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Targeting the bone marrow niche, moving towards leukemia eradication

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Hematopoiesis is a complex and tightly regulated process that drives the formation of mature blood cells from a single hematopoietic stem cell. This complex process occurs within the bone marrow, which, once disrupted or deregulated, subverts normal hematopoietic development, allowing leukemic cells to emerge, proliferate, and thrive. Notably, several cellular populations and paracrine factors within the bone marrow fuel leukemia expansion and progression. This review presents an overview of the main microenvironmental components that promote myeloid leukemia progression, discussing the emerging therapeutical strategies that target both leukemic cells and the supportive bone marrow microenvironment – targeting both the seed and the soil.

KEYWORDS

hematopoiesis, leukemia, myeloid neoplasia, bone marrow microenvironment, bone marrow targeting

1 Hematopoiesis

Hematopoiesis is the lifelong, complex, and hierarchical mechanism that orchestrates the differentiation of all blood cells. From a single cell, hematopoiesis produces white blood cells, red blood cells, and platelets, which are responsible for immune responses, oxygen delivery, and stopping bleeding in case of blood vessel damage, respectively (1).

This process relies on hematopoietic stem cells (HSCs), which possess the unique capacity for self-renewal and differentiation into two primary lineages: lymphoid and myeloid. From HSCs, common lymphoid progenitors generate B and T lymphocytes and dendritic and natural killer cells. Moreover, common myeloid progenitors initiate the production of erythrocytes, megakaryocytes, macrophages, granulocytes, and other cell types from this lineage (2–4).

HSCs progressively lose their self-renewal capability and become committed to specific lineages upon differentiation (5, 6). This model is considered a tree-like hierarchy. However, single-cell sequencing technologies have brought numerous advantages, including insights into cell heterogeneity, developmental processes, identification of rare

cell types and subpopulations, and tracking cell fate decisions. According to these studies, it is suggested that multipotent HSCs gradually become lineage committed through a transitional process, where the progenitor cells are in intermediate states before their full differentiation. Therefore, current views perceive HSC differentiation as a continuum (7–9).

HSC differentiation occurs in specialized microenvironments (or niches) located within the bone marrow (BM) that are intricately regulated and sustained by a combination of intrinsic factors, like transcription factors and epigenetic regulators, extrinsic factors (2, 5), and also non-hematopoietic cells (10).

Extrinsic factors like cytokines, chemokines, and growth factors secreted by BM cellular components also regulate hematopoiesis. Among the most pivotal for HSC regulation are the stromal cell-derived factor 1 (SDF-1, also known as CXCL12), which binds to the CXC-chemokine receptor 4 (CXCR4), and stem cell factor (SCF) that interacts with the c-Kit receptor (CD117) (1, 5). Additionally, interleukin-3 (IL-3), interleukin-5 (IL-5), interleukin-6 (IL-6), thrombopoietin (TPO), Fms-like tyrosine kinase 3 ligand (FLT3L), and vascular endothelial growth factor (VEGF) are other paracrine molecules essential for hematopoiesis (6).

2 Leukemia

Leukemia is a BM disorder characterized by the abnormal proliferation of mutant HSCs and progenitor cells, disrupting regular hematopoietic differentiation. While this malignant disorder comprises two primary categories—myeloid and lymphoid— this review will mainly focus on myeloid malignancies: Acute Myeloid Leukemia (AML), Chronic Myeloid Leukemia (CML), and BCR-ABL1 negative Myeloproliferative Neoplasms (MPN).

Extensive research over the years has identified several mutations occurring within the developing HSCs that result in AML (11, 12). The mutations implicated in AML can be divided into two main groups. The first group, class I mutations, provide cells with a proliferative advantage, while class II mutations predominantly interfere with hematopoietic differentiation and subsequent apoptosis (13).

Mutations in the *FLT3* and *KIT* genes are canonical examples of class I mutations in AML. These genes encode tyrosine kinase receptors, whose mutation initiates internal signaling pathways, leading to uncontrolled growth and expansion of HSCs, contributing to leukemogenesis (14, 15). On the other hand, class II mutations encompass examples such as those found in the *CEBPA* and *RUNX1* genes, which encode transcription factors crucial for hematopoietic differentiation (16, 17).

