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Narrative Review

The Therapeutic Potential of Stem Cells in Leukemia: Mechanisms and Clinical Directions

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Abstract

Leukemia remains a significant clinical challenge despite advances in chemotherapy, targeted therapies. Stem cell–based therapies represent a cornerstone in the treatment of leukemia, offering the potential for both curative and regenerative outcomes. Hematopoietic stem cell transplantation (HSCT) remains the most effective and widely used therapeutic approach, capable of restoring normal hematopoiesis following intensive chemotherapy or radiotherapy. Recent advances in stem cell biology and genetic engineering have further expanded the landscape of leukemia treatment. Induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs) are being explored for their roles in disease modeling, drug screening, and as supportive agents to enhance engraftment and reduce transplant-related complications. This review provides a comprehensive overview of leukemia and its current therapeutic approaches, and examines the role of stem cells in modulating malignant hematopoiesis. Evidence from preclinical and clinical studies demonstrates that stem cells, particularly MSCs, hematopoietic stem cells (HSCs), and umbilical cord–derived or Wharton's jelly–derived stem cells, can exert anti-leukemic effects through mechanisms such as apoptosis induction, cell cycle arrest, and modulation of the bone marrow microenvironment. The therapeutic potential of stem cells is explored in the context of major leukemia subtypes, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL), highlighting both *in vitro* and *in vivo* findings, including clinical trial evidence. Furthermore, emerging therapeutic directions are discussed, including the use of stem cells as drug delivery vehicles, gene therapy carriers, and sources of extracellular vesicles, alongside strategies to disrupt leukemic stem cell niches and enhance chemotherapy efficacy. While stem cell–based interventions hold considerable promise, their dualistic effects on tumor progression, context-dependent outcomes, and safety concerns underscore the need for further mechanistic studies and carefully designed clinical trials. Collectively, this review emphasizes the evolving role of stem cell–based therapies in leukemia management and identifies future directions for optimizing their clinical application toward long-term disease control and improved patient outcomes.

Keywords: Stem Cell, Stem Cell Therapy, MSC, Leukemia, AML, ALL, CML, CLL

Introduction

Leukemia, a malignant disorder of hematopoietic stem and progenitor cells, remains a major global health challenge despite significant advances in diagnostic techniques and therapeutic strategies. It is characterized by the uncontrolled proliferation and impaired differentiation of abnormal leukocytes, which ultimately disrupt normal hematopoiesis and compromise immune function.[1] According to epidemiological reports, In 2022, leukemia was reported as the thirteenth most frequently diagnosed cancer worldwide, accounting for 486,777 new cases and more than 305,033 deaths, making it the tenth leading cause of cancer-related mortality.[2] Although leukemia occurs across all regions, incidence is generally higher in developed nations, whereas developing countries tend to report greater mortality rates, reflecting disparities in healthcare access and treatment outcomes. According to the American Cancer Society's Cancer Facts and Figures for 2020, an estimated 178,520 individuals in the United States were expected to be diagnosed with leukemia, lymphoma, or myeloma, representing about 9.9% of all new cancer cases projected for that year (1,806,590 cases in total). Leukemia affects both sexes but is consistently more common in males. In 2018, the

age-standardized incidence in the U.S. was 6.1 per 100,000 for men and 4.3 per 100,000 for women, while mortality rates were similarly higher among men (4.2 per 100,000) compared with women (2.8 per 100,000).[3] Despite progress in chemotherapy, targeted therapy, and immunotherapy, many patients continue to experience relapse, treatment resistance, and severe therapy-associated toxicities.[4-6] These limitations underscore the urgent need for innovative and safer therapeutic modalities that not only improve survival but also enhance the quality of life for patients.

In recent years, stem cells have emerged as promising candidates for novel therapeutic strategies in hematologic malignancies.[7] Stem cells represent a distinct cell population characterized by three fundamental properties: the ability to self-renew over extended periods, the capacity to generate clonal populations from single cells, and the potential to differentiate into multiple specialized cell types.[8] Broadly, stem cells are classified into two main categories: embryonic stem cells (ESCs) and somatic or adult stem cells (SSCs). ESCs are pluripotent cells originating from the inner cell mass of the blastocyst, an early embryonic stage. Their capacity for indefinite self-renewal and pluripotency is maintained through intrinsic cellular mechanisms as well as supportive culture conditions.[9] Adult stem cells are typically multipotent, giving rise to specific lineages such as neural stem cells (NSCs), mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and endothelial progenitor cells (EPCs).[10] In addition to their self-renewal and differentiation capabilities, stem cells possess distinctive biological features, including the ability to home toward tumor sites, release a wide range of bioactive molecules, and modulate immune responses. These properties make them attractive candidates for enhancing tumor-specific targeting and overcoming limitations that hinder conventional gene therapy approaches. Evidence from preclinical studies highlights the considerable potential of stem cell-based strategies as platforms for targeted anticancer therapies.[11] A wide range of stem cell-based approaches are currently being explored in preclinical studies, demonstrating both significant therapeutic potential and notable challenges in cancer treatment.[12]

There are various identified mechanisms underlying the action of stem cells in cancer. First, HSCs display a strong capacity for homing to bone marrow niches, a process largely regulated by CXCR4–SDF-1 signaling and supported by adhesion molecules and matrix-degrading enzymes.[13,14] MSCs also exhibit a tumor-tropic effect, migrating toward the tumor micro environment in response to hypoxia, inflammation, and chemokines such as CXCL16, SDF-1, CCL25, and IL-6, as well as pro-inflammatory cytokines like TNF-α and IL-1β.[15-18] Once localized to tumor sites, stem cells secrete a wide array of paracrine factors, including extracellular vesicles (EVs) and soluble mediators, which can regulate tumor survival, metastasis, immune responses, and angiogenesis.[19,20] Their differentiation potential further contributes to therapeutic outcomes, with HSCs restoring hematopoiesis, neural stem cells (NSCs) replacing damaged neurons, and pluripotent stem cells (ESCs/iPSCs) serving as sources for effector immune cells.[21] Additionally, cancer stem cells (CSCs) arise from dysregulation of signaling pathways such as Notch, Hedgehog, Wnt/β-catenin, PI3K/PTEN, JAK/STAT, and NF-κB. These cells maintain self-renewal, drive tumor growth, and contribute to recurrence, metastasis, and resistance to conventional therapies.[22-25] Understanding these mechanisms is critical for developing stem cell-based cancer treatments.

The scope of this review is to critically evaluate the therapeutic applications of stem cells in leukemia, focusing on the different subtypes of the disease. In recent years, remarkable progress has been made in developing innovative therapeutic strategies that extend beyond conventional chemotherapy and radiotherapy in leukemia management. Among these, cancer vaccines aim to stimulate the immune system to recognize and eliminate leukemic cells through antigen-specific responses. Chimeric antigen receptor (CAR)–modified immune cells, particularly CAR-T and CAR-NK cells, have shown transformative potential by redirecting immune activity toward leukemia-associated antigens. Stem cell–derived exosomes have emerged as promising cell-free therapeutic tools capable of delivering bioactive molecules, modulating immune responses, and enhancing hematopoietic regeneration. In parallel, oncolytic viruses offer a dual benefit by directly lysing malignant cells while promoting systemic antitumor immunity. Advances in nanoparticle-based drug delivery systems have further improved the precision and efficacy of leukemia treatments by enhancing targeted delivery and reducing systemic toxicity. Finally, hematopoietic stem cell

transplantation (HSCT) remains a cornerstone therapy, providing both curative potential and a foundation for integrating these emerging modalities. Collectively, these approaches reflect a rapidly evolving therapeutic landscape focused on improving outcomes through precision, immunomodulation, and regenerative strategies. Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) represent aggressive hematologic malignancies characterized by rapid disease progression and high relapse rates, where novel stem cell-based interventions could hold significant promise.[26,27] Chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL), while often presenting with more indolent courses, pose unique therapeutic challenges such as treatment resistance to tyrosine kinase inhibitors in CML and immunosuppressive microenvironmental interactions in CLL.[28,29] By exploring the role of stem cells across these subtypes, this review aims to provide a comprehensive perspective on their potential as disease-modifying agents and supportive therapies. Additionally, we highlight the translation of stem cell-based strategies from bench to bedside. A growing number of preclinical models and clinical trials are investigating the efficacy and safety of stem cells in leukemia therapy. These studies range from the use of naïve stem cells to genetically modified stem cells engineered to deliver therapeutic molecules, as well as MSC-derived EVs as cell-free alternatives. The outcomes of these investigations will be crucial in defining the therapeutic value of stem cells, optimizing their application, and addressing safety concerns such as unwanted tumor-promoting effects.

Overview of Leukemia: Classification, Pathophysiology, and Current Therapies

Leukemia is a heterogeneous group of hematologic malignancies characterized by the uncontrolled proliferation of abnormal leukocytes and impaired differentiation of hematopoietic stem and progenitor cells. The disease originates in the bone marrow and often infiltrates the blood and other tissues, ultimately disturbing normal hematopoiesis and compromising immune competence. Despite significant advances in diagnostics and treatment modalities, leukemia continues to impose a substantial clinical burden, with diverse subtypes displaying variable incidence, biology, prognosis, and therapeutic responses.[30] To better understand its complexity, leukemia can be examined through three primary dimensions: its classification, underlying pathophysiology, and current therapeutic strategies.

Leukemia is further classified into various subtypes according to French-American-British (FAB) scheme and World Health Organization (WHO) scheme.[31] According to FAB classification, leukemia is broadly classified according to two major criteria; the pace of disease progression (acute or chronic) and the lineage of hematopoietic cells involved (myeloid or lymphoid). Based on this framework, four principal categories of leukemia are defined.

