Remodeling of the bone marrow microenvironment during acute myeloid leukemia progression

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Abstract: Hematopoiesis requires a complex interplay between the hematopoietic stem and progenitor cells and the cells of the bone marrow microenvironment (BMM). The BMM is heterogeneous, with different regions having distinct cellular, molecular, and metabolic composition and function. Studies have shown that this niche is disrupted in patients with acute myeloid leukemia (AML), which plays a crucial role in disease progression. This review provides a comprehensive overview of the components of vascular and endosteal niches and the molecular mechanisms by which they regulate normal hematopoiesis. We also discuss how these niches are modified in the context of AML, into a disease-promoting niche and how the modified niches in turn regulate AML blast survival and proliferation. We focus on mechanisms of modifications in structural and cellular components of the bone marrow (BM) niche by the AML cells and its impact on leukemic progression and patient outcome. Finally, we also discuss mechanisms by which the altered BM niche protects AML blasts from treatment agents, thereby causing therapy resistance in AML patients. We also summarize ongoing clinical trials that target various BM niche components in the treatment of AML patients. Hence, the BM niche represents a promising target to treat AML and promote normal hematopoiesis.

Keywords: Bone marrow niche (BM niche); acute myeloid leukemia (AML); hematopoietic stem cells (HSC); leukemic stem cells (LSC); leukemia

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Introduction

Acute myeloid leukemia (AML) arises from the hijack of normal hematopoiesis by malignant hematopoietic stem and progenitor cell (HSPC) clones. According to the American Cancer Society, AML is the second most common type of leukemia found in the adult population, accounting for 31% of all leukemia cases. The prognosis rate is significantly low in AML patients with 5 years survival rate being less than 28% (1). Despite many advances in treating AML, these therapies fail to cure the disease completely. Disease relapse is largely due to leukemic stem cells (LSCs) escaping from chemotherapeutic drugs and anti-cancer agents. The bone marrow (BM) niche is considered to be remodeled to favor AML progression by bidirectional interactions between BM microenvironmental cells and the leukemic cells (2). During leukemogenesis, deviancy of the BM niche also results in enhanced competitiveness between AML-HSPC and leukemic blast proliferation (3). Understanding various hematopoietic stem cell (HSC)-niche interactions during normal hematopoiesis becomes important. Further insights into the dynamics of remodeling of BM niches during leukemogenesis form an integral part of modern cancer research. Targeting these leukemic niches is emerging as a new avenue for developing novel treatment strategies for AML treatment.

Normal hematopoiesis

Hematopoiesis and HSCs

In adult mammals, HSCs primarily reside in the BM compartments of long bones. The frequency of HSCs in human BM is about 1 in 3×10^6 cells, analyzed by limiting dilution assay performed in non-obese diabetic severe combined immunodeficient (NOD/SCID) mice (4). The extremely rare frequency of HSCs makes the study of HSC biology a complicated and exhaustive work. The work done on HSCs in the last few decades has been very helpful in shedding light on the orchestrated process of HSC self-renewal and commitment to form intermediate progenitors that finally give rise to fully differentiated specific blood cell types. The process is very complex and recent studies on single-cell tracking, transcriptional regulation, and epigenetic mechanisms have made the understanding of the process much clearer. Any deviation in this extremely balanced and orchestrated process leads to various kinds of hematological disorders including various kinds of leukemia.

Hematopoietic niches

Although stem cells possess the property to self-renew and differentiate, the micro-environment surrounding the stem cells is known to regulate the fate, functionality, and quiescence of these stem cells. This unique micro-environment supporting the maintenance of stem cell properties was first characterized by Schofield in 1978 and was termed as “Stem Cell Niche” (5). In addition to cell intrinsic properties, HSCs are also governed by external cues from surrounding cells. The complex micro-environment surrounding the HSCs is made up of different cell types and extra-cellular elements. This unique micro-environment facilitates the maintenance of the HSCs in their multi-potent state and supports the maturation of progenitors (6).

The complex structure of the BM niche is made up of a variety of cell types and their spatial locations in BM. along with persistent niche dynamics of everchanging BM cell populations, blood flow, and oxygen concentrations (7). A single HSC residing in its niche, responds to the array of signals arising from the numerous types of surrounding cells simultaneously. These HSCs although reside in special niches, have contentious cross-talk with the long-distance cells via molecular and cellular mediators which modulate HSC response and decide their fates. HSC niches are studied and characterized in detail using invertebrate models of *C. elegans* (8) and *D. melanogaster* (9). Further studies on mammalian systems using murine and human cells have helped us understand the imperative role of the BM-niche in modulating stem cell functionality (10-14). Advancement of science and development of several novel technologies for imaging of cells, analyzing the cellular dynamics using sophisticated methods of proteomic analysis, single-cell RNA sequencing, and bioinformatic platforms for studies of cell-cell interactions have helped us increase our understanding about the HSC-niche interactions. The picture of the HSC niche is now becoming explicit, and the role of different niche components is now becoming a lot more comprehensive.

In the marrow, the BM stromal cells provide the basis for the physical structures of the BM microenvironment. Stromal cells arise from the mesenchymal stem cells (MSCs) and have a multipotent capacity to differentiate into various cell types. BM stromal cells express an array of HSC-supportive molecules and orchestrate the process of HSC self-renewal, proliferation, and differentiation.

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This process is majorly modulated through the production of cytokines, expression of cell-to-cell surface signaling molecules, secretion of the extracellular matrix, or via soluble mediators (15). Along with MSCs, osteoblasts (16), endothelial cells (ECs) (17) sympathetic nerve fibers, perivascular MSCs, and $CD169^+$ macrophages (18) regulate the HSC functionality and form the important cellular constituents of the HSC niche. Marrow adipocytes which are yet another cell type derived from MSCs, reduce the hematopoietic activity of the BM compartment (19). Thus, the niche acts as a complex cellular unit, composing a variety of cell types coordinately functioning to produce different regulatory and signaling molecules. The BM niche is not a static entity and it constantly changes in response to molecular signals which consequently display changes in the HSC functionality. However, the mechanisms involved in the cellular crosstalk within the BM microenvironment remain poorly understood.

The BM HSC niches are divided into the endosteal/osteoblastic niche and vascular niche. The endosteal niche facilitates HSC maintenance and quiescence, whereas the vascular niche is permissive to the proliferation and differentiation of HSCs (18,20,21). Even though the role of specific cellular components of the HSC niche is extensively studied, the multi-level complexity of BM niche composition makes precise definition of the BM niche a difficult task.