Nonetheless, AML extends beyond the class I/II mutations framework, encompassing a spectrum of additional genetic alterations that involve pivotal epigenetic regulators and housekeeping genes (11, 13). The *DNMT3A* gene encodes a methyltransferase crucial for HSC differentiation. Mutations in *DNMT3A* are early events in leukemogenesis, leading to diminished enzymatic activity (18). Similarly, mutations in *TET2*, occurring at the onset of leukemogenesis, result in DNA hypermethylation. This aberrant methylation alters the expression of genes critical to HSC function, thereby deregulating hematopoiesis (19). Housekeeping genes are also crucial in AML. The *NPM1* gene encodes a chaperone protein involved in cellular homeostasis. Mutations in *NPM1* disrupt its subcellular localization, affecting the stabilization and localization of essential proteins, such as $p14^{ARF}$, a regulator of the p53 pathway (20). Moreover, the *IDH1* and *IDH2* genes, which encode enzymes essential for metabolic processes, are also mutated in AML. These mutations lead to the production of 2-Hydroxyglutarate (2-HG), an oncometabolite that inhibits DNA demethylation enzymes (21).

The *BCR-ABL1* fusion oncogene characterizes CML, and the resulting fusion protein exhibits constitutive kinase activity. Such constitutive activation sustains the fueling of downstream signaling pathways that are associated with cell growth and proliferation (JAK-STAT, PI3K-Akt, and MEK-ERK), contributing to the leukemic transformation of HSCs and disease progression (22, 23).

Essential Thrombocytosis (ET), Polycythemia vera (PV), and Primary myelofibrosis (PMF) constitute a distinct subset of myeloid malignancies known as BCR-ABL1 negative myeloproliferative neoplasms (MPN), distinguished by specific genetic alterations in the *JAK2*, *MPL*, and *CALR* genes. The *JAK2V617F* mutation, characterized by the substitution of valine with phenylalanine at codon 617, results in the continuous phosphorylation of JAK2 kinase, constitutively activating the JAK-STAT pathway and disrupting HSC regulation. Similarly, mutations in the *MPL* gene, which encodes a thrombopoietin receptor critical for megakaryopoiesis, also lead to autonomous activation of the JAK-STAT pathway, enabling abnormal HSC proliferation. Moreover, the *CALR* gene encodes calreticulin that regulates protein folding and calcium signaling, and mutations in this gene modulate receptor signaling activation, ultimately driving aberrant proliferation and survival in developing HSCs (24).

3 The bone marrow microenvironment

The BM is a remarkably complex tissue, housing a variety of cell types, both hematopoietic and non-hematopoietic, that support HSC differentiation and expansion (25–27). Recent advances in cutting-edge imaging techniques, such as confocal and intravital microscopy, more complex and physiological animal models, and RNA sequencing studies, led to identifying several cell types that promote HSC development and their localization within specific BM niches. However, this increased level of resolution has also led to conflicting data across different studies. These discrepancies arise from variations in techniques, animal models, and the types of bones analyzed, making the precise localization of HSCs within the BM a subject of ongoing debate and controversy (3, 28). Nonetheless, despite these current controversies and conflictual data, in this review, we decided to discuss cellular components of the BM microenvironment, focusing on two particular regions: the endosteal niche, which is adjacent to the bone endosteum, and the perivascular niche, located within the BM central region (6, 29).

The endosteal niche comprises mainly osteoblasts (OBs) and osteoclasts (OCs). OBs play a pivotal role by providing essential paracrine signals, such as SDF-1, SCF, and Osteopontin (OPN), that are crucial for HSC function, homing, self-renewal, and quiescence (30–34). In myeloid neoplasia, OBs demonstrate a tumor-suppressor role, as reduced numbers in patient samples correlate with disease progression (35). Conversely, restoring OB frequency in mouse models decreases leukemic burden and extends survival (36). Additionally, myeloid leukemia cells have been found to influence OB differentiation, promoting their proliferation and expansion even with chemotherapy exposure (36–40). The OCs are responsible for bone reabsorption (41) and contribute to HSC regulation by physically creating endosteal niches (42) and degrading paracrine factors implicated in HSC mobilization (43). However, studies investigating the role of OCs in modulating myeloid leukemia progression are scarce.