AML is an aggressive malignancy arising from the clonal expansion of immature myeloid progenitors, or myeloblasts, which fail to differentiate into functional granulocytes, monocytes, or other myeloid lineages. The disease progresses rapidly and often presents with bone marrow failure, anemia, neutropenia, and thrombocytopenia. AML is the most common acute leukemia in adults and has a variable prognosis depending on age, cytogenetic profile, and molecular abnormalities. AML has a complex pathogenesis involving genetic mutations, chromosomal abnormalities, and dysregulation of transcription factors and signaling pathways.[32] AML is classified into subtypes M0–M7 under the FAB system, while the WHO classification incorporates these categories along with additional subtypes defined by specific genetic and molecular abnormalities.[31-33]

ALL is a rapidly progressing cancer of the lymphoid lineage that results from the malignant transformation of B- or T-lymphoid progenitor cells. It is the most common type of leukemia in children, though it also occurs in adults. ALL leads to the overproduction of immature lymphoblasts that crowd out normal hematopoietic cells in the bone marrow, causing severe cytopenias and immune dysfunction. Clinical features often include bone marrow suppression, hepatosplenomegaly, lymphadenopathy, and central nervous system involvement. Advances in chemotherapy have dramatically improved survival rates in pediatric ALL; however, prognosis in adults remains less favorable.[34] ALL is categorized into L1, L2, and L3 subtypes according to the FAB system, whereas the WHO classification divides ALL into B-cell and T-cell lineages based on immunophenotypic and genetic features.[31]

CML is a myeloproliferative neoplasm characterized

by the presence of the Philadelphia chromosome, a reciprocal translocation between chromosomes 9 and 22 [t(9;22)(q34;q11)], which generates the BCR-ABL1 fusion gene. This fusion gene encodes a constitutively active tyrosine kinase that drives uncontrolled cell proliferation. CML typically progresses through three clinical phases, chronic, accelerated, and blast crisis, if left untreated. The introduction of tyrosine kinase inhibitors (TKIs), such as imatinib, revolutionized CML treatment and transformed it into a manageable chronic condition for most patients.[35]

CLL is a clonal malignancy of mature, functionally incompetent B lymphocytes that accumulate in the blood, bone marrow, and lymphoid tissues. It is the most common adult leukemia in Western countries and typically follows an indolent clinical course, although some patients experience more aggressive disease progression. CLL pathogenesis involves genetic and epigenetic alterations, interactions with the tumor microenvironment, and signaling through the B-cell receptor pathway. Modern therapeutic strategies include monoclonal antibodies, B-cell receptor inhibitors, and other targeted agents. Clinical manifestations include lymphadenopathy, splenomegaly, recurrent infections, and immune dysregulation.[36,37] The CLL and CML can also be classified analogous to the classification schemes of ALL and AML.

Beyond these four categories, additional subtypes and rare entities exist, such as hairy cell leukemia, prolymphocytic leukemia, and mixed phenotype acute leukemia (MPAL), which reflect the biological diversity of the disease spectrum.[38-40]

The development of leukemia is a multistep process involving genetic, epigenetic, and microenvironmental alterations that disrupt normal hematopoiesis and confer survival advantages to malignant clones.[41] Leukemogenesis is frequently driven by chromosomal translocations such as the t(9;22) translocation in CML,[42] t(15;17) in acute promyelocytic leukemia (APL),[43] and various karyotypic changes in AML and ALL, gene mutations like RUNX1,[44] CEBPA,[45] NOTCH1 that impair differentiation,[46] and epigenetic dysregulation, such as mutations in DNMT3A,[47] TET2,[48] and IDH1/2,[49] which alter DNA methylation and histone modification patterns, leading to transcriptional dysregulation.

Leukemia cells interact extensively with the bone marrow niche, where stromal cells, MSCs, endothelial cells, and extracellular matrix components collectively form a supportive microenvironment.[50,51] This “leukemic niche” provides signals that enhance malignant cell survival, mediate resistance to chemotherapy, and suppress normal hematopoiesis. Key mediators include chemokines (such as SDF-1/CXCL12), adhesion molecules, and growth factors.[52] Besides the role of the bone marrow microenvironment in the pathogenesis of leukemia, clonal heterogeneity can also contribute to disease progression, relapse, and treatment resistance.[53]

The therapeutic landscape of leukemia has expanded considerably over the past decades, with advances in chemotherapy, targeted agents, immunotherapy, and stem cell transplantation. Despite these developments, challenges remain, including drug resistance, relapse, and treatment-related toxicity.[54] Chemotherapy remains the backbone of treatment for most leukemias, especially acute subtypes. Induction therapy aims to eradicate leukemic blasts and achieve remission, followed by consolidation or maintenance regimens.[55] Common agents include cytarabine,[56] anthracyclines like, daunorubicin,[57] idarubicin,[58] and alkylating agents.[59] While effective, chemotherapy is associated with significant toxicities, including myelosuppression, infections, and organ damage.[60]

Furthermore, the development of targeted therapies has significantly transformed the management of leukemia by providing treatment options tailored to specific molecular abnormalities.[5] In CML, the introduction of tyrosine kinase inhibitors (TKIs), beginning with imatinib and followed by second- and third-generation agents such as dasatinib, nilotinib, bosutinib, and ponatinib, has dramatically improved survival rate of CML cases.[61] In AML, the identification of recurrent genetic mutations has led to the use of mutation-specific agents, including FLT3 inhibitors (midostaurin, gilteritinib) and IDH1/2 inhibitors (ivosidenib, enasidenib), which have demonstrated improved clinical outcomes in genetically defined patient subgroups.[62,63] Similarly, targeting apoptosis pathways with the BCL-2 inhibitor venetoclax has shown substantial efficacy in both CLL and AML.[64] Furthermore, inhibitors of Bruton's tyrosine kinase (BTK), such as ibrutinib and acalabrutinib, have provided highly effective therapeutic options for B-cell malignancies.[65] Collectively, these targeted approaches represent a paradigm shift in leukemia therapy, emphasizing precision medicine strategies that align treatment with disease biology.

In recent years, cancer immunotherapy has achieved remarkable advances, with several approaches becoming part of standard clinical practice for solid tumors and certain hematological malignancies, including ALL. However, comparable progress in AML has been slower, and effective immunotherapeutic strategies for this disease remain under active investigation.[66]

Antibody–drug conjugates (ADCs) combine monoclonal antibodies with cytotoxic agents to selectively target tumor cells.[67] In AML, CD33 is the primary target, and gemtuzumab ozogamicin (GO), an anti-CD33 ADC, was initially approved in 2000 but withdrawn in 2010 due to safety and efficacy concerns.[68,69] Later studies showed that GO plus chemotherapy improves overall survival, particularly in patients with favorable or intermediate cytogenetic risk.[70-72]

T cell–recruiting antibody constructs consist of two single-chain variable fragments linked to bring tumor cells and T cells into close proximity, triggering CD3-mediated T cell activation and Granzyme B/perforin–dependent tumor lysis.[73,74] Blinatumomab (CD19/CD3) exemplifies this approach and was FDA-approved in 2014 for relapsed/refractory Ph-negative B-precursor ALL, achieving a CR/CRi rate of 43% in phase II trials.[75] Its superiority over conventional chemotherapy was later confirmed in a phase III trial.[76]

CAR-T cells enhance the concept of T cell–recruiting antibody constructs by overcoming T cell exhaustion, anergy, and senescence, and have demonstrated promising results in hematologic malignancies. CARs are genetically engineered receptors that combine extracellular antigen recognition with intracellular signaling, enabling MHC-independent target binding and potent cytotoxic activity. Since the development of first-generation CARs in 1989,[77] the incorporation of costimulatory domains such as CD28 or 4-1BB in second-generation constructs has markedly improved anti-tumor efficacy and facilitated their translation into clinical trials.[78] CD19 remains the primary target for CAR T cell therapy due to its restricted expression and favorable safety profile. In relapsed/refractory B-ALL, anti-CD19 CAR T cells with 4-1BB costimulation achieved MRD-negative complete remission in 86% of 29 patients.[79]

Allogeneic HSCT remains the one the critical curative options for many high-risk leukemias. It provides both a source of healthy hematopoietic stem cells and a graft-versus-leukemia (GVL) effect mediated by donor immune cells. However, HSCT is limited by donor availability, treatment-related mortality, and complications such as graft-versus-host disease (GVHD). GVHD is a major complication of allogeneic hematopoietic stem cell transplantation, in which donor immune cells attack the recipient's tissues. Autologous HSCT is less commonly used but can be beneficial in specific settings.[80] Besides that, some studies have indicated that MSCs exert a suppressing role in hematologic malignancies, with increasing evidence suggesting they can inhibit tumor cell proliferation. However, their role in leukemia remains uncertain and less explored to date and future investigations may clarify and improve this effect.[81,82]

Despite progress, several challenges persist in leukemia management. Relapse due to minimal residual disease, and the emergence of drug resistance remain major hurdles.[83-85] Furthermore, treatment-associated toxicities limit the applicability of aggressive regimens, particularly in elderly or comorbid patients.[86] Ongoing challenges highlight the need for innovative strategies, including stem cell-based therapies, to achieve more durable remissions and improved survival for patients.

Stem Cell-Based Therapeutic Strategies in Cancer

The management of cancer is largely determined by the tumor type, stage of progression, and therapeutic goals. Surgical resection is typically the primary option for localized solid tumors, enabling direct removal of the malignant mass. Radiotherapy eliminates cancer cells by inducing DNA damage, while chemotherapy employs cytotoxic agents to inhibit or halt tumor growth. More recently, immunotherapeutic approaches such as monoclonal antibodies, checkpoint inhibitors, cancer vaccines, and adoptive cell transfer, have emerged as transformative modalities, significantly enhancing patient outcomes. Nevertheless, most conventional treatments face critical limitations, including poor specificity and inadequate targeting of tumor tissue, with the exception of effector CAR T cells. These shortcomings contribute to limited therapeutic efficacy, drug resistance, and eventual tumor relapse. Furthermore, adverse events associated with off-target effects and immune-related toxicities remain a major clinical concern.[87-89] In this context, stem cell–based therapies have gained attention as a promising avenue in oncology. By leveraging the tumor-homing properties of stem cells, these strategies

offer improved precision in targeting malignant cells while minimizing collateral damage to healthy tissue. Moreover, stem cell–mediated delivery systems have the potential to enhance the effectiveness of existing therapeutic modalities and mitigate treatment-related toxicities. Although still largely in the preclinical stage, stem cell–based approaches have demonstrated encouraging potential as well as significant challenges that must be addressed before their integration into clinical practice.[12]