Endosteal niche

The quiescent HSCs, reside adjacent to the bone endosteum in the undifferentiated state and move gradually towards of the central axis of the BM upon activation (22,23). Endosteal niche is made up of spatially distributed populations of osteo-lineage primed MSCs (osteo-MSCs), pre-osteoblasts, osteoblasts, osteoclasts, and mature cells of BM lining (24). This HSC niche is termed an endosteal niche. Imaging of long bones in mice confirms the presence of the long term (LT)-HSCs in the endosteal zone of the BM microenvironment (25). Tracking transplanted HSCs shows that these HSCs finally home near the osteoblasts in the BM endosteal niche (26-28). Similar studies also suggest that the HSCs reside close to the sinusoidal ECs in the trabecular region of the BM cavity (29,30).

Osteoblasts, also known as bone-forming cells, are the best characterized HSC niche cells. Osteoblasts are known to be present at the inner lining of the BM and interact with the quiescent and primitive LT-HSCs. Studies on osteoblasts and their effect on hematopoiesis have shown a positive correlation between osteoblast number in BM with the number of LT-HSC in the BM (16,31). Conditional deletion of bone morphogenetic protein receptor 1α (*Bmpr1α*) causes an increase in the frequency of osteoblasts in BM which correspondingly results in an increased HSC population, confirming the role of osteoblasts in HSC maintenance and proliferation (25). BM imaging studies show the close physical interaction of HSC with osteo-lineage cells (30,32). Another report on tracking transplanted cells in BM confirms the association of engrafted LT-HSCs with osteoblasts, but at the same time, progenitor cells of hematopoietic lineage do not show such selective association with osteo-lineage cells (33). Growing evidence of reports on osteoblastic cells suggests that the osteoblasts can support the quiescent state of HSC along with the maintenance of their stemness and functionality. Osteoblasts are also used as feeder cells for *ex vivo* culturing of HSCs and have been shown to support HSC growth and maintain their functionality (34). Furthermore, HSCs co-cultured with osteoblasts show better engraftment potential and can completely reconstitute the complete hematopoietic system (30,35). Adherence of HSCs to the osteoblasts results in their self-renewal, while when the HSCs leave these osteoblastic niches, they undergo differentiation (36). The osteoblasts are known to secrete an extended array of HSC-supportive factors such as cytokines chemokine (C-X-C) ligand 12 (CXCL12) (37), angiopoietin-1 (Ang-1) (38), thrombopoietin (THP) (39,40), WNT (41), Notch (42), n-cadherin (43), osteopontin (44,45), granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-12 (IL-12) (34). Exosomes derived from osteoblasts alleviate the radiation-induced hematopoietic injury by targeting programmed cell death 4 (PDCD4) via micro RNA-21 (46).

Osteoclasts are cells specially equipped for bone resorption. Their activity antagonizes the activity of osteoblast cells. The balanced activity of osteoblasts and osteoclasts determines bone formation activity (47). The role of osteoclasts in HSC regulation is not much studied. According to several reports, osteoclasts are thought to be the dispensable elements of the HSC niche. A mouse model with a disrupted receptor activator of nuclear factor kappa B gene (*RANK*), cytokine required for osteoclast differentiation, does not show any change in its HSC compartment (48). In yet another study, mice completely deficient in osteoclast production also yielded

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similar observations (49). Contrastingly, Mansour *et al.* demonstrated that osteoclast activity is required for HSC niche formation. Using a mouse model with impaired endochondral ossification caused by the loss of osteoclast activity, they showed that this loss of osteoclast activity results in the increase of mesenchymal progenitors with reduced osteoblast formation. Whereas restoration of osteoclast activity reversed the defects in the BM niche resulting in a reduced HSC population and defective homing. This indirect regulation of the HSC niche by the osteoclasts is dependent on their bone resorption activity and linked with their capacity to support osteoblast commitment (50).

Vascular niche

The histochemical analysis of femoral bones from mice for signaling lymphocytic activation molecules expressing HSCs (SLAM HSCs) identified by expression of CD150$^+$CD48$^-$ CD41$^-$Lineage$^-$ markers also reveals that the majority of the SLAM HSCs are present in the proximity of sinusoidal ECs. This has led to the identification of a second type of HSC niche termed as vascular niche (17). The components of the vascular niche are mainly MSCs, ECs, CXCL12 abundant reticular (CAR) cells, platelet-derived growth factor receptor-α (PDGFR-α$^+$) expressing MSCs, Nestin$^+$ MSCs, and macrophages.

The cells that are known to form the HSC niche and modulate HSCs are majorly of mesenchymal origin. These cells are mainly derived from MSCs. MSCs are cells with self-renewing capacity and are also able to differentiate into osteoblasts, chondrocytes, fibroblasts, and adipocytes (51). MSCs secrete various types of growth factors and cytokines required for HSC survival and maintenance. They also have immuno-modulatory activity. For this reason, MSCs have been used in HSC transplantations to recuperate hematopoiesis after transplantation (52,53). The use of MSCs along with HSCs for transplantation helps to facilitate HSC engraftment and prevent graft failure resulting in graft-versus-host disease (54). MSCs also regulate HSCs via secreted extracellular vesicles. The crosstalk between the MSCs and HSCs mediated by the extracellular vesicle secreted by MSCs regulates the functionality of HSCs (55).

The heterogeneous population of cells appearing from undifferentiated MSCs and expressing melanoma-associated cell adhesion molecule (MCAM) are referred to as BM stromal cells. These include CAR cells, PDGFR-α$^+$ MSCs, Nestin$^+$ MSCs, and leptin receptor (LepR$^+$) MSC. The BM stromal cells can maintain HSCs and preserve their function and express high levels of HSC-supportive factors such as stem cell factor (SCF) and CXCL12 (56-58). These cells also play a crucial role in HSC proliferation, self-renewal, and trafficking (59). Tagging CXCL12 with green fluorescent protein (GFP) confirmed the highest expression of CXCL12 in CAR cells (60). CAR cells are primitive mesenchymal cells and possess the ability to differentiate into adipocytes and osteoblasts. The ablation of CAR cells in a transgenic mouse model results in a decrease in HSC frequency and long-term reconstitution activity along with an increase in HSC quiescence, highlighting the importance of CAR cells in the HSC niche (61). PDGFR-α$^+$ cells are also considered to be one of the major constituents of the HSC niche and show a good amount of colony forming units-fibroblast (CFU-F) activity (62), which is a gold standard assay used for analysis of MSC functionality. CAR cells are reported to express PDGFR-α, and thus, PDGFR-α$^+$ MSCs are overlapping populations of CAR cells. PDGFR-α$^+$ MSCs have been reported to be present in perivascular niches and support the expansion of hematopoietic progenitors (56). Nestin$^+$ MSCs are considered yet another type of HSC-supportive stromal cell population. Like CAR cells, Nestin$^+$ MSCs can differentiate into adipocytes, chondrocytes, and osteoblasts (63). These cells are found to be in proximity to sympathetic nerve fibers which regulate the HSCs in a variety of ways (64). Nestin$^+$ MSCs express very high levels of CXCL12 and their ablation in BM results in reduced LT-HSC frequency (15). Mesenchymal stem/progenitors are also known to express LepR on their surface and are termed LepR$^+$ MSCs (57,58). This is yet another overlapping population of CAR cells and Nestin$^+$ MSCs (56,65). Due to the expression of SCF and CXCL12 by LepR$^+$ stromal cells, they are regarded as positive regulators of HSC activity (57,58).