The perivascular niche is a highly dynamic microenvironment characterized by several cell types like adipocytes, Endothelial cells (ECs), Sympathetic neural cells (SNCs) and Mesenchymal Stem cells (MSCs).

Adipocytes, originating from MSCs, are reservoirs for HSCs and progenitor cells (44) and can support hematopoiesis by secreting SCF (45–47). In leukemia, adipocytes are critical in the dysregulation of cellular energetics by providing fatty acids for cell metabolism (48), sustaining cell survival and migration, and conferring protection against chemotherapy cytotoxicity (49–52). Interestingly, obesity, associated with increased adipose tissue, has been shown to correlate with poorer outcomes (53).

The BM vasculature forms a network of arterioles and sinusoids that deliver essential nutrients and oxygen (54). The ECs are the key components, reside at the interface between blood vessels and the BM, and express distinctive surface markers like CD31, MECA-32, VE-Cadherin, VCAM-1, and VEGFR-2 (55, 56). Moreover, ECs regulate HSC homeostasis by secreting SDF-1 and SCF and expressing Notch ligands (57, 58). In myeloid leukemias, blasts migrate towards ECs, establishing direct interactions through cell adhesion molecules and indirect effects via paracrine factors, also providing protection against chemotherapy-induced cytotoxicity (59–65).

The central nervous system (CNS) also regulates hematopoiesis (66), and central to this regulation are the SNCs (29, 67). By releasing catecholamines, sympathetic neuronal fibers innervate OBs and MSCs and modulate SDF-1 and SCF secretion, thereby modulating HSC homeostasis. Additionally, non-myelinating Schwann cells govern HSC quiescence through transforming growth factor – β (TGF-β) signaling (68–70). In leukemic pre-clinical models, reduced SNC activity resulted in remodeled BM, which, in turn, affected MSCs and sympathetic neurons, leading to leukemic blast proliferation and expansion (39, 71).

MSCs differentiate into several cell types like OBs, adipocytes, and stromal cells (72). These cells exhibit a wide range of surface markers like Nestin, Leptin receptor (LepR), CD51, CD140a, and Sca-1, reflecting their functional diversity regarding self-renewal, multipotency, and distribution (73, 74). Moreover, MSCs are the main source of SCF and SDF-1 within the BM (57, 75), particularly the MSC Nestin$^+$ LepR$^+$ cells (76, 77). In leukemia, MCSs facilitate the homing and retention of AML blasts and, due to their increased Notch and NF-κB signaling, also stimulate the proliferation, survival, and chemoresistance of leukemic blasts (78–82). Similarly, in CML, SDF-1 expression levels also increase the proliferation and chemoresistance of leukemic blasts (83). In MPN, MSCs emerge as crucial drivers of fibrosis, and several molecular players have been identified: the alarmin complex S100A8/S100A9 and the TGFβ, JAK2/STAT3, and NFκB signaling pathways (84, 85).

4 Targeting the bone marrow microenvironment

Leukemia patients frequently resist treatment, often due to the emergence of genetic mutations that alter the drug targets (86). Nonetheless, BM components are also crucial modulators of leukemia pathophysiology, and recognizing its importance in protecting leukemic cells from therapeutic interventions stirred the development of alternative strategies that disrupt this symbiosis. Thus, the concept of targeting both the 'seed' (leukemic cells) and the 'soil' (the supportive BM microenvironment) has emerged. It suggests that effective treatment requires eliminating leukemic cells and their supportive microenvironment and has gained traction due to compelling evidence from (pre)-clinical studies demonstrating that a combined treatment strategy yields superior efficacy (6, 87–91). Recently, we discussed four distinct strategies: adhesion molecules, angiogenesis, hypoxia, and the SDF-1/CXCR4 axis (6). Here, we explore the latest advancements and broaden our discussion to other topics (Figure 1 and Table 1).