Stem cells differ in their proliferative, migratory, and differentiation capacities, which shape their potential in cancer therapy.[90] ESCs, derived from the inner cell mass of embryos, can generate all cell types except placental tissue. Their clinical use, however, is limited by ethical concerns. The discovery of Yamanaka factors in 2006 enabled the generation of iPSCs from somatic cells, providing ESC-like properties without ethical issues.[91] Both ESCs and iPSCs have been employed for producing effector T and NK cells as well as developing anti-cancer vaccines.[92] Adult stem cells can differentiate into specialized cells within their tissue of origin. Among them, HSCs, MSCs, and NSCs are most relevant in oncology. HSC transplantation, especially from cord blood, is currently the only FDA-approved stem cell therapy for malignancies such as leukemia and multiple myeloma.[13] MSCs, widely distributed in tissues, contribute to regeneration and are frequently explored as delivery vehicles for therapeutic agents in cancer treatment.[93] NSCs, residing in the central nervous system, can generate neurons and glia, and have been tested in preclinical models for treating both primary and metastatic tumors, including breast, lung, and prostate cancers.[94]

Several stem cell–based approaches have been explored in oncology, including HSC transplantation, MSC infusion, stem cell–mediated drug delivery, immune effector cell generation, and vaccine development. HSC transplantation remains the standard therapy for hematologic malignancies such as leukemia, lymphoma, and multiple myeloma following intensive chemo therapy or radiotherapy.[13] It is also under clinical investigation for solid tumors, including brain cancers, sarcomas, neuroblastoma, and breast cancer. A major obstacle is GVHD, particularly in allogeneic transplants, which often requires long-term immunosuppression with limited efficacy and significant side effects.[95] Aggressive cancer treatments frequently damage healthy tissues and the hematopoietic system. MSC infusion has been shown to support HSC survival and proliferation, mitigate immune complications such as refractory GVHD, and enhance tissue repair.[96-98] Clinical studies indicate that MSC co-transplantation improves patient outcomes without severe adverse effects.[99-101] Moreover, MSCs facilitate recovery from high-dose chemotherapy and may improve tolerance to intensive cancer regimens, thereby increasing therapeutic efficacy.[19]

Stem cell carriers can also be utilized in the treatment of cancer to protect therapeutic agents from rapidly biological degradation, reduce systemic side effects and increase local levels of therapeutics due to intrinsic tumor-targeting effect of stem cells. The anti-tumor effectiveness of this system depends on the extent of stem cell accumulation within the tumor micro environment. MSCs and NSCs can be genetically modified, often via viral transduction, to secrete therapeutic molecules such as prodrug-converting enzymes or tumor-toxic cytokines.[102] A well-established approach, gene-directed enzyme prodrug therapy (GDEPT), enables engineered stem cells to convert inactive prodrugs into active cytotoxins at tumor sites.[103] For instance, cytosine deaminase (CD)-expressing MSCs or NSCs convert 5-fluorocytosine into 5-fluorouracil, while carboxylesterase-expressing NSCs enhance irinotecan activity by generating its highly toxic metabolite, SN-38.[104] Several phase I/II trials have evaluated these strategies, demonstrating safety and tolerability in patients with recurrent gliomas and advanced gastrointestinal cancers.[105-107] Stem cells have also been engineered to deliver cytokines such as TRAIL, which otherwise shows limited stability in systemic circulation. NSCs engineered to secrete TRAIL suppressed brain tumor growth and prolonged survival in preclinical models, and are currently being tested in clinical trials. Moreover, dual-expression systems combining suicide genes (e.g., CD) with antitumor cytokines (e.g., IFN-β) have shown synergistic effects by simultaneously inhibiting tumor growth and inducing apoptosis.[108-109]

Nanoparticles (NPs) have long been applied in cancer drug delivery, but their rapid clearance, poor targeting, and nonspecific uptake limit efficacy.[110] Stem cells, with inherent tumor-homing capacity, offer an alternative vehicle for NP delivery, either through intracellular loading or surface conjugation. NP internalization

occurs via passive or active endocytosis, influenced by particle size, surface properties, concentration, and incubation time.[111] Key challenges include cytotoxicity, uncontrolled drug loading, and premature exocytosis. Nonetheless, lipid and PLA NPs were efficiently internalized by MSCs without impairing viability, enabling tumor-directed delivery in glioma models.[112] Similarly, paclitaxel-loaded NP–MSCs localized to orthotopic lung tumors, forming intratumoral drug depots that reduced tumor growth and improved survival at lower doses than free PTX or PTX-NPs.[113] MSCs initially lodge in the lung parenchyma and subsequently migrate to tumor sites.[114] Uptake can be enhanced by strategies such as TAT peptide–mediated PLGA NP internalization.[115] Surface conjugation also improves NP retention, typically via amine or thiol groups.[116] Cyclooctyne-modified NPs linked to azide-functionalized MSCs significantly increased drug loading (~48 pg PTX per cell vs. ~1–20 pg by other methods) while preserving phenotype.[117] Hybrid systems, such as TRAIL-expressing MSC spheroids combined with drug-loaded NPs, further enhanced retention and therapeutic efficacy in glioblastoma models.[118]

Oncolytic viruses (OVs) selectively replicate in cancer cells, inducing lysis and releasing danger signals that activate antitumor immunity.[119] However, free OVs are quickly eliminated by the immune system. Stem cells can protect and deliver OVs to tumors. For instance, NSCs carrying CRAd-Survivin-pk7 combined with radiation and temozolomide enhanced glioma cell killing and prolonged survival in GBM-bearing mice.[120] Similarly, MSCs efficiently delivered oncolytic measles virus and HSV, suppressing hepatocellular carcinoma and GBM growth in mice.[121,122] Notably, MSCs from ovarian cancer patients showed comparable OMV-carrying ability to healthy donors, even after cryopreservation.[123] Both MSCs and NSCs support OV replication, though NSCs release higher viral loads and demonstrate greater efficacy in prolonging survival in glioma models.[106]

Stem cell-derived exosomes is another potential anti-cancer strategy being used in cancer therapy. Exosomes released from stem cells can encapsulate therapeutic miRNAs, siRNAs, proteins, or drugs, offering advantages such as biocompatibility, stability, and efficient tumor cell uptake.[124] Functionalization with surface ligands further improves targeting.[125-127] In some studies, the efficiency of encapsulation of RNAs have reported. miR-146b–expressing MSC exosomes reduced glioma growth in rats,[128] while miR-122–exosomes enhanced sorafenib activity in hepatocellular carcinoma,[129] and MSC-derived exosomes delivered siRNA to silence polo-like kinase 1 in bladder cancer cells.[130] Drug priming of MSCs also enables exosome-mediated delivery: paclitaxel-loaded MSC exosomes suppressed pancreatic adenocarcinoma, leukemia, and multiple myeloma growth.[131-133] and similar strategies have been applied with doxorubicin, gemcitabine, and cisplatin.[134] Alternatively, drugs can be post-loaded into exosomes via electroporation, extrusion, or dialysis, improving loading efficiency and enabling delivery of both hydrophilic and hydrophobic compounds.[124]

Stem cell can also act as a source for production of immune cells. CAR-T and natural killer (NK) cells are effective immunotherapies, but their use is limited by difficulties in cell expansion, reduced quality in elderly or heavily treated patients, and short-lived antitumor activity.[135,136] To overcome these barriers, human pluripotent stem cells (iPSCs and ESCs) offer an unlimited source for generating CAR-immune cells through cytokine-driven differentiation.[92,137,138] In addition, CAR-engineered HSCs can engraft in bone marrow and continuously produce CAR-expressing T cells, NK cells, and myeloid cells, enabling sustained and synergistic antitumor immunity.[135]

Given the critical role of cancer stem cells (CSCs) in tumor initiation and progression, CSC-targeted therapies could greatly improve treatment outcomes. Among these, anti-cancer vaccines are promising due to their high immunogenicity.[25] Vaccines can be generated from oncofetal peptides or CSC/ESC/iPSC-derived whole cells, often through antigen loading onto dendritic cells to elicit T-cell responses or support adoptive therapy.[139] While peptide-based vaccines show limited efficacy due to tumor heterogeneity,[139] whole-cell lysates or ESC/iPSC-derived multi-antigen vaccines demonstrate broader potential, though risks of teratoma formation and autoimmunity remain.[140] Allogeneic ESC and autologous iPSC vaccines have shown superior protection against relapse in mice by enhancing immune activation,[141] but their use is more suited for prophylaxis, as established tumors with immunosuppressive microenvironments reduce efficacy.[142] Combining vaccines with surgery, chemotherapy, radiotherapy, checkpoint inhibitors, or adjuvants may

enhance therapeutic benefit.[140] (Figure 1).

There are also some side effects and potential risks of stem cell therapy. Tumorigenesis,[143] GVHD,[144] drug toxicity and drug resistance,[145] viral infection,[146] increased immune responses and autoimmunity[147] can be considered as the side effects and potential risks of stem cell therapy. Normal stem cells can acquire cancerous traits under unfavorable microenvironmental conditions, as they share key signaling pathways with CSCs.[148] Prolonged culture of transplanted stem cells increases the risk of malignant transformation, up to 45.8% of MSCs were reported to transform after one month in culture.[149] Pluripotent stem cells (PSCs) are more tumorigenic than adult stem cells (ASCs), though controlled irradiation can reduce teratoma formation.[141] Additionally, stem cells may enhance tumor progression; MSCs have been shown to promote migration of weakly metastatic breast cancer cells *in vivo*.[150]

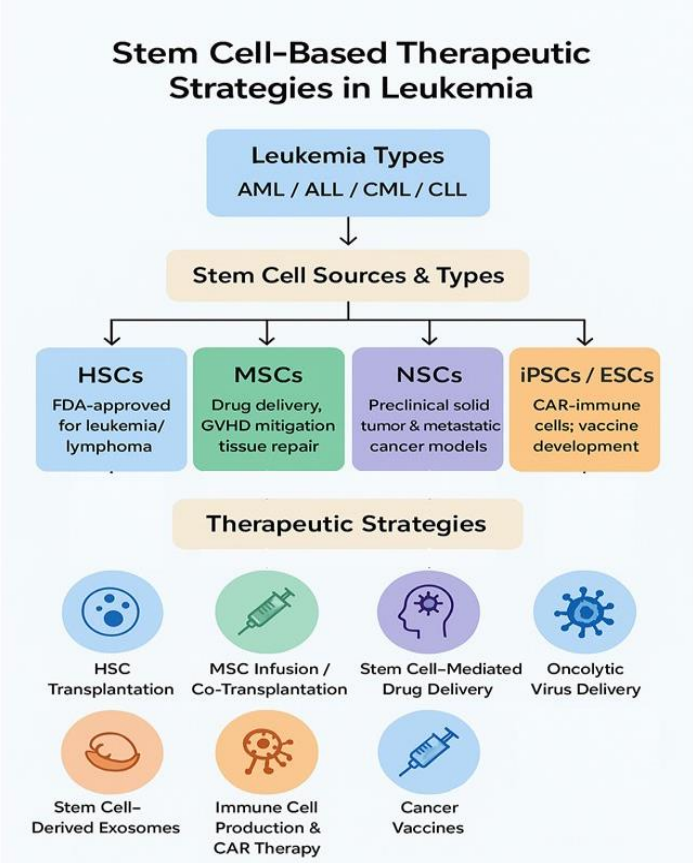

Figure 1. Combining Vaccines with Surgery, Chemotherapy, Radiotherapy, Checkpoint Inhibitors, or Adjuvants may Enhance Therapeutic Benefit.