ECs have the same origin as that of HSCs; both cells originate from a common primitive cell type called hemangioblast (66). ECs also participate in the lining of the blood vessels and vascular niche formation, suggesting their important role in HSC regulation (57,67). Earlier studies report the HSC-supportive ability of ECs and their use in *in-vitro* HSC cultures (68). BM dysfunction is frequent in mice lacking the functional cytokine receptor glycoprotein130 in ECs (69). The BM ECs guide hematopoiesis through the expression of fibroblast growth factor (FGF) (70), epidermal growth factor (EGF) (71), and Ang-1 (17). ECs when transplanted with HSCs assist the

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HSC homing resulting in higher engraftment and increased hematopoietic activity in recipients (72). Blocking vascular endothelial growth factor receptor-2 (VEGFR2) during BM recovery impairs hematopoietic reconstitution (73). Reports also demonstrate that protecting the ECs during irradiation helps in the speedy recovery of BM with an increase in the long-term reconstitution potential of HSCs (74).

Sympathetic nerves control the HSC trafficking and the expression into the peripheral blood. They do so by regulating the periodical adrenergic signal release (75). Sympathetic nerves coordinate with Nestin$^+$ stromal cells and modulate the expression of Ang-1, CXCL12, vascular cell adhesion molecule-1 (VCAM-1), and SCF. These genes are required for HSC maintenance and their down-regulation results in the egress of HSCs into the bloodstream (64). The Schwann cells that wrap around these nerves are found to activate (transforming growth factor-beta) TGF-β signaling in HSCs and maintain their quiescence (76).

Macrophages regulate HSCs indirectly through the modulation of Nestin$^+$ stromal cells, osteoblast, and sympathetic nerves (77). Like sympathetic nerves, macrophages regulate HSC mobilization by regulating the CXCL12 expression in other types of niche cells (78).

As discussed in this section, various BM niche cells regulate HSCs by interacting with them via a systemized molecular network. BM niches thus coordinate to regulate normal hematopoiesis by endosteal niche favoring the maintaining the pool of quiescent HSCs while the vascular niche favors the proliferation and maintenance of HSC numbers. A few of these molecules, their source, and their role in the regulation of HSCs under normal and stress conditions are summarized in *Table 1*.

Leukemic BM niche

Remodeling of hematopoietic niches in AML

Numerous studies have highlighted that the BM microenvironment (BMM) is drastically modified by AML cells to promote leukemic progression and inhibit normal hematopoiesis. Studies using patient data and mouse models have shown that AML cells induce complex molecular changes within BM niche cells, resulting in the structural and functional disruption of normal BMM. These changes create a pro-leukemic niche that preferentially favors the survival and proliferation of immature leukemic blasts while suppressing the proliferation and differentiation of normal HSPCs. The next sections will elucidate how the endosteal and vascular BM niches are modified, and how the altered niches support leukemic progression (*Table 2*).

Remodeling of endosteal niche

The leukemic endosteal niche is marked by a loss of balance of osteoprogenitor cells and mature osteoblasts that result in disruption of the normal endosteal physiology. MSCs present within the endosteal niche can undergo differentiation to give mature adipocytes, osteoblasts, and chondrocytes. While for normal hematopoiesis the differentiation balance is maintained, this balance is disrupted in AML. Study by Battula *et al.* showed that AML cells secrete bone morphogenic proteins (BMPs) that induce MSCs to differentiate into osteoprogenitors through the activation of the Smad (suppressor of mothers against decapentaplegic)-1/5 signaling pathway (87). Furthermore, activation of the Smad1/5 pathway induced connective tissue growth factor (CTGF) expression in MSCs, which enhanced leukemic engraftment in mouse models of AML. The same group had previously shown that AML-MSCs were unable to differentiate into functional adipocytes (104).

While AML-primed MSCs exhibit increased differentiation potential towards osteo-lineage cells, the resulting cells produced are immature and unable to support hematopoietic cells. Scadden's group has shown a decreased number of mature osteo-lineage cells in the BM niche of mice transplanted with mixed lineage leukemia-AF9 (MLL-AF9) AML cells (105). Through lineage tracing, Hanoun *et al.* showed that while MSCs from leukemic mice were primed towards osteogenic differentiation, they gave rise to osteoblast precursors lacking osteocalcin expression, a maker of mature osteoblasts, which resulted in a signification reduction of mineralized trabecular bone volumes (94). Another study using MSCs from AML patients showed decreased bone formation potential of MSCs *in vivo* (106). Furthermore, AML-derived exosomes induced the expression of Dickkopf WNT signaling pathway inhibitor 1 (DKK1), a suppressor of osteogenesis, thereby resulting in the loss of osteoblasts (91). Several studies have highlighted the roles of AML-derived exosomes on the modulation of BM niche (107,108). In the same study, the authors showed that AML exosomes induced downregulation of key HSC supporting factors CXCL12, SCF, and insulin-like growth factor 1 (IGF1) in BM stromal cells, thereby decreasing their ability to support normal HSCs. Another study by Huan *et al.* demonstrated

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Table 1 BM niche cells express HSC regulatory molecules

