CML LSCs), nanocarriers can distinguish between malignant populations and healthy hematopoietic stem cells. A notable advancement in this area is the development of stimuli-responsive "smart" systems that trigger drug release in response to the acidic microenvironment of the bone marrow. Furthermore, polymeric nanocarriers provide a robust strategy to overcome multidrug resistance (MDR) through the co-delivery of chemotherapeutic agents and gene-silencing molecules (siRNA), which collectively restore chemosensitivity and minimize off-target toxicities such as myelosuppression and gastrointestinal distress. Beyond therapy, the integration of fluorescent probes or magnetic contrast agents into these polymeric frameworks facilitates real-time "theranostic" monitoring [42]. This allows clinicians to visualize drug biodistribution and

assess therapeutic response simultaneously, fulfilling the requirements of personalized precision medicine. Despite remaining challenges regarding immunogenicity and large-scale scalability, polymeric nanocarriers represent a versatile and powerful tool for the integrated diagnosis and treatment of leukemia.

Carbon-based nanomaterials

The treatment of cancer has created a lot of interest in carbon-based nanomaterials, including graphene, fullerenes, carbon nanotubes (CNTs), carbon quantum dots (CQDs), and nanodiamonds. They are useful for targeted drug administration, photothermal therapy, and imaging applications due to their unique physicochemical characteristics, which include a large surface area, biocompatibility, and simplicity of functionalization. CNTs are widely used in gene therapy and drug delivery because of their effective cellular penetration and strong drug-loading capability [43]. Graphene and graphene oxide (GO) exhibit strong photothermal effects and are often combined with chemotherapy to enhance therapeutic efficacy [44]. Fullerenes act as free radical scavengers and possess antioxidant properties, making them valuable in reducing oxidative stress in cancer cells [45]. CQDs serve as efficient bioimaging agents due to their fluorescence properties and are being explored for drug delivery applications [46]. Nanodiamonds, known for their excellent biocompatibility, further enhance targeted cancer treatment by improving drug stability and controlled release. These diverse carbon-based nanomaterials offer innovative approaches for cancer therapy, providing multifunctional platforms for treatment and diagnosis.

Carbon-based nanomaterials are extensively explored as carriers for drug delivery in cancer treatment research [47,48]. The cytotoxic effects of magnetite (Fe_3O_4) nanoparticles (NPs) and carbon nanotubes (CNTs), both alone and in hybrid form, against myeloid leukemia cell lines. The study successfully synthesized and characterized Fe_3O_4 NPs and Fe_3O_4/CNTs-GA nano hybrids, demonstrating significant cytotoxicity while maintaining relative safety towards normal hematopoietic cells. The proposed mechanism of action involves increased creation of reactive oxygen species (ROS), cell cycle disruption, and the initiation of apoptosis, or programmed cell death, mediated by key proteins such as p53, BAX, and caspase-3 offers promising insights into the potential of these nanostructures as therapeutic agents for Acute Myeloid Leukemia (AML), and potentially CML [49]. The broader application of carbon nanomaterials (CNMs) in cancer therapy, with implications for CML. It emphasizes the versatility of CNMs, such as graphene sheets, carbon quantum dots (CQDs), and CNTs, as drug delivery agents. The advantages of CNMs include their low toxicity, potential for functionalization with targeting ligands, and ability to encapsulate various therapeutic payloads, including siRNA. The importance of using organic

material for the synthesis of CNMs to reduce toxicity is also mentioned in the diagnostic potential of a single-walled carbon nanotube (SWCN)-aptamer-modified interdigitated electrode (IDE) sensor for the detection of CD19, a biomarker relevant to CML. The sensor demonstrated high sensitivity, detecting CD19 at concentrations as low as 10 nm, and exhibited excellent selectivity in serum samples. The use of amine-modified SWCNs facilitated efficient aptamer immobilization, enhancing the sensor's performance [50]. The therapeutic research highlights the ability of engineered nanomaterials to induce targeted cytotoxicity through specific molecular pathways, and the diagnostic study demonstrates the power of nanomaterial-based biosensors for sensitive and selective biomarker detection.