4.1 Adhesion molecules

The physical interaction between leukemia cells and their microenvironment is crucial for their sustained expansion, and several adhesion molecules are under investigation. The E-Selectin receptor is an essential regulator of HSC function and mediates the chemoresistance of AML blasts (123). Uproleselan, an E-Selectin inhibitor, enhanced chemotherapy efficacy and reduced leukemia burden in an AML pre-clinical model (60). Currently, it is undergoing evaluation in several clinical trials (phase I/II/III) to assess its efficacy in combination with chemotherapy (NCT03616470, NCT03701308, NCT04848974, and NCT05054543). Notably, preliminary data from a phase I/II trial (NCT02306291) showed impressive patient responses, with high remission rates and reduced mortality observed by combining both strategies (124). VLA-4 is implicated in AML proliferation and chemoresistance (80, 92), and its inhibition in mouse models increased chemotherapeutic effects and extended mouse survival (93–95). Targeting VLA-4 is currently being evaluated in a phase II clinical trial (NCT01010373). The CD44 receptor regulates the BM homing of leukemic blasts (125, 126). In AML and CML pre-clinical models, CD44 inhibition with antibodies reduced leukemia burden (96, 97, 127). RG7356, an anti-CD44 monoclonal antibody, was evaluated in a phase I clinical trial (NCT01641250) and showed encouraging results on safety and tolerability (98).

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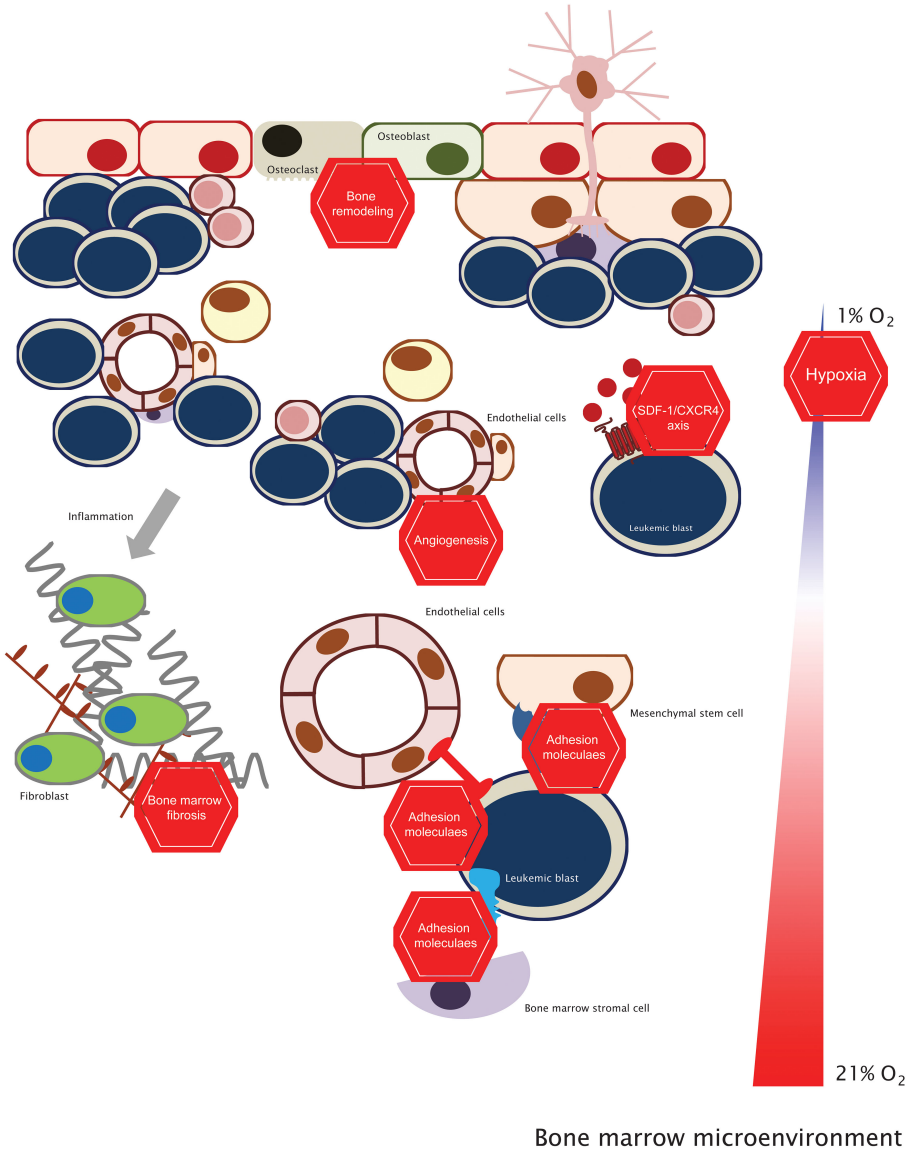