No.	Cell type	Molecules expressed	Effect on HSCs	References
1.	Mesenchymal stromal cells	CXCL12	Maintenance of quiescent HSC	(79)
2.	CXCL12-abundant reticular (CAR) cells	CXCL12	Maintenance of quiescent HSC pool	(59)
		SCF	Maintenance of HSCs	(18)
3.	N-cadherin$^+$ mesenchymal stromal cells	SCF	Maintenance of HSC functionality	(80)
4.	LepR$^+$ stromal cells	SCF	Maintenance of hematopoietic stem/progenitor cell population and functional erythropoiesis	(81)
		Pleiotrophin	Maintenance of quiescent HSC pool during steady state	(82)
5.	Perivascular stromal cells	CXCL12	Deletion depletes HSCs and progenitors, mobilization of HSCs	(58)
6.	Nestin$^+$ MSCs	CXCL12, SCF, angiopoietin, IL7, VCAM, osteopontin	Maintenance of HSC, HSC homing	(56,63)
7.	Osteoblasts	Jagged 1	Increase in the number of HSCs	(16)
		THPO	Transiently increase in quiescent HSC population and subsequently induction of HSC proliferation	(40)
		GCSF	Normal myelopoiesis	(83)
		Ang-1	Maintenance of HSC quiescence and long-term repopulating ability	(38)
		CXCL12	Deletion depletes progenitors, not HSCs	(58)
		Osteopontin	Negatively regulate HSC expansion	(44)
8.	Spindle-shaped N-cadherin + CD45-osteoblasts	BMP	Controls the number of HSCs and HSC niche size	(25)
9.	Adipocytes	TGF-β	Inhibitor of hematopoiesis	(84)
10.	Endothelial cells	SCF	Maintenance of HSCs	(81)
		Pleiotrophin	Regeneration of HSCs after irradiation stress	(82)
		CXCL12	Deletion depletes HSCs, progenitors unaffected	(58)
11.	Megakaryocytes	CXCL4	Regulates cell cycle activity and quiescence of HSCs	(85)
		THPO	Regulates cell cycle activity and quiescence of HSCs	(86)

BM, bone marrow; HSC, hematopoietic stem cell; MSCs, mesenchymal stem cells.

that AML-derived exosomes induced downregulation of critical retention factors SCF and CXCL12 in stromal cells resulting in HSPC mobilization from the BM (90).

Intravital imaging studies in mouse models of AML identified distinct changes that take place within the endosteal niche during leukemic progression. Endosteal vessels and the adjacent mature osteoblasts are gradually lost during the course of leukemogenesis, due to increased secretion of inflammatory cytokines tumor necrosis factor (TNF) and CXCL2 by AML cells within the endosteal regions which in turn results in a decreased number of functional HSCs. This in turn resulted in decreased number of normal, functional HSCs within the endosteal niche (93).

Arterioles within the bone metaphysis region are associated with neuron glial antigen 2 (NG2)$^+$ niche cells and the sympathetic nervous system (SNS) network, which is critical for maintaining HSC migration (64). Chen *et al.* found decreased sympathetic nerve fibers and Schwann cells in the BM of AML patients (109). Furthermore, using the MLL-AF9 mouse model of AML, Hanoun *et al.* showed

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Table 2 BM niche modification during AML

No.	BM component	Modification in AML	References
1.	MSCs	AML cell-derived BMPs induce MSC differentiation into osteoprogenitors through the Smad1/5 signaling pathway and promote AML progression	(87)
		MSCs transfer mitochondria to AML blasts through AML-derived tunneling nanotubes, which increases AML cell survival	(88)
		AML-MSCs secrete CXCL12 to increase long-term survival and proliferation of AML cells through the mTOR pathway	(89)
		AML-derived exosomes decrease key HSC supporting factors CXCL12, KITL, IGF1, and SCF in BM stromal cells	(90,91)
2.	Osteoblasts	AML-derived exosomes inhibit osteogenesis through DKK1	(91)
		AML-derived oncometabolite kynurenine induces a proinflammatory state in osteoblasts through serotonin receptor 1B which promotes AML blast proliferation	(92)
3.	Endosteal vessels	Loss of endosteal vessels through secretion of TNF and CXCL2 by AML cells	(93)
4.	Sympathetic nerves and Schwann cells	Sympathetic nerves and Schwann's cells are lost in the BM of AML patients	(94)
		Decreased β2 adrenergic signaling in sympathetic nerves extends leukemic cell proliferation	(94)
5.	Macrophages	M2 polarization of macrophages in AML BM through Gfi1 and arginase II	(95,96)
6.	Sinusoidal vessels	Increased BM micro-vessel density through VEGFA in AML patients	(97)
		Increased vascular leakiness in AML BM through nitric oxide signaling resulting in preferential proliferation of leukemic HSCs compared to normal HSCs	(98,99)
		AML blasts up-regulate E-selectin on BM vasculature inducing PI3K/AKT and RAS/MAPK survival pathways in AML blasts	(100,101)
7.	Pericytes	Decreased pericyte coverage of BM vasculature in BM biopsies of AML patients	(97)
8.	Adipocytes	Increased lipolysis of adipocytes results in the release of fatty acids which promotes AML blast survival and proliferation	(102,103)

BM, bone marrow; AML, acute myeloid leukemia; MSC, mesenchymal stromal cell; BMP, bone morphogenic protein; mTOR, mammalian target of rapamycin; HSC, hematopoietic stem cell; SCF, stem cell factor; TNF, tumor necrosis factor.

that these niche cells are lost in AML, and the AML cells co-opt the SNS fibers to promote AML progression (94).

The endosteal region also harbors macrophages that interact with LT-HSCs to support their quiescence (110). Several studies have shown the presence of pro-leukemogenic macrophages within the AML niche. Using the MLL-AF9 mouse model, Al-Matary *et al.* found increased infiltration of M2 macrophages in AML BM and identified transcriptional repressor growth factor independent 1 transcriptional repressor (*Gfi1*) to play an important role in macrophage polarization (95). Furthermore, AML blasts secrete increased arginase II, resulting in M2 polarization of macrophages, which in turn inhibits T cell proliferation (96).

Remodeling of the vascular niche

The modifications within the vascular niche are distinct from those observed in the endosteal niche. In the AML patient's BM, an increased number of sinusoidal blood vessels fill the central marrow region. Padró *et al.* showed that the BM of patients with AML had significantly increased BM micro-vessel density (MVD) compared to healthy individuals (111). This is likely due to increased expression of VEGFA expression by AML cells in BM (97). Additionally, a study reported a positive correlation between MVD and the proliferation index of leukemic blasts (112). Kuzu *et al.* showed that AML patients exhibited increased MVD independent of increase in BM cellularity or presence of leukemic blasts and it was associated with shorter overall

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survival (113). To understand the significance of increased microvascular density in AML, Passaro *et al.* analyzed vascular permeability in a mouse model of AML. They showed that increased nitric oxide signaling in ECs resulted in vascular leakiness and increased hypoxia in BM (98).