Lipid-Based Nanocarriers (Liposomes)

Liposomes are spherical vesicular nanostructures (50–100 nm) characterized by a phospholipid bilayer architecture that closely mimics biological membranes, ensuring high biocompatibility and minimal immunogenicity. Their dual-compartment structure allows for the simultaneous encapsulation of hydrophilic agents in the aqueous core and hydrophobic drugs such as second-generation TKIs or BCL-2 inhibitors within the lipid bilayer. This protective encapsulation shields payloads from enzymatic degradation, improves aqueous solubility, and facilitates controlled, sustained release kinetics, which are essential for maintaining therapeutic drug concentrations in the systemic circulation [51]. The clinical superiority of liposomes in leukemia management is largely driven by their adaptability for active targeting and stimuli-responsive action. By functionalizing the lipid surface with bone-targeting ligands (e.g., alendronate-hyaluronic acid conjugates) or immune-targeting antibodies (e.g., anti-CD26), these platforms can penetrate the bone marrow microenvironment to eradicate quiescent leukemic stem cells (LSCs). For example, redox-responsive liposomal systems utilizing disulfide-linked cholesterol have demonstrated the ability to selectively release cytarabine or venetoclax within the LSC-rich niche, significantly reducing minimal residual disease while sparing healthy hematopoietic tissues. Despite their versatility, the clinical transition of complex liposomal formulations remains challenged by environmental sensitivity and the technical demands of large-scale, reproducible synthesis. However, their ability to achieve durable remission by targeting CD26+ or CD44+ populations positions lipid-based nanocarriers as a primary tool in the evolution toward precision leukemia therapy [52].

Inorganic Nanomaterials

The synthesis of inorganic nanomaterials is relatively simple, allowing precise control over size and surface properties, which facilitates easy functionalization. Their distinct optical, electrical,

and magnetic characteristics make them highly suitable for applications in imaging, targeted drug delivery, and combination therapy. Common types of inorganic nanomaterials include gold nanoparticles, manganese oxide nanoparticles, silica nanoparticles, and magnetic nanoparticles [53] used in the drug delivery process are shown in Table 2.

Table 2: Summary of Various Inorganic Nanoparticle-Based Nano Formulations Used in CML Treatment

S. No	Nanoparticle type	Mechanism of Action	Ref.
1.	Gold nanoparticles	Induced apoptosis in drug-resistant CML cells by down-regulating DNMT1 and miR-221, restoring p15ink4b and p27kip1 tumor suppressor expression, and P-gp expression.	[63]
2.	Arsenic sulfide nanoparticles	Directly degraded BCR-ABL by down-regulating hypoxia-inducible factor 1α and ROS.	[64]
3.	Mesoporous silica nanoparticles	Released 59% of doxorubicin, inhibiting K562 cells.	[65]
4.	Thioxanthone-derived gold nanoparticles	5µl of conjugated doxorubicin exhibited 7.3% cytotoxicity against K562 cells.	[66]
5.	Silver nanoparticles	Exhibited anticancer activity in K562 cells with an IC50 value of 19.5 mg/ml.	[67]
6.	Cobalt ferrite nanoparticles	9µM of coated $CoFe_2O_4$ showed strong apoptotic effects on K562 cells after 72 h of treatment.	[68]
7.	Arsenic trioxide nanoparticles	F56 (20%) and DSS6 (50%) oligopeptides targeted vascular and endothelial niches, suppressing colony formation and proliferation of K562 cells (IC50 = 3.29 µM).	[69]
8.	Ferrous oxide and zinc oxide nanoparticles	Reduced K562 cell proliferation through apoptosis and G1 arrest via FOXO3a and SIRT1 upregulation, inhibiting the NF-κB signaling pathway.	[70]
9.	Ultra-small platinum nanoparticles	Induced ROS fluctuation and triggered autophagy by increasing Beclin-1 levels, leading to BCR-ABL degradation. Also, downregulated PI3K and AKT phosphorylation.	[71]