FIGURE 1
Targeting the bone marrow microenvironment. This concept stems from the fact that targeting leukemic cells (with standard chemotherapy or targeted therapy) and inhibiting the BM microenvironmental factors will be more effective in the clinical setting than just targeting leukemic cells. See the text for further details.

TABLE 1 Summary of the therapeutic strategies targeting the bone marrow microenvironment.

Targeting strategy	Target	Agent	Mechanism of action	Clinical trial	Condition	Current status*/ Main findings	Reference
Adhesion molecules	E-Selectin	Uproleselan	E-Selectin antagonist	NCT03616470	AML	Active - 388 patients enrolled	NA
				NCT03701308	AML	Suspended	NA
				NCT04848974	AML	Active - 37 patients enrolled	NA
				NCT05054543	AML	Status unknown	NA
				NCT02306291	AML	Treatment well tolerated; Increased remission rate (35% CR - phase I and 52% CR – phase II) and overall survival	(84)

(Continued)

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TABLE 1 Continued

Targeting strategy	Target	Agent	Mechanism of action	Clinical trial	Condition	Current status*/ Main findings	Reference
	VLA-4	AS101	VLA-4 inhibitor	NCT01010373	AML	Suspended	NA
	CD44	RG7356	Anti-CD44 monoclonal antibody	NCT01641250	AML	Treatment well tolerated and safe; few patients responded (2/44) and achieved stable disease with hematological improvement (1/44)	(92)
Angiogenesis	VEGF	Bevacizumab	Anti-VEGF monoclonal antibody	NCT00096148	AML	Completed - no results posted	NA
				NCT00023920	CML	Completed - no results posted	NA
				NCT00015951	AML	Treatment associated-toxicity; half of the patients partially responded (48% - OR)	(93)
				NTR904	AML	No improvement of therapeutic outcomes with the treatment	(94)
				NCT00667277	MPN	Study prematurely terminated due to high toxicity; no responses observed	(95)
	Tubulin	OXi4503	EC cytoskeleton destabilizer	NCT01085656	AML	Treatment tolerated; poor response rate (1/18 - CR; 1/18 - PR)	(96)
				NCT02576301	AML	Treatment tolerated; low response rate (19% - OR) with extended OS in responding patients	(97)
	Angiopoietin-1/2	Trebananib	Angiopoietin-1/2 inhibitor peptide	NCT01555268	AML	Treatment tolerated; some patients responded (1/13 - PR) and achieved stable hematological disease (2/13)	(98)
Bone marrow fibrosis	IL1β	Canakinumab	Anti-IL-1β monoclonal antibody	NCT05467800	MPN	Active - recruiting	NA
	Lysyl Oxidase	PAT-1251	LOXL2 inhibitor	NCT04054245	MPN	Study withdraw	NA
		PAT-1251	LOXL2 inhibitor	NCT04679870	MPN	Active - 21 patients enrolled	NA
		PXS-5505	pan LOX inhibitor	NCT04676529	MPN	Active - recruiting	NA
		Simtuzumab	Anti-LOXL2 monoclonal antibody	NCT01369498	MPN	Treatment well tolerated but no improvement of treatment outcomes	(99)
	TGF-β	GC1008	Anti-TGF-β monoclonal antibody	NCT01291784	MPN	Treatment-associated toxicity; very modest response rate	(100)
		AVID200	TGF-β 1/3 trap	NCT03895112	MPN	Treatment well tolerated; suppression of TGF-β signaling in most patients; clinical benefit in 2/21 patients	(101)
		KER-050	Activin ligand trap	NCT05037760	MPN	Active - recruiting	NA
Bone remodeling	MET, AXL, and VEGFR	Cabozantinib	Receptor tyrosine kinase inhibitor	NCT01961765	AML	Treatment tolerated; some patients displayed blast reduction (4/18)	(102)
	Ubiquitin-proteosome	Bortezomib	26S proteosome subunit inhibitor	NCT00505700	AML	Treatment tolerated; majority of patients achive complete response (19/31 - CR and 3/31 - PR)	(103)