Pericytes are mural cells that are present along ECs on the vasculature. They provide structural support to blood vessels and are also crucial for hematopoiesis. Using BM biopsies of AML patients, preliminary study by Weidenaar *et al.* have shown that pericyte coverage is decreased in AML patients (97). Similarly, Passaro *et al.* showed reduced normal pericyte coverage in the BM of a patient-derived xenograft model of AML (98). Collectively, these studies suggest loss of pericyte coverage as a potential mechanism of altered vascular permeability in AML.

Alteration of BM adipocytes is also involved in AML development. Morphological changes and lipolysis are induced in adipocytes due to the uncontrolled proliferation of AML blasts resulting in a limited marrow cavity (102).

Altogether, these studies highlight a transformed BM niche in AML. The altered BM niche in AML reciprocally interacts with the AML blasts and influences their proliferation, survival, and apoptosis through various mechanisms. The following sections will focus on how these altered BM components affect leukemogenesis.

Regulation of leukemic blasts by the endosteal niche

As described in the sections above, AML blasts remodel the endosteum, and these remodeled endosteal regions are unable to support non-leukemic HSCs and cause disruption of normal hematopoiesis. Krevvata *et al.* showed that depletion of osteoblasts through genetic and pharmacological means in mice with AML promoted disease progression, while preservation of osteoblast numbers resulted in recovery of normal marrow function and prolonged survival of mice (114). Studies focusing on osteoblasts have identified diverse mechanisms in regulating leukemic pathogenesis. Krause *et al.* have shown that activation of TGF-β1 signaling through parathyroid hormone receptors on osteoblasts enhances engraftment in the *MLL-AF9* mouse model (115). Kode *et al.* have also shown that activation of β-catenin in osteoblasts upregulates Notch signaling in HSCs and is sufficient to induce leukemic transformation in mice and may be implicated in the pathogenesis of human AML (116). A detailed metabolic study by Galán-Díez *et al.* showed that AML-derived oncometabolite kynurenine induces a proinflammatory state in osteoblasts through serotonin receptor 1B. This results in the secretion of inflammatory molecule acute-phase protein serum amyloid A by osteoblasts, which in turn selectively promotes AML blast proliferation (92). Together these studies highlight the importance of osteoblast-leukemia cell cross-talk in leukemic progression.

A study by Chow *et al.* described the importance of sympathetic neuropathy in AML mouse models (77). They showed that mice with denervated BM had increased infiltration of LSCs upon transplantation and decreased survival. Furthermore, they showed that inhibition of the β2 adrenergic receptor by antagonists resulted in extended leukemic cell proliferation while treatment with β2 adrenergic agonist limited LSC expansion by rescuing the healthy BM niche (94).

Regulation of leukemic blasts by the vascular niche

The reprogrammed vascular niche plays a critical role in the regulation of leukemic pathogenesis. A study by Winkler *et al.* initially reported using the MLL-AF9 AML model that AML blasts up-regulate E-selectin expression on the BM ECs in mice with AML (100). Through experiments involving genetic or pharmacological inhibition of E-selectin expression, they proved that E-selectin is required for maintenance of LSCs in the BM. The same group later showed that contact of AML blasts with vascular E-selectin induces phosphoinositide 3-kinase PI3K/AKT, and rat sarcoma protein (RAS)/mitogen-activated protein kinase (MAPK) survival and regenerative signaling pathways within the BM AML blasts (101).

Vascular remodeling and increased vessel leakiness results in a hypoxic BMM and leukemic cells are better adapted to survive in hypoxic microenvironments compared to HSCs. Indeed, a study by Jensen *et al.* showed that hypoxic conditions in BM of leukemic rats severely inhibited the proliferation of normal HSCs compared to leukemic HSCs (99). Another study reported that hypoxic BM-induced transcription of macrophage inhibitor factor (MIF) by hypoxia-inducible factor 1α (HIF-1α) in AML blasts and targeted inhibition of MIF improved survival in models of AML (117). Interestingly, the anti-leukemic role of HIF-1α has also been reported previously. A study showed that HIF-1α repressed the expression of miR-17, and miR-20a, which inhibited the expression of *p21*, and signal transducer and activator of transcription 3 (STAT3), which

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ultimately resulted in decreased proliferation and induction of differentiation of AML cells (118).

Altered MSCs in the leukemic BM play a crucial role in leukemic progression. A study analyzed the gene expression patterns of MSCs derived from AML patients and found that AML-MSCs gene expression patterns impaired their ability to support the expansion of normal committed hematopoietic progenitors from umbilical cord blood compared to healthy donors, highlighting their contribution towards emergence or progression of leukemia (119). Another study identified that MSCs transfer mitochondria to AML blasts through AML-derived tunneling nanotubes, which increased AML cell survival, and inhibition of mitochondrial transfer improved survival in a mouse model of AML (88). Through *in vitro* co-culture experiments, a study reported that BM MSCs secrete soluble mediators like CXCL12, which increased activation of the mammalian target of rapamycin (mTOR) pathway and its downstream targets in primary AML cells, which ultimately increased long-term survival and proliferation of AML cells (89).

While adipocytes are generally known to inhibit normal hematopoiesis, they play an interesting role in leukemic pathogenesis. A study by Shafat *et al.* showed that adipocytes support the survival and proliferation of AML blasts *in vitro*. Furthermore, they showed that AML blasts induce lipolysis of adipocytes which results in the release of fatty acids, which are in turn utilized by the AML blasts for their survival and proliferation (103).

Mechanism of immune evasion

As discussed in the earlier sections, there is emerging evidence that normal hematopoiesis is suppressed by the LSCs which remodel the BM niche into a leukemia-friendly microenvironment by increased hypoxia and inflammation in addition to metabolic adaptation (*Figure 1*). This ultimately enables immune system avoidance and the initiation of protective pathways that promote the advancement of leukemia (110). LSCs by their dominant proliferation-promoting signals deregulate the BM niche (120). MSCs through Toll-like receptor 4 (TLR4) offer protection to AML blasts from natural killer (NK) cell-mediated killing by cell-cell contact-dependent mechanism (121-123). MSCs derived from AML patients further show their inhibitory effects by inducing regulatory T cells (Tregs) and upregulating the indoleamine 2,3-dioxygenase (IDO) pathway (124). MSCs derived from AML exhibit enhanced immunosuppressive and anti-inflammatory properties. This is demonstrated by their increased ability to inhibit lymphocyte growth *in vitro*, as well as more significant reduction in pro-inflammatory cytokine secretion, such as IL-10, when compared to MSCs derived from healthy donors (125).