Gold Nanoparticles

Gold nanoparticles (GNPs) emerge as versatile tools in cancer therapy, particularly for myeloid malignancies, due to their stability, adsorption capacity, and potential for targeted drug delivery. Studies demonstrate GNPs' efficacy as carriers for tyrosine kinase inhibitors (TKIs) like Bosutinib in Chronic Myeloid Leukemia (CML), enhancing the therapeutic index by delivering payloads directly to tumour sites using active/passive targeting. Furthermore, green synthesis of GNPs utilizing C.sinensis leaf aqueous extract yielded nanoparticles (~20-30nm) that exhibited significant *in-vivo* regulation comparable to daunorubicin's effects on immunological, hematological, and histopathological parameters, while demonstrating dose dependent cytotoxicity against various myeloid leukemia cell lines (HL-60/vcr, 32D FLT3 ITD, C1498) with minimal impact on normal endothelial cells (HUVEC). This collective evidence underscores the potential of

GNPs, both chemically and biologically synthesized, as effective drug nanocarriers and therapeutic agents for myeloid leukemias, including CML and Acute Myeloid Leukemia (AML) [54].

Manganese oxide nanoparticles

Manganese oxide nanoparticles have garnered a lot of attention due to their versatile structures and varied morphologies. Between them, manganese dioxide (MnO_2) stands out due to its large surface area, making it an excellent candidate for drug delivery with high drug-loading capacity. In the acidic tumor microenvironment (TME), where glutathione (GSH) is overexpressed, Mn^{4+} in MnO_2 facilitates the controlled release of loaded drugs. Additionally, MnO_2 is reduced to Mn^{2+}, which reacts with reactive oxygen species (ROS) to deplete GSH, thereby enhancing the overall therapeutic efficacy [55].

Silicon-based nanomaterials

Porous silica nanomaterials hold significant promise in biomedicine; they are extensively utilized as drug delivery carriers owing to their remarkable porosity and superior drug-loading capacity [56], and utilize mesoporous silica nanoparticles (MSNs) as carriers to develop nanodrugs for actively targeting leukemia cells. Anticancer medications based on platinum may become more cytotoxic when mesoporous silica microparticles are incorporated [57].

Magnetic Nanoparticles

Usually ranging in size from 1 to 100 nm, magnetic nanoparticles are a significant class of functional materials. Because of their special characteristics, these nanoparticles have attracted a lot of interest in bioengineering and magnetic material applications. Their unique properties enable easy separation under an ambient magnetic region, facilitating the isolation of target biological products [58]. Additionally, their ability to rapidly accumulate in magnetic fields makes them viable options for the tailored delivery of medication. Currently, magnetic nanoparticles are extensively researched as drug carriers for targeted therapies and as tools for bioseparation technologies.

A FeO_4-PLA nanocomposite has been developed for drug delivery, and its efficacy in treating drug-resistant leukemia K562 cells with daunorubicin (DNR) has been investigated. By enhancing the interface between DNR and cancer cells, this nanocomposite promotes greater drug accumulation in leukemia cells [59]. Similarly, magnetic FeO_4 nanoparticles coupled with the natural cephalotaxine alkaloid Homoharringtonine (HHT) have shown promise as tumor therapy medication carriers [60].

Magnetic nanoparticles also offer advantages. El-Boubbou et al. produced a nano formulation based on iron oxide that contains the anticancer medicine doxorubicin for drug loading and

delivery. This formulation especially functions as a targeted medication carrier for different acute myeloid leukemia (AML) subtypes [61]. Additionally, chitosan-coated magnetic nanoparticles further expand the potential applications of magnetic nanomaterials in targeted leukemia therapies [62]. Various Inorganic Nanoparticle-Based Nanoformulations Used in CML Treatment are given in Table 2, and the plausible mechanism of nanoparticle's targeted action in CML is given in Figure 3.