(Continued)

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TABLE 1 Continued

Targeting strategy	Target	Agent	Mechanism of action	Clinical trial	Condition	Current status*/ Main findings	Reference
				NCT00382954	AML	Treatment tolerated; some patients achived complete response (20% - CR)	(104)
				NCT01736943	AML	Treatment tolerated; the majority of patient responses were transient	(105)
				NCT00742625	AML	Treatment tolerated; majority of patients achieved complete response (65% - CR and 4% - PR)	(106)
				NCT01371981	AML	Treatment-associated toxicity and no improvement of treatment outcomes	(107)
				NCT00666588	AML	Treatment tolerated but no improvement of treatment outcomes	(108)
		Carfilzomib		NCT01137747	AML	Treatment tolerated; modest anti.leukemic responses (2/18 - PR and 4/18 - no progression)	(109)
		Ixazomib		NCT02070458	AML	Treatment tolerated; half of the patients partially responded (53% - CRi)	(110)
Hypoxia	DNA	PR-104	Hypoxia activated DNA cross-linking drug	NCT01037556	AML	Some adverse effects observed; modest response rate (10/31 - OR)	(111)
		TH-302	Hypoxia activated DNA alkylating drug	NCT01149915	AML	Treatment tolerated; very limited response rate (6% - OR)	(112)
	Mitochondrial Complex I	IACS-010759	Mitochondrial Complex I inhibitor	NCT02882321	AML	Treatment-associated toxicity and no improvement of treatment outcomes	(113)
SDF-1/ CXCR4 axis	CXCR4	Plerixafor	CXCR4 inhibitor	NCT00512252	AML	Treatment well tolerated; half of the patients responded (46% - OR) and increased blast peripheral mobilization	(114)
				NCT01319864	AML	Treatment well tolerated; patients response rate was low (3/13 - OR) but resulted in increased blast peripheral mobilization	(115)
				NCT00906945	AML	Treatment well tolerated; patients response rate was low (30% - OR) but resulted in increased blast peripheral mobilization	(116)
				NCT01435343	AML	Treatment tolerated; half of the patients responded (50% - OR)	(117)
				NCT01352650	AML	Treatment tolerated; half of the patients responded (43% - OR) and increased blast peripheral mobilization was observed	(118)
				NCT00943943	AML	Treatment tolerated; some patients responded (36% - OR) and increased blast peripheral mobilization was observed	(119)

(Continued)

TABLE 1 Continued

Targeting strategy	Target	Agent	Mechanism of action	Clinical trial	Condition	Current status*/ Main findings	Reference
		BL-8040		NCT01838395	AML	Treatment well tolerated; some patients responded (29% - OR); increased blast peripheral mobilization and extended survival was observed	(120)
		LY2510924		NCT02652871	AML	Treatment tolerated; some patients responded (36% - OR)	(121)
		Ulocuplumab	Anti-CXCR4 monoclonal antibody	NCT01120457	AML	Treatment tolerated; half of the patients responded (51% - OR) and increased blast peripheral mobilization was observed	(122)

AML, Acute Myeloid Leukemia; CML, Chronic Myeloid Leukemia; CR, complete response; MPN, BCR-ABL1 Myeloproliferative Neoplasm; NA, not applicable; OR, overall response; OS, overall survival; PR, partial response.
*The information was retrieved from clinicaltrials.gov on the 13th June, 2024.