Allogeneic HSC transplantation effectively treats hematologic cancers but often causes chronic GVHD, organ dysfunction, and secondary malignancies, impacting long-term quality of life.[151] Using related umbilical cord blood can lessen GVHD severity, while MSC co-transplantation shows promise in reducing transplantation-associated complications.[144]

The therapeutic efficacy of stem cell–based gene or drug delivery depends on efficient tumor targeting; however, only about 2–5% of injected stem cells localize to tumor tissue after systemic administration. Most cells become transiently trapped in the lungs and subsequently migrate to the liver, spleen, and lymph nodes before being cleared.[152] This limited targeting can cause systemic toxicity due to off-target drug distribution and insufficient tumor drug levels, potentially leading to resistance.[145]

Viral transfection efficiently modifies stem cells for gene delivery but carries risks such as immune reactions, toxin release, cell elimination, and limited transgene capacity. Careful vector design and thorough preclinical testing are essential to ensure safety and efficacy before clinical use.[146]

Allogeneic stem cells from unrelated donors can

trigger strong T- and B-cell immune responses, risking graft rejection in subsequent transplants.[147] Autologous iPSC-based vaccines may also induce autoimmunity, though initial studies suggest safety, warranting further investigation.[140] (Figure 2)

The interactions between MSCs and HSCs in the bone marrow (BM) are crucial for understanding hematopoietic regulation and hold significant implications for developing stem cell–based therapies in leukemia. BM is a complex organ containing HSCs and MSC-derived cells, such as osteoblasts and adipocytes.[153,154] Together with the extracellular matrix (ECM), they form a specialized microenvironment essential for hematopoiesis.[155] MSCs support HSC self-renewal, prevent apoptosis, and inhibit premature differentiation.[156] Recent studies reveal a dynamic niche shaped by diverse MSC subsets, including CD146+, CD271+, CXCL12-abundant reticular cells, and Nestin+ MSCs, each with distinct regulatory roles.[157-159,97,96]. Nestin+ MSCs, particularly near sinusoids and the sympathetic nervous system, produce CXCL12 and stem cell factor, both critical for HSC maintenance.[160] Further characterization of MSC subsets by function, localization, and cytokine profiles could inform therapeutic applications.[161] Osteoblasts, also MSC-derived, regulate primitive hematopoietic cells by producing cytokines and supporting lymphopoiesis and myelopoiesis, with their numbers directly affecting HSC maintenance.[162-164] Conversely, BM adipocytes may inhibit hematopoiesis, restricting progenitor expansion while preserving the HSC pool.[165] MSCs also influence hematopoiesis via EVs, including exosomes and microvesicles.[164,166] MSC-EVs help maintain homeostasis, activate HSCs under stress, and modulate Wnt/β-catenin signaling to promote proliferation while suppressing differentiation.[167] They carry miRNAs that enhance survival and regulate lineage commitment[168] and exert immunomodulatory effects on multiple immune cells, influencing overall immune balance.[169]

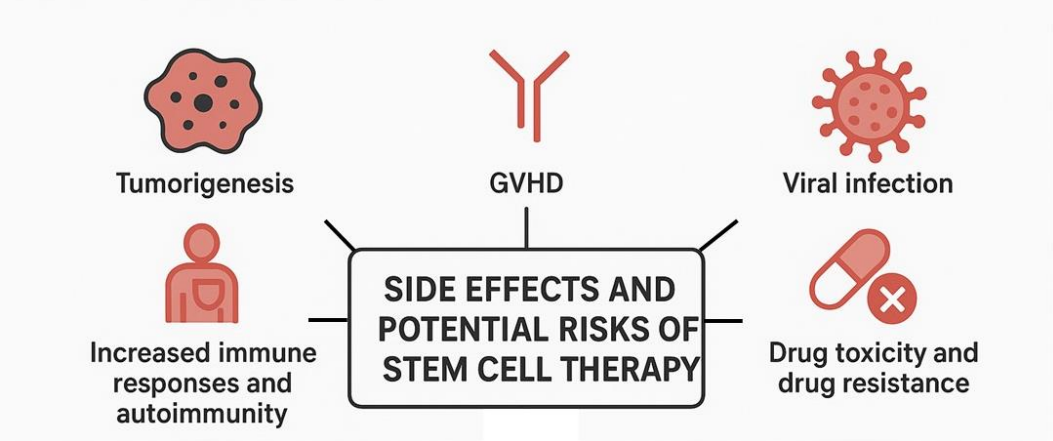

Figure 2. Autologous iPSC-based Vaccines may also Induce Autoimmunity, though Initial Studies Suggest Safety.

Overall, stem cell–based strategies offer promising avenues for cancer therapy through diverse mechanisms. HSC transplantation remains a cornerstone for hematologic malignancies, though GVHD limits efficacy; co-infusion of MSCs has shown clinical benefit in reducing GVHD and repairing chemotherapy- or radiotherapy-induced damage. MSCs, NSCs, and their exosomes, with tumor-tropic properties, have been widely studied as therapeutic carriers. Advances in generating CAR immune cells from iPSCs and HSCs enable scalable production of universal clinical-grade cells, while CSC-targeting vaccines derived from CSC or PSC antigens show potential for preventing tumor growth, metastasis, and relapse, despite safety concerns. Combining stem cell therapies with immune checkpoint inhibitors may enhance outcomes, as demonstrated by engineered HSCs coated with PD-1 antibody–decorated platelets that homed to bone marrow, boosted T cell activation, and prolonged survival in leukemia models.[170] Nevertheless, standardization of exosome and vaccine production, alongside optimization of culture conditions, dosage, and administration protocols, remains essential. Collectively, these approaches highlight the potential of stem cell technologies in oncology, though further refinement is required to ensure safety, efficacy, and clinical translation.

The Therapeutic Effects of Stem Cells in AML

AML accounts for nearly 80% of adult leukemia cases.[171] Its etiology is multifactorial, encompassing antecedent hematologic disorders such as myelodysplastic syndrome, inherited conditions including Down syndrome, environmental exposures such as ionizing radiation, tobacco smoke, and benzene, as well as prior treatment with cytotoxic chemotherapy.[172,173] At the molecular level, AML is driven by genetic alterations that disrupt normal hematopoiesis, leading to clonal proliferation of immature myeloid precursors.[174,175] The disease is markedly heterogeneous and is stratified into favorable, intermediate, or adverse prognostic groups according to cytogenetic and molecular profiles.[176]

Allogeneic HSCT remains a key post-remission strategy in AML and offers the potential for long-term cure.[177] Since the first successful bone marrow transplantation was reported in 1957, the use of HSCT in AML has progressively expanded.[178] Currently, AML represents the leading indication for transplantation worldwide, accounting for more than one-third of all HSCT procedures, whereas autologous HSCT contributes to less than 3% of cases.[179] HSCT can achieve cure in patients with hematologic malignancies and bone marrow failure syndromes; however, its toxicity profile is considerably higher than that of conventional chemotherapy or immunosuppressive therapy. Thus, HSCT is reserved for cases where the expected survival and quality of life outweigh alternative treatments, with eligibility carefully assessed in light of current guidelines and transplant outcomes.[80] HSCT can also be used in AML patients with minimal residual diseases[180,181] Cord blood transplantation (CBT) is a viable alternative in AML, with recent evidence indicating comparable survival outcomes to those achieved with 8/8 HLA-matched unrelated HSCT in adult patients.[182]

While HSCT and CBT remain cornerstone strategies for AML management, their limitations and associated toxicities have driven interest in alternative and adjunctive therapies, including the use of oncolytic viruses. As mentioned before, oncolytic viruses have emerged as promising therapeutic agents for AML alongside conventional chemotherapy.[183] Although systemic administration of oncolytic viruses presents several limitations, it remains the primary approach for treating hematologic malignancies.[184] To overcome these challenges, carrier cells have been explored as delivery vehicles.[185] Various candidates, including NSCs[186] and monocytes,[187] have demonstrated the ability to protect OVs from antibody-mediated neutralization and nonspecific uptake in preclinical models. MSCs have attracted the greatest attention as oncolytic viruses carriers.[188] Notably, McKenna and colleagues reported the use of MSCs for systemic delivery of a binary vector encoding an oncolytic adenovirus engineered to express IL-12 and a programmed death-ligand 1 (PD-L1) inhibitor.[189] Reovirus, a widely studied oncolytic virus, demonstrates anti-leukemic activity; however, its systemic efficacy is often limited by neutralizing antibodies following intravenous administration. Recent findings highlight the potential of human umbilical cord-derived MSCs (UC-MSCs) as vehicles for reovirus delivery. In Yong et al. investigation, it was indicated that UC-MSCs infected with reovirus released exosomes capable of transferring the virus to AML cells independently of direct cell–cell contact. Inhibition of exosome release using GW4869 reduced both exosome secretion and reovirus transfer, underscoring the critical role of exosomes in this process. Mechanistic studies revealed that exosomes derived from reovirus-infected UC-MSCs (MSCREO-EXOs) exert tumor-lytic effects and deliver reovirus primarily through clathrin-mediated endocytosis and macropinocytosis. These findings suggest that MSC-derived exosomes (MSC-EXOs) can function as effective carriers of reovirus, offering a novel strategy to enhance viral delivery and therapeutic efficacy in AML.[190]