Leukemic cells also present deregulated energy metabolism, increasing competition for critical nutrients that result in increased release of metabolites such as reactive oxygen species (ROS) that have inhibitory effects on the immune subsets (126). Additionally, the metabolic requirements of leukemia cells are sustained by MSCs that differentiate into adipocytes, forming a distinctive microenvironment (127,128). Within this environment, the transfer of fatty acids to leukemia cells is facilitated through fatty acid binding protein 4 (FABP4), promoting fatty acid oxidation (FAO) (103,129). An abundance of fatty acids can impede the functions of effector T-cells and promote regulatory T-cell (Tregs) differentiation (130). FAO can also hinder the activation of effector T-cells by increasing programmed cell death protein 1 (PD-1) expression and suppressing interferon-gamma (INF-γ) secretion while stimulating Treg cell production via the activation of the MAPK signaling pathway (131).

The oxygen-regulated component HIF-1α is overexpressed in the leukemic niche (132). HIF-1α signaling on both the AML blasts and the stromal cells promotes the expression of VEGF, C-X-C chemokine receptor type 4 (CXCR4), CXCL12, and SCF (133). AML blasts and especially LSCs express CXCR4 on their surface and migrate in response to CXCL12 (134), decreasing normal HSCs in the leukemic niche resulting in altered immune cell homing (94). Increased levels of CXCR4 in AML blast cells have been demonstrated to be associated with unfavorable outcomes (135). Further, upregulation of surface CXCR4 is induced by chemotherapy which causes stromal protection from additional chemotherapy-induced apoptosis (136).

Role of niches in treatment-refractory AML patients*: *mechanisms of therapy resistance

Analogous to normal HSCs, AML cells engage in both physical and functional interactions with the stroma in the BMM (137). AML arises when LSCs modify the regular BMM for their benefit (137). This transformed niche collaborates with the LSC, supporting its quiescence and

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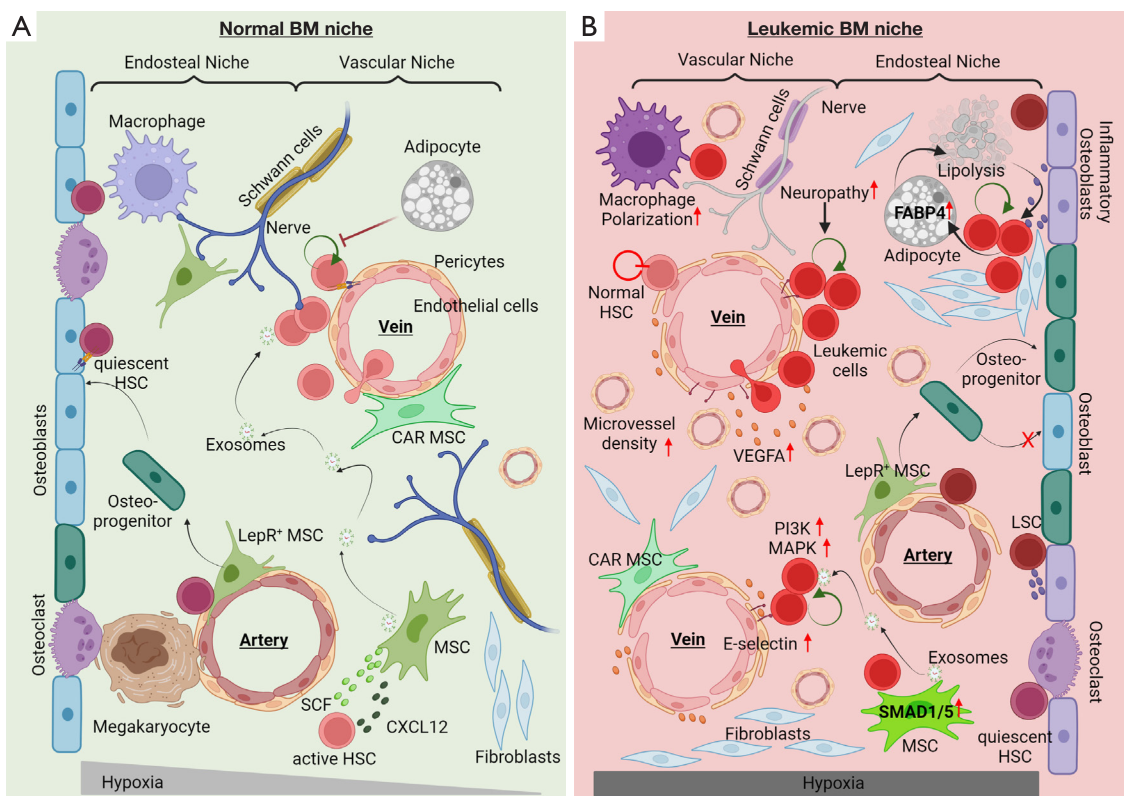

Figure 1 Remodeling of hematopoietic BM niche during AML. (A) Normal BM niche is made up of two compartments of (I) endosteal niche-harboring quiescent HSCs and (II) vascular niche—HSC proliferative niche supporting normal hematopoiesis. All the components of BM niches act in the orchestrated manner to support balanced hematopoiesis producing required numbers of mature blood cells as and when required. (B) BM niche transforms drastically during leukemogenesis. These changes inhibit normal hematopoiesis and support LSC and leukemic blast proliferation. Various changes such as—loss of osteoblast/osteoprogenitor ratio, increased frequency of inflammatory osteoblasts, reduced osteoclasts, in endosteal niche; increased SMAD1/5 signaling in MSCs, increased E-selectin and VEGFA in endothelial cells, increased microvessel numbers, reduced pericyte coverage leading to leaky vessels. Along with this increase in macrophage polarization and neuropathy is observed during AML progression. Further, increased hypoxia in BM, lipolysis in adipocytes and inflammation in BM microenvironment favors the shifting of hematopoiesis from normal to leukemic state. Red arrows indicate increased levels of corresponding molecules or phenomenon. Black arrows denote the trajectory of effect of corresponding molecules. Green circular arrows represent proliferation while red circular blunt arrows represent blockage of proliferation. This figure was created with Biorender.com. BM, bone marrow; AML, acute myeloid leukemia; HSC, hematopoietic stem cell; MSC, mesenchymal stem cell; CAR MSC, CXCL12 abundant reticular MSC; SCF, stem cell factor; LSC, leukemic stem cell.

survival by offering structural reinforcement or secreting various cytokines to elude treatment (137,138). These connections are crucial in the onset, advancement, and recurrence of AML (139). Quiescent LSCs located in osteoblast-rich regions of BM are sheltered from cell cycle-dependent chemotherapy (140). Both soluble elements and cell-cell contact-mediated paths safeguard AML cells from chemotherapy while being cocultured with stromal cell layers (141,142). For instance, both direct stromal interaction and stroma-derived soluble factors play a role in extracellular regulated kinase (ERK)-mediated resistance to FMS-like tyrosine kinase 3 (FLT3) inhibitors (137).