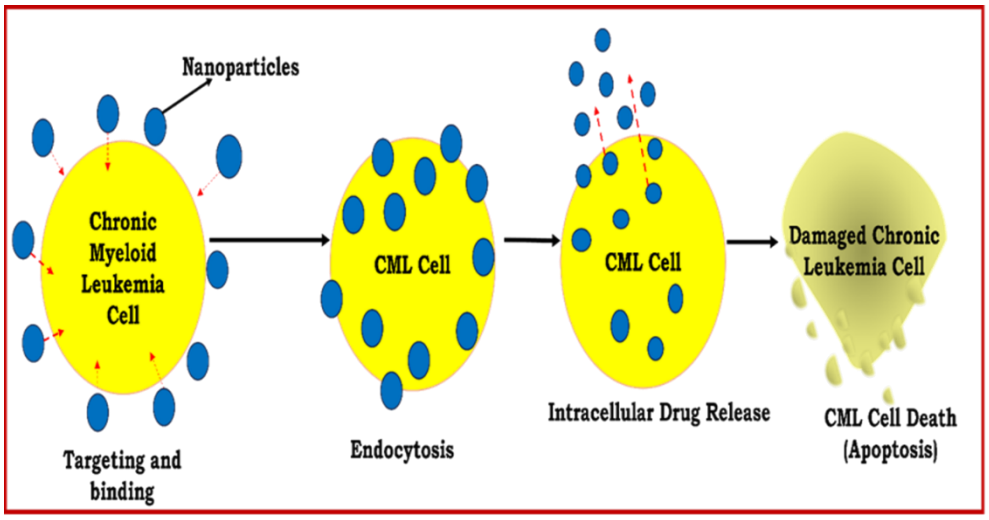

Figure 3: Mechanism of Nanoparticle's Targeted Action in CML

Nanotechnology-Enabled Inhibition of the BCR-ABL1 Signaling Axis

The constitutive activation of the BCR-ABL1 non-receptor tyrosine kinase is the fundamental driver of Chronic Myeloid Leukemia (CML). This oncoprotein triggers a cascade of downstream signaling networks—most notably the RAS/MAPK, PI3K/Akt/mTOR, and JAK/STAT pathways—which collectively orchestrate unregulated myeloproliferation and the evasion of apoptosis [72]. While small-molecule Tyrosine Kinase Inhibitors (TKIs) are designed to competitively block the ATP-binding site of the BCR-ABL1 kinase domain, their clinical efficacy is often compromised by suboptimal intracellular drug accumulation and the emergence of kinase domain mutations. Nanotechnology provides a strategic platform to optimize these inhibitory pathways by ensuring the localized delivery of high-potency TKIs directly to the intracellular target. For instance, biomimetic lipid nanoparticles encapsulating Ponatinib have demonstrated a superior ability to suppress the Akt pathway, which is critical for the survival of T315I-mutant cells that are typically resistant to first- and second-generation TKIs . Similarly, gold nanoparticle-based delivery of Dasatinib has been shown to enhance the competitive inhibition of the SRC kinase family, a secondary driver of TKI resistance in advanced-phase CML [73].

Furthermore, the engineering of high-density lipoprotein (HDL) nanoformulations and functionalized polymeric nanoparticles allows for the simultaneous inhibition of phosphate transfer across multiple tyrosine kinases, including Bcr-Abl and SRC. By protecting the TKI payload from premature metabolic degradation and enhancing its uptake via receptor-mediated endocytosis, these nanoplatforms facilitate a more complete suppression of the leukemic signaling architecture. This transition from systemic administration to nanotechnology-enabled targeted inhibition represents a critical step in achieving deep molecular remission and bridging the gap toward precision leukemia management.

CONCLUSION

Nanotechnology-enabled platforms represent a transformative paradigm in leukemia management, effectively bridging the gap between systemic cytotoxicity and molecularly targeted precision medicine. As detailed in this review, next-generation nanocarriers—including organic, inorganic, and biomimetic systems—offer unique mechanistic advantages by enhancing the bioavailability of poorly soluble agents, prolonging systemic circulation, and facilitating the co-delivery of synergistic therapeutic payloads. By leveraging stimuli-responsive release and active ligand-mediated targeting, these "smart" systems can penetrate the protective bone marrow microenvironment to eradicate quiescent leukemic stem cells (LSCs), thereby addressing the primary drivers of multidrug resistance and disease relapse. Despite significant preclinical success in modulating oncogenic pathways like BCR-ABL1 and improving the therapeutic index of TKIs, the clinical translation of these complex nanostructures remains challenged. Critical bottlenecks include the formation of the "protein corona" in vivo, which can mask targeting ligands, as well as the technical hurdles of scalable, reproducible manufacturing and long-term biosafety. To move beyond the current limitations of formulations like PEGylated liposomes and iron oxide nanoparticles, future efforts must prioritize interdisciplinary synergy between materials science, molecular oncology, and clinical hematology. With a focused emphasis on standardizing regulatory frameworks and optimizing biomimetic designs, nanotechnology holds the potential to transition leukemia from a chronic, resistance-prone condition into a curable disease.

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