In addition to engineered MSCs and their exosomes, co-culture studies have further elucidated how stromal cells regulate leukemic cell behavior and therapeutic responses. Co-culture studies have highlighted the regulatory role of bone marrow stromal cells in AML. When AML cell lines (U937, HL-60, and drug-resistant HL-60/VCR) were cultured with the human bone marrow stromal cell line HFCL in Gao et al. study, their proliferation was suppressed compared to monocultures, and a modest increase in NBT-positive differentiated cells was observed. AML cells co-cultured with HFCL displayed an accumulation in the G0/G1 phase and a reduction in the S phase, accompanied by upregulation of differentiation markers CD11b and CD14. Moreover, exposure of HL-60 and HL-60/VCR cells to topotecan (TPT) induced

apoptosis, characterized by Annexin V positivity, caspase-3 activation, reduced Bcl-2 expression, and morphological apoptotic features. However, co-culture with HFCL cells attenuated TPT-induced apoptosis, decreasing Annexin V-positive cells, lowering sub-G1 fractions, reducing caspase-3 activation, and restoring Bcl-2 expression. Collectively, these findings suggest that bone marrow stromal cells can inhibit AML cell proliferation, promote partial monocytic differentiation, and protect leukemic cells from chemotherapy-induced apoptosis through the modulation of apoptotic regulators such as Bcl-2 and caspase-3. This underscores the pivotal role of the bone marrow microenvironment in AML progression and therapy resistance.[191] In another investigation, it was indicated that hESC-MSCs have been shown to suppress AML cell proliferation, with growing evidence indicating that their secreted microvesicles (hESC-MSC-MVs) contribute significantly to this antitumor effect. In Ji et al. study, it was reported that both hESC-MSCs and their microvesicles inhibit leukemia cell growth in a concentration-dependent manner. Mechanistically, they showed that hESC-MSC-MVs modulate key regulators of cell death pathways by decreasing the Bcl-2/Bax ratio, increasing Beclin-1 expression, and promoting LC3-II conversion, thereby enhancing autophagy and apoptosis. These findings suggest that hESC-MSC-derived microvesicles not only impair AML cell proliferation but also trigger autophagy-mediated apoptotic pathways, highlighting their potential therapeutic relevance in leukemia.[192] These results are in consistent with Ramasamy et al. findings, reporting MSCs co-culture with KG1a cell line, inhibited the proliferation of cancerous cells.[193] (Table 1).

Taken together, current findings highlight the therapeutic potential of stem cells and their derivatives in AML, both as established transplantation modalities and as innovative vehicles or modulators in experimental therapies. Nonetheless, the complexity of stem cell–AML interactions calls for further mechanistic and translational studies to refine these approaches, minimize risks, and maximize their clinical benefit.

Table 1. The Therapeutic Effects of Stem Cells in AML

Cell Line	Mechanism	Ref
THP-1, HL-60	Exosomes derived from reovirus-infected UC-MSCs exerted tumor-lytic effects and deliver reovirus primarily through clathrin-mediated endocytosis and macropinocytosis.	[190]
U937, HL-60, and drug-resistant HL-60/VCR	Co-culture of AML cell lines with human bone marrow stromal cell line HFCL, suppressed the proliferation of cancerous cells, displayed an accumulation in the G0/G1 phase and a reduction in the S phase, displayed an accumulation in the G0/G1 phase and a reduction in the S phase, accompanied by upregulation of differentiation markers CD11b and CD14, however, protected leukemic cells from chemotherapy-induced apoptosis through the modulation of apoptotic regulators such as Bcl-2 and caspase-3.	[191]
HL60	Both hESC-MSCs and their microvesicles inhibited leukemia cell growth and induced autophagy in a concentration-dependent manner, through decreasing the Bcl-2/Bax ratio, increasing Beclin-1 expression, and promoting LC3-II conversion.	[192]
KG1a	MSCs co-culture with KG1a cell line, inhibited the proliferation of cancerous cells.	[193]

The Therapeutic Effects of Stem Cells in ALL

ALL is a hematologic malignancy characterized by the unchecked proliferation of immature B- or T-cell lymphoblasts, resulting in bone marrow failure and infiltration of extramedullary organs.[194] Although its precise etiology remains unclear, both genetic predisposition and environmental exposures have been implicated in disease development.[195] B-cell ALL (B-ALL) represents the most frequent pediatric cancer, with the majority of cases diagnosed before the age of 18 and incidence peaking between 2 and 10 years.[196] At the molecular level, ALL arises from genetic and epigenetic alterations that disrupt lymphoid differentiation and drive the clonal expansion of leukemic blasts.[197]

HSCT is an effective therapeutic option in ALL; however, due to its substantial acute and long-term toxicities, it is primarily considered for patients with high-risk disease in first complete remission (CR1), or for those with refractory or relapsed disease. Advances in frontline therapies for newly diagnosed ALL, along with more sensitive methods for detecting treatment response, particularly minimal residual disease (MRD), have progressively refined HSCT indications. Moreover, the advent of novel immunotherapies and cellular approaches, such as CAR T-cell therapy, is reshaping both the timing and overall role of HSCT in the modern management of ALL.[198] Both the American Society for Transplantation and Cellular Therapy and the European Society for Blood and Marrow

Transplantation have issued consensus guidelines for HSCT in pediatric ALL.[199,200] Nonetheless, clinical practice remains influenced by factors such as patient characteristics, donor availability, and evolving evidence from recent trials. Allogeneic HSCT is generally regarded as the standard of care for pediatric patients with high-risk ALL in first complete remission (CR1) and in second remission (CR2). Beyond CR2, the role of HSCT becomes less defined, owing to higher risks and reduced efficacy, particularly in the context of emerging alternatives such as CAR T-cell therapy. Notably, tisagenlecleucel, a CD19-directed CAR T-cell product, has been approved as standard therapy for pediatric and young adult patients with relapsed or refractory ALL, specifically, those with primary refractory disease, relapse after two or more prior therapies, or post-HSCT relapse, with approval varying slightly across the US, Canada, and Europe.[199,201,202]

In parallel with these advances in transplantation and immunotherapy, increasing attention has been directed toward the therapeutic potential of MSCs, which provide insights into their capacity to modulate leukemic cell behavior and influence treatment response. MSCs possess strong immunosuppressive properties that affect nearly all immune cell types of both lymphoid and myeloid origin. This broad activity is largely attributed to their ability to selectively arrest the cell cycle at early stages of commitment (G0/G1), leading to marked inhibition of proliferation while preserving most effector functions.[203] Owing to these characteristics, MSCs have been investigated in the context of HSC transplantation, where preliminary findings indicate their potential to enhance engraftment and mitigate GVHD following allogeneic transplantation. However, achieving clinical efficacy often requires the administration of large, non-physiological numbers of MSCs.[204-206] In Song et al. study it was reported that in mice model of allogeneic hematopoietic stem cell, intravenous administration of MSCs in mice injected with A20 lymphoma cells reduced lymphoma incidence, prolong survival, enhance the proportion of $CD3^+CD8^+$ T cells, while decreasing $CD3^+CD4^+$ and $CD4^+CD25^+$ T cell subsets in peripheral blood, ultimately alleviating the manifestations of acute aGVHD. Besides *in vivo* investigation, the co-culture of MSCs with A20 and P388 murine ALL cells, inhibited the proliferation of the mouse lymphoma and leukemia cells *in vitro*, leading to cell cycle arrest and reducing the secretion of IL-10.[207] Furthermore, i*n vitro* studies have demonstrated that MSCs can exert antiproliferative effects on leukemic cells. For example, co-culture experiments using the Jurkat T-cell leukemia line revealed that MSCs suppress leukemic cell proliferation in a dose-dependent manner, indicating their potential regulatory role in modulating malignant hematopoietic cell growth.[193] In another investigation it was reported that MSCs co-cultured with Molt-4 cell line as ALL cells, resulted in a significant increase in the pro-caspase-8 and cleaved-caspase 8 and 9 expression levels. Moreover, protein expression levels of glycogen synthase kinase-3 beta (GSK-3β) and extracellular signal-regulated kinases 1/2 (ERK1/2) were significantly decreased.[208] The reduction of GSK-3β and ERK1/2 can lead to mitochondrial dysfunction resulting in caspase cascades.[209] These results, indicate that MSCs co-culture with Molt-4 cells can induce the apoptosis of cancerous cells and act as a therapeutic strategy.[208] These observations are consistent with Yuce et al. reports demonstrating the ability of MSCs to inhibit leukemia cell proliferation and promote apoptosis. Yuce et al. reported that co-culture of T-MSCs with Molt-4, reduced cell viability under both normal and febrile (40 °C) conditions. Mechanistic analyses revealed that T-MSCs promoted apoptosis and induced cell cycle arrest at the G2/M phase, with transcriptional profiling confirming the activation of apoptotic pathways, particularly under hyperthermic conditions.[210] Given the close relationship between lymphoid organs and cancer progression, T-MSCs have been explored as candidates for exerting anti-leukemic effects.[211] These findings suggest that T-MSCs may exert direct anti-tumor effects on leukemia cells through apoptosis induction and cell cycle regulation, highlighting their potential as a novel stem cell-based therapeutic approach.

Recent studies have explored the potential of MSCs as vehicles for drug delivery in leukemia therapy, aiming to enhance the efficacy of conventional chemotherapy. In this context, MSCs loaded with paclitaxel (PTX) have demonstrated strong antitumor activity against ALL cells. Preclinical investigations revealed that PTX-primed human MSCs (hMSCsPTX) and mouse MSCs (SR4987PTX) exert significant anti-leukemic effects both *in vitro* and *in vivo*. In co-culture systems, these modified MSCs inhibited Molt-4 and L1210 cell proliferation, induced apoptosis and necrosis,

and interfered with leukemic cell adhesion to endothelial cells by downregulating adhesion molecules such as ICAM-1 and VCAM-1. In murine models, hMSCsPTX, co-injected with Molt-4 cells suppressed tumor growth and angiogenesis, while in BDF1-mice-bearing L121, SR4987PTX significantly prolonged survival. Importantly, priming MSCs with PTX is a straightforward, non-genetic approach, underscoring its translational promise as a strategy to enhance leukemia treatment.[212] (Table 2).