Attachment and activation of pro-survival and proliferative pathways in the leukemic blasts occur through the interaction of the β-1 integrin receptor family members, specifically very late antigen-4 (VLA-4) and VLA-5, as well as the β-2 integrin lymphocyte function-associated antigen 1 (LFA-1) found on leukemic cells. These receptors interact

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with stromal ligands such as VCAM-1, fibronectin, and intracellular adhesion molecule 1 (ICAM-1) (143-145). Interaction of VLA-4 on the leukemia cells with ICAM-1 on the MSC activates the nuclear factor kappa B (NF-κB) signaling pathway which reduces the sensitivity to chemotherapy in the leukemia cells (146).

Leukemic cell survivability is increased by yet another mechanism, where MSCs transfer mitochondria through endocytic pathways or tunneling nanotubes or gap junctions to AML cells; this process is further improved by chemotherapy and linked with increased adenosine triphosphate (ATP) synthesis in AML cells through oxidative phosphorylation (147,148). Initiation of mitochondrial transfer occurs via AML-derived NOX2 through superoxide generation (88), and the surface molecule CD38 also has a crucial role (149). High levels of ROS generated in the leukemic niche due to continuous activation of NOX and mitochondrial production from oxidative phosphorylation enable AML blasts to evade anti-leukemic effector lymphocytes. Free radicals deactivate T and NK cells by triggering PAR-1 dependent apoptosis (150-152). Further, in the leukemic niche, extracellular ATP is significantly increased which is converted to immunosuppressive mediator adenosine by tumor cells, Tregs, and myeloid-derived suppressor cells (MDSCs) (153,154). AML progression causes substantial remodeling of vascular endothelium mainly in the endosteal BM region with increased vascular permeability, decreased blood flow, and vessel loss resulting in a hypoxic leukemic niche (93,98). Due to this, several BM regions are hypo-perfused resulting in decreased drug biodistribution and immune cell trafficking (155,156). Additionally, the ability of immune cells to adhere to the endothelium is diminished due to the elevated E-selectin levels caused by increased inflammation from AML blasts (157). There are many reports suggesting cholesterol homeostasis as one of the mechanisms of AML chemoresistance. Cholesterol levels are significantly increased in AML samples exposed *in vitro* to chemotherapy. Blocking these elevated acute cholesterol levels may sensitize AML cells for therapy (74,158). These mechanisms of therapy resistance are briefly illustrated in *Figure 2*.

Future therapeutic options targeting leukemic niches for AML treatment

The BMM is significantly altered by leukemic cells for their survival and proliferation. This remodeling is a result of the complex interplay between LSC, their BM niche, and the outcome of treatment. The molecular players involved are highly dynamic, inducing molecular changes that converge to activate survival, protective autophagy, or quiescence of LSCs. The influence of the leukemic microenvironment on therapeutic outcomes or the probable targets of the leukemic microenvironment has not been better characterized. Identifying these protective mechanisms to target LSC along with the current therapeutic regime can be the combinatorial future approach (159). Targeting niche cells/LSCs to reduce leukemic progression without disrupting the normal stem cell self-renewal or encouraging migration of leukemic cells out of the protective BM niche can be a promising strategy to increase their susceptibility to treatment (160).

Disrupting the CXCL12/CXCR4 axis that releases AML blasts from the BM by small-molecule inhibitors [plerixafor (AMD3100)], short peptides [BL-8040 (BKT140)], and antibodies [ulocuplumab (BMS-936564/MDX-1338)] reported can be used to effectively overcome therapy resistance (137,161). A tellurium compound AS101 can be used to disrupt the pro-survival and proliferative pathways in the leukemic blasts through VLA-4 (137). A potent E-selectin inhibitor GMI-1271 may reduce the adhesion of AML cells to the stroma and enhance chemotherapy efficiency (137) (*Table 3*).

As discussed earlier, MSCs transfer mitochondria to leukemic blasts via endocytic pathways, tunneling nanotubes, or gap junctions. Daratumumab, a monoclonal anti-CD38 antibody approved to treat multiple myeloma, has demonstrated the ability to hinder the transportation of mitochondria to AML cells by deactivating peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1 alpha, decreasing superoxide levels with N-acetylcysteine, and obstructing connexin-43 gap-junctions. This ultimately reduces the oxygen consumption rate and suppresses the growth of leukemic cells (88,162-164). A phase II clinical trial has been reported for daratumumab-hyaluronidase in treating chemotherapy-resistant and relapsed minimal residual disease (MRD) in T-cell acute lymphoblastic leukemia. Counteracting hypoxia by repairing the malfunctioning tumor vasculature with NOS inhibitors could potentially augment drug delivery and improve T-cell functionality (98). There is an interesting report, where the cholesterol-lowering drug lovastatin induced cell-autonomous inhibition of LSCs in a co-culture with MSCs and further prolonged the survival of mice injected with lovastatin pretreated LSC-stromal co-cultures (158,165). Targeting the deregulated energy consumption of LSCs by

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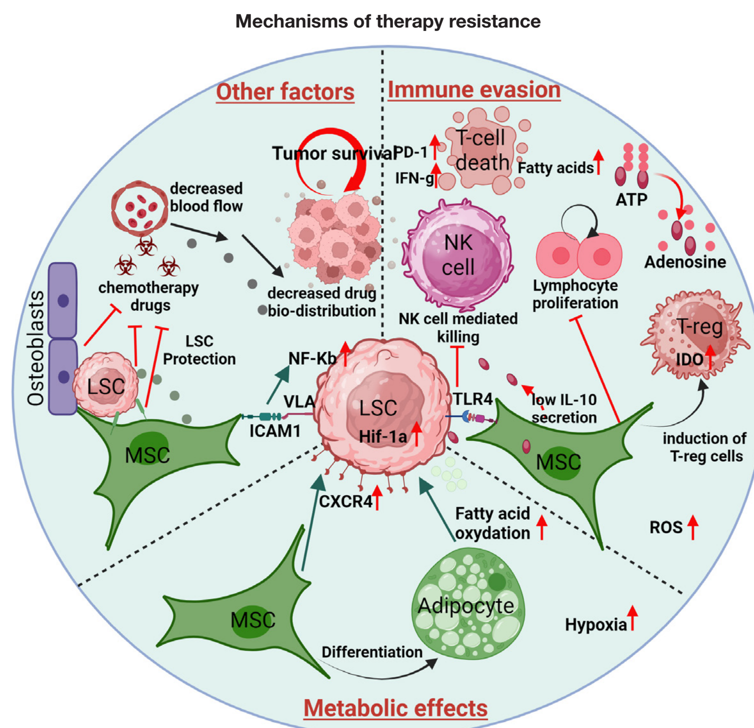

Figure 2 Mechanisms of therapy resistance in AML. Immune evasion: MSCs protect LSCs and AML blast from NK cell mediated killing through TLR4, and also induce T-reg cells. MSCs also suppress the lymphocyte proliferation by reduced secretion of pro-inflammatory cytokines. Along with this, increased T cell death due to increased fatty acids, increased ROS and increased adenosine helps AML blasts to escape ant-leukemic effector lymphocytes. Metabolic effects: AML MSCs differentiate into AML supportive adipocytes. Stromal cells also protect LSCs from drug-induced apoptosis by CXCR4 upregulation and increasing *Hif-1α* expression in them. Other factors: interaction of VLA4 from AML cells with ICAM1 on MSCs reduced chemotherapy sensitivity of AML cells via NF-κβ pathway. Decreased blood flow in AML BM also decreases the bio-distribution of anti-cancer drug. Osteoblasts protect the quiescent LSCs from chemotherapy. Red arrows indicate increased levels of corresponding molecules or phenomenon. Black and green arrows denote the trajectory of effect of corresponding molecules. Black circular arrows represent proliferation while red circular arrows represent increased proliferation. Red lines with blunt heads represent the blockage of the activity. This figure was created with Biorender.com. AML, acute myeloid leukemia; MSC, mesenchymal stem cell; LSC, leukemic stem cell; NK, natural killer; ROS, reactive oxygen species; BM, bone marrow.

FAO inhibitors like avocatin B in combination with other drugs can eliminate residual LSC populations with adapted energy homeostasis (166). The compounds/drugs under clinical trial such as CXCR4 inhibitors, VLA-4 inhibitors, E-selectin inhibitors, Hypoxia-activated agents, and cholesterol synthesis inhibitors are listed with intervention/treatment regimen, patient population, and clinical trial phase details in *Table 3*.

Conclusions

A better understanding of LSCs, the surrounding microenvironment, and the molecular signals may help develop niche-targeted treatment of refractory AML. Accordingly, novel strategies can be developed to combat LSCs protected in the BM niche by targeting deregulated molecular pathways or dysfunctional components within the niches along with conventional chemotherapy.

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Table 3 Clinical trials targeting the bone marrow niche modification during acute myeloid leukemia

No.	Inhibitors	Intervention/treatment	Patient population	ClinicalTrials.gov ID	Phase
1.	CXCR4 inhibitors	Plerixafor + daunorubicin/cytarabine	Untreated, 18–70 years	NCT00990054	I
		Plerixafor + daunorubicin/clofarabine and daunorubicin/cytarabine	Untreated, 60 years and older	NCT01236144	I
		Plerixafor + G-CSF, mitoxantrone/etoposide/cytarabine	Relapsed/refractory, 18 years and older	NCT00906945	I
		Plerixafor + decitabine	Untreated, 60 years and older	NCT01352650	I
		Plerixafor + cytarabine/etoposide	Relapsed/refractory, 3–30 years	NCT01319864	I
		Ulocuplumab + mitoxantrone/etoposide/cytarabine	Relapsed/refractory, 18 years and older	NCT01120457	I
		CX-01 + idarubicin/cytarabine	Untreated, 18–80 years	NCT02056782	I
		Plerixafor + mitoxantrone/etoposide/cytarabine	Relapsed/refractory	NCT00512252	I/II
		Plerixafor + clofarabine	Untreated, 60 years and older	NCT01160354	I/II
		Plerixafor + fludarabine/idarubicin/cyarabine/G-CSF	Second-line induction, up to 65 years	NCT01435343	I/II
		Plerixafor + busulfan/fludarabine/thymoglobulin	Allogeneic stem cell transplantation, 18–65 years	NCT00822770	I/II
		BL-8040 (BKT140) + cytarabine	Relapsed/refractory, 18–75 years	NCT01838395	IIa
2.	VLA-4 inhibitor	AS101 + chemotherapy	Untreated, 60 years and older	NCT01010373	II
3.	E-selectin inhibitor	GMI-1271 (uproleselan) + chemotherapy	Relapsed/refractory, 18–60 years	NCT04839341	I
		GMI-1271 + fludarabine + cytarabine	Relapsed/refractory, up to 17 years	NCT05146739	I
		GMI-1271 + mitoxantrone/etoposide/cytarabine	Relapsed/refractory or untreated, 60 years and older	NCT02306291	I/II
		GMI-1271 + chemotherapy	Relapsed/refractory, 18 years and older	NCT02306291	I/II
		GMI-1271 + chemotherapy	Relapsed/refractory, 18–75 years	NCT05054543 and NCT03616470	III
4.	Hypoxia-activated agents	TH-302	Relapsed/refractory, 18 years and older	NCT01149915	I
5.	Cholesterol synthesis inhibitor	Pravastatin + idarubicin + cytarabine	Untreated, 18–74 years	NCT01831232	NA
		Pravastatin + idarubicin + cytarabine	Untreated and relapsed/refractory, 18 years and older	NCT00107523	I
		Atorvastatin	Relapsed/refractory, 18 years and older	NCT03560882	I
		Pitavastatin + venetoclax/azacytidine/decitabine	Relapsed/refractory, 18 years and older	NCT04512105	I
		Pravastatin + cyclosporine + etopside/mitoxantrone	Relapsed/refractory, 18 years and older	NCT01342887	I/II
		Lovastatin + cytarabine	Relapsed/refractory, 18–99 years	NCT00583102	I/II
		Pravastatin + idarubicin + cytarabine	Relapsed/refractory, 18 years and older	NCT00840177	II

G-CSF, granulocyte-colony stimulating factor.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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