Table 2. The Therapeutic Effects of Stem Cells in ALL

Cell Line	Mechanism	Ref
A20, P388	Co-culture of MSCs with A20 and P388 murine ALL cells, inhibited the proliferation of the mouse lymphoma and leukemia cells in vitro, leading to cell cycle arrest and reducing the secretion of IL-10. In mice model of allogeneic hematopoietic stem cell, intravenous administration of MSCs in mice injected with A20 lymphoma cells reduced lymphoma incidence, prolong survival, enhance the proportion of $CD3^+CD8^+$ T cells, while decreasing $CD3^+CD4^+$ and $CD4^+CD25^+$ T cell subsets in peripheral blood, ultimately alleviating the manifestations of acute aGVHD.	[207]
Jurkat	Co-culture experiments using the Jurkat T-cell leukemia line revealed that MSCs suppress leukemic cell proliferation in a dose-dependent manner.	[193]
Molt-4	MSCs co-cultured with Molt-4 cell line, resulted in a significant increase in the pro-caspase-8 and cleaved-caspase 8 and 9 expression levels, and decrease in GSK-3β and ERK1/2.	[208]
Molt-4	co-culture of T-MSCs with MOLT-4, promoted apoptosis and induced cell cycle arrest at the G2/M phase, with transcriptional profiling confirming the activation of apoptotic pathways under both normal and febrile (40 °C) conditions.	[210]
Molt-4, L1210	Co-culture of Molt-4 and L1210 with MSCs loaded with paclitaxel (hMSCsPTX) inhibited the proliferation of cancerous cells, induced apoptosis and necrosis, and interfered with leukemic cell adhesion to endothelial cells by downregulating adhesion molecules such as ICAM-1 and VCAM-1. In murine models, hMSCsPTX, co-injected with Molt-4 cells suppressed tumor growth and angiogenesis, while in BDF1-mice-bearing L121, SR4987PTX significantly prolonged survival	[212]

In conclusion, MSCs demonstrate multifaceted therapeutic potential in ALL by modulating leukemic cell proliferation, inducing apoptosis, and regulating the cell cycle. Both *in vitro* co-culture studies and *in vivo* models highlight the ability of MSCs to inhibit leukemia cell growth, enhance immune cell-mediated responses, and mitigate graft-versus-host disease in the context of hematopoietic stem cell transplantation. Furthermore, MSCs derived from various sources, including bone marrow, umbilical cord, and tonsil tissue, can exert direct anti-leukemic effects through soluble factors, cell–cell interactions, and the activation of apoptotic pathways. Their capacity to serve as drug delivery vehicles, exemplified by paclitaxel-primed MSCs, further expands their therapeutic applicability, enabling targeted inhibition of leukemia cells and interference with tumor angiogenesis and adhesion. Collectively, these findings support MSCs as a promising adjunctive strategy in ALL therapy, offering both immunomodulatory and anti-tumor benefits.

The Therapeutic Effects of Stem Cells in CML

CML is a myeloproliferative neoplasm defined by the Philadelphia chromosome, t(9;22)(q34;q11.2), which generates the BCR-ABL1 fusion oncoprotein.[213] The disease primarily involves the uncontrolled proliferation of granulocytes, affecting both peripheral blood and bone marrow.[214] Although the precise etiology of CML is not fully understood, its pathophysiology is driven by the BCR-ABL1 oncoprotein, a constitutively active tyrosine kinase that dysregulates signaling pathways controlling cell growth, survival, apoptosis, and transcription.[215,216] Tyrosine kinase inhibitors (TKIs) such as imatinib, dasatinib, and nilotinib have transformed CML therapy; however, challenges remain due to the persistence of leukemia stem cells (LSCs) and suboptimal molecular responses in a subset of patients.[217-219] Moreover, resistance to TKIs, which may develop at various disease stages, continues to be a major clinical obstacle, emphasizing the need for deeper insights into CML pathogenesis and the development of more effective therapeutic strategies.[82]

Stem cell transplantation (SCT) for CML was first pioneered by Buckner and colleagues, and later advanced by Goldman and others, with the initial strategy of using myeloablative radiation followed by autologous chronic-phase (CP) bone marrow transplantation to revert accelerated-phase (AP) or blastic-phase (BP) CML to a more stable disease state.[220-222] Although this approach proved largely ineffective in controlling leukemia, it laid the foundation for allogeneic (allo)-SCT, first explored with syngeneic grafts by Fefer et al.[223] and subsequently with HLA-matched sibling bone marrow

transplants reported in 1982 by several groups.[224-226] Early outcomes in CP-CML were promising; however, relapse rates were higher in T cell–depleted recipients and in patients who did not develop GVHD.[227,228] These findings highlighted the critical role of alloreactive T cells in mediating a graft-versus-leukemia (GVL) effect, a concept definitively confirmed by Kolb et al., who demonstrated that donor lymphocyte infusions (DLIs) could induce durable second remissions in patients relapsing after SCT.[229-232] With progressive refinements in transplant protocols during the 1990s, outcomes steadily improved, and recent reports show overall survival rates exceeding 85% in CP-CML patients receiving matched-donor transplants.[228] The introduction of imatinib by Druker et al. revolutionized chronic-phase CML (CP-CML) management, as its safety and efficacy rapidly reduced the use of SCT, as reflected in international registries.[233,234] TKIs became the standard frontline therapy, offering a less toxic alternative; however, SCT remains indicated for advanced-phase disease, TKI intolerance, resistance, or mutations such as T315I, where agents like ponatinib and omacetaxine show only partial activity.[235,236] Importantly, CML stem cells are not fully dependent on BCR-ABL signaling and persist despite TKI therapy, underscoring the continued relevance of SCT in select patients.[237,238]

While stem cell transplantation remains a cornerstone in leukemia therapy, complementary strategies such as stem cell–cancer cell co-culture models provide valuable insights into the cellular interactions that shape therapeutic outcomes and resistance mechanisms. Ramasamy et al. reported that the co-culture of MSCs with BV173 and K562 as CML cell lines, inhibited the proliferation of malignant cells. To explain the inhibition of cancerous cells proliferation, they indicated that the antiproliferative effects of MSCs on leukemic cells are mediated not only by direct cell–cell contact but also by soluble factors. In transwell experiments, where MSCs and tumor cells were physically separated, as well as in cultures supplemented with MSC-conditioned media, inhibition of leukemic cell proliferation was still observed, albeit to a lesser extent than in direct co-cultures. Interestingly, blocking TGF-β signaling with neutralizing antibodies did not reverse this inhibitory effect, suggesting that other soluble mediators are responsible for MSC-induced suppression of leukemic cell growth. *In vivo* studies have further highlighted the role of MSCs in modulating leukemic growth. In NOD-SCID mice, co-injection of MSCs with BV173 leukemia cells markedly increased tumor formation, with 75% of co-injected animals developing tumors compared to only 12% of those injected with BV173 cells alone. The resulting tumors retained the phenotype of human B cells without detectable MSC persistence at the injection site. Interestingly, small populations of MSCs were occasionally detected in the bone marrow of tumor-bearing mice, whereas leukemic cells were absent at the time of harvest. However, when bone marrow cells from these animals were cultured, leukemic populations with indefinite self-renewal capacity emerged, indicating that MSCs may facilitate a microenvironment favorable to leukemia cell persistence and expansion *in vivo*. More *in vivo* analyses demonstrated that MSCs inhibited BV173 proliferation by inducing G1 phase arrest, accompanied by reduced bromodeoxyuridine (BrDU) incorporation and downregulation of key cell cycle regulators, including cyclin D2 and cdk4, with partial restoration of proliferation upon MSC removal. This inhibitory effect, however, was reversible, raising questions about its durability. Importantly, MSCs also reduced apoptosis in BV173 cells, particularly under low-serum conditions, suggesting a protective role that may help reconcile their antiproliferative effects *in vitro* with their ability to enhance leukemic engraftment and growth *in vivo*.[193] In support of these findings Yuce et al. reported that co-culture of K562 cells with T-MSCs significantly decreased the viable cell number under the febrile and normal culture conditions and induced apoptosis on K562.[210] These findings are further supported by another investigation. In Fathi et al. study bone marrow–derived mesenchymal stem cells (BMSCs) were shown to induce G0/G1 cell cycle arrest and promote late apoptosis in K562 leukemia cells. Analysis of the conditioned media from BMSC–K562 co-cultures revealed a marked increase in TIMP-1 (tissue inhibitor of metalloproteinases-1) and moderately elevated levels of CINC-1 (cytokine-induced neutrophil chemoattractant-1). These findings suggest that TIMP-1 and CINC-1 secreted by BMSCs may contribute to the inhibition of K562 proliferation through activation of BAX- and caspase-3–mediated apoptotic pathways.[239]

Human umbilical cord blood–derived mesenchymal stem cells (hUCB-MSCs) represent a less invasive

alternative to bone marrow–derived MSCs for cell-based therapies.[240] Fonseka et al. demonstrated that hUCB-MSCs inhibit the proliferation of K562 cells in a dose-dependent manner, primarily through G0/G1 cell cycle arrest. The anti-proliferative effect was attenuated in transwell systems, indicating that direct cell-to-cell contact contributes to this suppression. Analysis of the conditioned media revealed prominent secretion of IL-6 and IL-8, while Th1 (IFNα), Th2 (IL-4), and Th17 (IL-17) cytokines were absent. Additionally, co-culture with K562 cells increased the proportion of hUCB-MSCs expressing membrane-bound latent TGFβ1 (LAP). These findings suggest that hUCB-MSCs inhibit leukemia cell proliferation via growth arrest and paracrine signaling, although the precise mechanisms regulating IL-6, IL-8, and TGFβ1 induction remain to be elucidated.[241]

Building on the evidence that hUCB-MSCs can inhibit leukemia cell proliferation and induce apoptosis, similar anti-leukemic effects have been observed with human Wharton's jelly–derived stem cells and their secreted factors, highlighting the broader potential of MSC-like cells in CML therapy. In Huwaikem et al. study it was reported that Human Wharton's jelly stem cells (hWJSCs) and their derivatives, including hWJSC -conditioned medium (hWJSC-CM) and hWJSC-lysate (hWJSC-L), demonstrated anti-leukemic potential *in vitro*. They reported that Co-culture of K562 cells with hWJSCs or exposure to their CM and lysate resulted in significant reductions in cell metabolic activity, with maximal decreases of 49.1%, 42.0%, and 68.8%, respectively, at 72 hours. Cell cycle analysis revealed increases in the G2/M population and modest decreases in the sub-G1 fraction, while Annexin V–based assays indicated enhanced apoptosis. Molecular analyses showed upregulation of pro-apoptotic BAX and CASP3 and downregulation of anti-apoptotic BIRC5 (Survivin). In addition, pro-inflammatory cytokines (IFN-γ, TNF-α, IL-1β, IL-6, IL-8, IL-12A) were decreased, whereas anti-inflammatory mediators (IL-4, IL-10) were elevated. Multiplex cytokine profiling confirmed these trends, highlighting a shift toward an anti-inflammatory microenvironment. Collectively, these findings indicate that hWJSCs and their secreted factors can inhibit CML cell proliferation by inducing cell cycle arrest and apoptosis, suggesting their potential as adjunctive anti-leukemic agents.[242]

In addition to direct co-culture, secreted microvesicles from MSCs have demonstrated potent anti-leukemic activity, effectively inhibiting proliferation and inducing apoptosis in leukemia cells through the transfer of bioactive molecules. hESC-MSCs secreted microvesicles (hESC-MSC-MVs) contribute significantly to this antitumor effect. Ji et al. investigation demonstrated that co-culture of K562 leukemia cells with hESC-MSCs or hESC-MSC-MVs reduced cell viability in a concentration-dependent manner. Mechanistically, hESC-MSC-MVs decreased the Bcl-2/Bax ratio and enhanced autophagy, as indicated by increased Beclin-1 expression and LC3-II conversion, ultimately promoting apoptosis. These findings highlight the dual role of hESC-MSC-derived microvesicles in both suppressing leukemic cell proliferation and activating autophagy-mediated apoptotic pathways, underscoring their potential therapeutic relevance in leukemia.[192]

Furthermore, recent studies have highlighted the potential role of MSCs in modifying the progression of CML through their immunomodulatory and differentiation -inducing properties. One therapeutic avenue involves exploiting the capacity of MSCs to restore impaired signaling pathways within leukemic cells. A notable example is the MPL signaling pathway, which plays a critical role in megakaryocytic differentiation but is frequently disrupted in CML. Evidence suggests that MSCs can secrete thrombopoietin, thereby reactivating downstream signaling cascades such as Janus kinase/ signal transducers and activators of transcription (JAK/STAT) and p38 mitogen-activated protein kinases (MAPKs). Restoration of these pathways has the potential to shift leukemic cells away from malignant proliferation and toward differentiation, ultimately alleviating disease progression.[243] (Table 3).

In summary, stem cells, particularly MSCs derived from bone marrow, umbilical cord blood, Wharton's jelly, and human embryonic sources, demonstrate significant anti-leukemic potential in CML through multiple mechanisms. These include the induction of cell cycle arrest, modulation of apoptotic pathways, and secretion of soluble factors and microvesicles that inhibit leukemia cell proliferation and enhance autophagy-mediated apoptosis. Co-culture studies consistently highlight the importance of both direct cell–cell contact and paracrine signaling, while *in vivo* models indicate that MSCs can influence the bone marrow microenvironment to affect leukemic cell survival and expansion. Additionally, MSCs exhibit

immunomodulatory properties and the ability to restore disrupted signaling pathways, such as MPL-JAK/STAT and p38 MAPK, potentially promoting differentiation over malignant proliferation. Collectively, these findings support the therapeutic promise of MSCs and their derivatives as adjunctive agents in CML treatment, particularly in cases of TKI resistance, disease persistence, or in combination with conventional therapies. However, further mechanistic studies and *in vivo* evaluations are essential to fully elucidate their clinical applicability and optimize strategies for safe and effective integration into CML therapy.

Table 3. The Therapeutic Effects of Stem Cells in CML

Cell Line	Mechanism	Ref
BV173, K562	In transwell experiments, where MSCs and tumor cells were physically separated, as well as in cultures supplemented with MSC-conditioned media, inhibition of leukemic cell proliferation was still observed, albeit to a lesser extent than in direct co-cultures. In NOD-SCID mice, co-injection of MSCs with BV173 leukemia cells markedly increased tumor formation. In fact, MSCs inhibited BV173 proliferation by inducing G1 phase arrest, accompanied by reduced bromodeoxyuridine (BrDU) incorporation and downregulation of key cell cycle regulators, including cyclin D2 and cdk4, with partial restoration of proliferation upon MSC removal.	[193]
K562	Co-culture of K562 cells with T-MSCs significantly decreased the viable cell number under the febrile and normal culture conditions and induced apoptosis on K562	[210]
K562	TIMP-1 and CINC-1 secreted by BMSCs may contribute to the inhibition of K562 proliferation through activation of BAX- and caspase-3–mediated apoptotic pathways.	[239]
K562	hUCB-MSCs inhibit the proliferation of K562 cells in a dose-dependent manner, primarily through G0/G1 cell cycle arrest and paracrine signaling.	[241]
K562	Co-culture of K562 cells with hWJSCs or exposure to their CM and lysate resulted in significant reductions in cell metabolic activity, upregulation of pro-apoptotic BAX and Cas3, downregulation of anti-apoptotic BIRC5, and inhibition of inflammation.	[242]
K562	Co-culture of K562 leukemia cells with hESC-MSCs and hESC-MSC-MVs decreased the Bcl-2/Bax ratio and enhanced autophagy, as indicated by increased Beclin-1 expression and LC3-II conversion, ultimately promoting apoptosis.	[192]
K562, LAMA-84	UC-MSCs secrete thrombopoietin, thereby reactivating downstream signaling cascades such as JAK/STAT and p38 MAPK leading to potential to shift leukemic cells away from malignant proliferation and toward differentiation, ultimately alleviating disease progression.	[243]

The Therapeutic Effects of Stem Cells in CLL

CLL is the most prevalent type of leukemia in the Western hemisphere.[244] CLL is characterized by the accumulation of mature but functionally impaired B lymphocytes.[245,246] It predominantly involves the peripheral blood, bone marrow, spleen, and lymph nodes.[247] Although its etiology remains unclear, both genetic predisposition and environmental factors have been implicated.[248] The pathogenesis of CLL is thought to occur in two stages, beginning with clonal B-lymphocyte expansion driven by aberrant B-cell receptor (BCR) signaling,[249,250] followed by progression from monoclonal B-cell lymphocytosis to overt CLL, mediated by genetic alterations and changes within the bone marrow microenvironment.[251,252]

Over the past decade, significant advances have been achieved in the treatment of CLL, with chemoimmuno therapy representing the most notable breakthrough.[253] Nevertheless, a subset of patients exhibits refractoriness to standard regimens or experiences early relapse, leading to poor clinical outcomes. For eligible individuals, allogeneic hematopoietic stem cell transplantation (HSCT) has been regarded as the treatment of choice in such high-risk scenarios.[254] In 2007, a consensus statement defined high-risk CLL (HR-CLL), characterized by refractoriness to purine analogs, relapse within two years following purine analog–based combination therapy, and/or the presence of del(17p)/TP53 mutations, as an indication for HSCT.[255] This classification of HR-CLL, also referred to as “highest-risk” or “ultra-high-risk” CLL,[256] has since been widely recognized and adopted within the scientific community.[257-259]

Nonetheless, growing evidence of favorable outcomes with novel agents has raised questions regarding the continued role of HSCT in patients with HR-CLL. The introduction of BCR inhibitors and BCL2 antagonists,[260] next-generation B-cell antibodies,[261] and immunomodulatory agents,[262] and the prospect of additional drug classes will inevitably reshape the therapeutic algorithms for CLL. In this evolving landscape, the traditional HR-CLL criteria that once guided HSCT indications may lose relevance. Nevertheless, a fully revised, evidence-based treatment framework for HR-CLL has yet to be established. In this context, Dreger et al. emphasized until such data emerge, HSCT should not be dismissed but rather

considered within the broader decision-making process, balancing established knowledge with ongoing uncertainties.[254]

In another study it was reported that despite the efficacy of novel agents (NAs), challenges such as drug intolerance, disease progression, primary resistance, and high-grade transformation continue to limit their long-term success. For patients who relapse or develop toxicity after exhausting all available NAs, clinical outcomes remain dismal.[263] This has renewed interest in potentially curative approaches, particularrly allogeneic HSCT. Roeker et al. conducted a multicenter retrospective cohort study of 65 patients who underwent allo-HSCT after exposure to at least one NA, reporting encouraging results with 24-month progression-free survival (PFS) and overall survival (OS) rates of 63% and 81%, respectively. Moreover, non-relapse mortality and relapse incidence were reported at 13% and 27%. Acute grade III–IV GVHD occurred in 24% of cases, while moderate-to-severe chronic GVHD developed in 27%. Importantly, factors such as prior NA exposure, type of remission status before transplant, and transplant characteristics did not independently predict PFS. Instead, the hematopoietic cell transplantation–specific comorbidity index emerged as an independent predictor of PFS. Furthermore, neither the number of NAs received, prior chemoimmunotherapy, nor the specific agent used immediately before transplantation (ibrutinib vs. venetoclax) significantly influenced survival outcomes. Collectively, these findings underscore that allo-HSCT remains a viable long-term disease control strategy in CLL, even after NA failure, and its success is more closely tied to patient comorbidity rather than prior treatment history.[264] (Table 4).

Table 4. The Therapeutic Effects of Stem Cells in CLL

Cell Line	Mechanism	Ref
Clinical trial	allo-HSCT after exposure to at least one NA, lead to encouraging results with 24-month progression-free survival (PFS) and overall survival (OS) rates of 63% and 81%, respectively. Acute grade III–IV GVHD occurred in 24% of cases, while moderate-to-severe chronic GVHD developed in 27%.	[264]

In summary, while the advent of novel targeted therapies has significantly improved the treatment landscape of CLL, their limitations, including resistance, intolerance, and relapse, underscore the need for alternative strategies in high-risk settings. Allo-HSCT continues to represent the one of the only potentially curative option, particularly for patients who fail novel agents, with recent evidence supporting its role in achieving durable disease control. Ultimately, careful patient selection and integration of HSCT into evolving treatment algorithms will remain essential to optimizing outcomes in CLL.

Emerging Therapeutic Directions in Stem Cell-Based Leukemia Treatment

Stem cells, defined by their capacities for self-renewal and differentiation, are broadly categorized into two main types: ESCs, derived from the inner cell mass of the blastocyst, and adult stem cells, which possess multipotent potential. Although ESCs offer broad differentiation capabilities, their clinical use is limited by ethical concerns and tumorigenic risk. In contrast, adult stem cells, particularly MSCs, present a more ethically acceptable and clinically practical option.[265] Ongoing clinical trials continue to evaluate the safety and efficacy of MSC-based therapies, highlighting the need to understand their interactions with the microenvironment to achieve optimal therapeutic outcomes.[266] With their self-renewal capacity, multipotency, and immunomodulatory properties, MSCs remain highly promising candidates for applications in cell therapy, tissue engineering, and regenerative medicine.[267,268]

Recent clinical investigations continue to highlight the pivotal role of HSCT and related stem cell–based therapies across different leukemia subtypes. In AML, multiple meta-analyses demonstrate that allogeneic HSCT in first complete remission (CR1) yields significantly improved outcomes for intermediate- and poor-risk patients compared to non-transplant consolidation.[269,270] For example, a meta-analysis in pediatric AML reported that HSCT in CR1 increased 5-year disease-free survival (DFS) vs chemotherapy alone from ~26 % to ~50 % in high-risk children.[271] Meanwhile, in ALL, HSCT remains the most potent consolidation therapy for high-risk adolescent and young adult patients, although treatment-related mortality remains considerable (~19 % in some cohorts) in the AYA age group.[272] Trials are also refining conditioning regimens, such as the study in children/adolescents comparing etoposide/treosulfan/

thiotepa vs total body irradiation (TBI) based conditioning prior to allogeneic HSCT in ALL.[273] Despite these advances, alternative "microtransplantation" approaches (infusing low-dose hematopoietic stem/progenitor cells) in AML remain investigational: a review of ~600 patients from 14 studies found no convincing effectiveness or safety evidence to date.[274] Taken together, these trials underscore that while HSCT and related stem-cell-based treatments are well-established in certain contexts of leukemia, important gaps remain in patient selection, optimal conditioning, sources (autologous vs allogeneic), and integration of novel adjunctive strategies.

In leukemia therapy, BM-MSCs are garnering increasing clinical interest. Renowned for their hematopoietic support, broad availability, and low immunogenicity, MSCs have been primarily employed to enhance outcomes in HSCT,[275,276] a cornerstone treatment for leukemia. Beyond facilitating HSC recovery, their therapeutic potential extends to additional roles that may directly influence leukemia progression and patient outcomes.[82]

MSCs have been proposed to inhibit hematologic malignancies through several mechanisms, including their use as delivery vehicles, suppression of vascular growth, and induction of cell-cycle arrest.[277] MSCs derived from various tissue sources consistently exhibit antitumor effects, supporting their potential application across different cancer types.[81] These effects are highly dependent on culture conditions, with MSC concentration influencing proliferation, morphology, and the profile of secreted factors.[278,279] The use of MSCs as delivery vehicles has gained particular interest due to their low immunogenicity and intrinsic ability to home to tumor sites.[280,281] They can also function as carriers for gene therapy, delivering therapeutic molecules such as IL-12, IL-24, and IFN-γ directly to cancer cells.[280,282-285] At the cellular level, MSCs exert effects via EVs containing miRNAs, RNA, and proteins that can be transferred to malignant cells.[286,287] These EVs have demonstrated anti-proliferative effects on leukemic cells and can enhance the cytotoxicity of chemotherapeutic agents.[288] Regarding vascular growth, MSCs can inhibit angiogenesis under specific conditions, which may be particularly relevant in hematologic malignancies reliant on vascular support.[289] Among the mechanisms of tumor suppression, induction of cell-cycle arrest is considered a central process.[191,290-293,193,207] Although the precise pathways mediating MSC-induced cell-cycle arrest are not fully elucidated, multiple studies report accumulation of cancer cells in the G0/G1 phase, highlighting MSCs' ability to inhibit tumor proliferation.[291,292,193]

Although MSCs are leveraged in therapies to enhance chemotherapy efficacy, their interactions with leukemia stem cells (LSCs) through physical adhesion and cytokine–receptor signaling present significant challenges. Current therapeutic strategies targeting MSCs in leukemia include CXCL12/CXCR4 inhibitors, chemotherapy-synergistic agents, adhesion blockers, and bone microenvironment–modulating drugs.[243] CXCL12/CXCR4 antagonists, such as plerixafor and related compounds, have progressed to clinical trials, demonstrating potential in disrupting MSC-mediated protection of LSCs and enhancing chemotherapy sensitivity.[294,295] Chemotherapy-synergistic agents are being explored for their ability to concurrently inhibit LSCs and MSCs, often by targeting the WNT/β-catenin signaling pathway, a key regulator of stemness in both cell types.[296-298] Adhesion inhibitors, focusing on molecules such as CD44 and E-selectin, aim to prevent LSC homing and increase chemosensitivity by blocking direct MSC–LSC interactions.[299-301] Additionally, clinical trials investigating bone homeostasis–modulating drugs, including proteasome inhibitors such as carfilzomib and ixazomib, aim to remodel the leukemia bone marrow microenvironment and induce apoptosis in leukemic cells.[302,303]

Recent advances in biotechnology and cell engineering have opened new avenues for enhancing the therapeutic efficacy and translational potential of stem-cell-based strategies in leukemia. Contemporary gene-editing tools such as CRISPR/Cas9, base editors and lentiviral vectors are being applied to HSCs to generate long-lived, self-renewing immune effector cells targeting leukemic clones. A recent systematic review noted that gene-edited HSCs can provide durable tumor clearance and multilineage immune reconstitution in preclinical models of leukemia and lymphoma.[304] While conventional CAR-T cell therapy has already made considerable impact in hematologic malignancies, newer iterations are emerging. For example, CAR-modified NK cells (CAR-NK) are showing promise in myeloid malignancies due to lower risk of GVHD and feasibility of off-the-shelf use.[305] Innovations in biomaterials, nanoparticle carriers, and scaffold systems are aiding

the targeted delivery of stem cells or stem-derived therapeutics. For instance, combining stem cell technology with nanoparticle -based drug delivery or microenvironment-specific scaffolds enhances homing, retention and therapeutic payload delivery.[306]

Despite these advances, challenges remain. Stem cells exhibit context-dependent effects, sometimes promoting tumor cell proliferation and survival.[307] Understanding the mechanisms underlying this duality is critical to optimizing therapeutic applications. Additionally, patient-specific factors, such as comorbidities and BM microenvironmental conditions, must be considered when integrating stem cell–based strategies into clinical care.

The reported effects of stem cells on tumors are controversial, exhibiting both inhibitory and proliferative actions across various cancers. This dual role highlights the importance of comprehensively understanding stem cells' impact on tumor cell proliferation. While the role of stem cells in solid malignancies is increasingly recognized, their function in leukemia remains less explored. Evidence suggests that stem cells in hematologic malignancies can suppress both tumor cell proliferation and apoptosis, although some studies indicate a direct promotion of these processes. Consequently, the therapeutic efficacy of stem cells in hematologic malignancies is uncertain, given the contradictory inhibitory and promoting effects observed *in vitro* and *in vivo*. Determining whether MSCs or HSCs are initially affected in leukemia is challenging, as both populations typically exhibit abnormalities within the bone marrow at diagnosis. The mechanisms underlying the dual effects of stem cells in hematologic malignancies remain largely elusive. Proposed antitumor mechanisms include stem cells acting as delivery vehicles, inhibiting vascular growth, and inducing cell-cycle arrest. As our understanding of stem cells' complex roles in hematologic malignancies advances, a critical challenge is to delineate specific mechanisms that can be harnessed for targeted therapies while accounting for their dual nature. Further research is essential to elucidate the full spectrum of stem cell actions in leukemia progression, providing a foundation for the development of safe and effective therapeutic strategies.

Conclusion

Stem cell–based strategies represent a promising and rapidly evolving frontier in leukemia treatment, offering potential advantages over conventional therapies through their abilities to modulate the bone marrow microenvironment, suppress leukemic cell proliferation, induce apoptosis, and enhance hematopoietic recovery. Across different leukemia subtypes, AML, ALL, CML, and CLL, both preclinical and clinical studies have highlighted the therapeutic utility of various stem cell types, including hematopoietic stem cells, mesenchymal stem cells, and umbilical cord–derived stem cells. Mechanisms such as direct cell–cell interactions, paracrine signaling, extracellular vesicle delivery, and gene-modified approaches contribute to their antileukemic effects, while strategies targeting leukemic stem cell niches or leveraging stem cells as drug delivery vehicles demonstrate emerging potential. Despite these advances, several challenges remain. The dualistic nature of stem cells, with context-dependent proliferative or inhibitory effects on leukemia, underscores the complexity of their application. Safety concerns, including the risk of tumorigenesis, immunogenicity, and undesired interactions within the bone marrow niche, necessitate rigorous preclinical evaluation and controlled clinical trials. Furthermore, optimizing delivery methods, dosing regimens, and combinatorial strategies with existing therapies are critical steps for translating stem cell–based interventions into routine clinical practice. Overall, stem cell–based therapies offer a multifaceted approach to leukemia treatment, with the potential to overcome limitations of conventional therapies and improve long-term outcomes. Continued research into their mechanisms of action, clinical efficacy, and safety profiles will be essential to fully harness their therapeutic potential. As the field advances, these strategies may become integral components of personalized, precision-based leukemia therapy, providing hope for improved disease control and patient survival.

Conflict of Interest

The authors declare no conflicts of interest.

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