4.2 Angiogenesis

The vasculature is another BM component whose targeting is an appealing therapeutic strategy in leukemia. One notable target, VEGF, is a crucial mediator of angiogenesis and is implicated in AML chemoresistance (62). Bevacizumab, an anti-VEGF antibody, was approved to treat solid cancers, but its efficacy in myeloid neoplasia has been very limited (128–130). Another compound, Combretastatin-A1-diphosphate (OXi4503), disrupts ECs microtubules, hindering the vascular architecture (131). In a pre-clinical AML model, OXi4503 disrupted BM vasculature, decrease tumor burden, and extend mouse survival (132). However, despite its safety and tolerability in clinical trials (NCT01085656, NCT02576301), it resulted in modest response rates when combined with standard chemotherapy (133, 134). The interaction between Angiopoietin and its receptor Tie is also pivotal in regulating AML physiology (99). Trebananib (AMG386), an Angiopoietin inhibitor, underwent evaluation in a phase I clinical trial (NCT01555268), but the outcomes were disappointing, with minimal patient response (100).

4.3 Bone marrow fibrosis

The development of BM fibrosis is the hallmark of PMF, the most aggressive condition in MPN (135). Fibrosis is characterized by the BM deposition of reticulin and collagen fibers, and pro-inflammatory cytokines, lysyl oxidase (LOX), and TGF-β signaling have been shown to modulate this process (101, 102, 136, 137).

IL-1β is one such pro-inflammatory cytokine (102, 137), and Canakinumab (anti-IL1β antibody) is currently being evaluated in a phase II clinical trial (NCT05467800). LOX is an extracellular enzyme that catalyzes the collagen-elastin cross-link, promoting fibrosis (136) and is upregulated in PMF patients (103, 104). Importantly, several clinical trials evaluated LOX inhibition without any known results (NCT04054245, NCT04679870, and NCT04676529). Nonetheless, Simtuzumab, an anti-LOX antibody, was assessed in a phase II clinical trial (NCT01369498) with minimal improvement of BM fibrosis (105). Regarding the TGF-β signaling, GC-1008, an anti-TGF-β antibody, demonstrated a modest reduction in spleen size reduction and anemia recovery (NCT01291784) (106). However, the AVID200, a potent and selective TGFβ 1/3 trap, suppressed TGF-β signaling and resolved BM fibrosis in a pre-clinical model (107). In the clinical setting (NCT03895112), AVID200 was tolerated and suppressed TGF-β signaling (108). The KER-050 compound is another TGF-β inhibitor currently being evaluated in clinical trials (NCT05037760).

4.4 Bone remodeling

Osteolytic lesions are common in cancer patients, resulting from dysregulated bone remodeling due to OB/OC dynamic imbalance. Cabozantinib, a receptor tyrosine kinase inhibitor, exhibits bone remodeling activity by inhibiting OC activity and bone resorption (138). In a phase I clinical trial (NCT01961765), Cabozantinib was well tolerated and demonstrated suppressive signaling activity in leukemic blasts (109).

The ubiquitin-proteasome network is an attractive target due to its importance in bone metabolism. Proteasome inhibitors, like Bortezomib, were tested in AML due to their clinical impact in Multiple Myeloma (MM) (110). Bortezomib, when combined with chemotherapy, was well tolerated (NCT00505700, NCT00382954) (139, 140) but failed to elicit sustained responses and delay disease progression in older (NCT01736943, NCT00742625) (141, 142) and pediatric patients (NCT01371981, NCT00666588) (111, 143). Other proteasome inhibitors like Carfilzomib and Ixazomib demonstrated bone-modulating capabilities by regulating OB/OC cellular function (112). In clinical trials, Carfilzomib demonstrated tolerability and induced modest anti-leukemic activity (NCT01137747) (113), but remarkably, Ixazomib treatment in combination with chemotherapy, induced responses in half of the patients (NCT02070458) (144).

4.5 Hypoxia

The BM is highly hypoxic, contributing to chemoresistance in leukemic cells by upregulating Hypoxia-inducible factor 1 (HIF-1) (145). Hypoxia-activated drugs are unique compounds that remain inactive under normoxic conditions but are activated in low oxygen conditions (hypoxia) and induce cytotoxicity by interfering with DNA synthesis (146). In AML, hypoxia-induced drugs (PR-104, TH-302, and IACS-010759) demonstrated robust efficacy in pre-clinical models by reducing tumor burden and extending survival (114, 147, 148). Unfortunately, phase I clinical trials revealed limited efficacy for PR-104 and TH-302 (NCT01037556, NCT01149915) (115, 116), while IACS-010759, besides limited efficacy, also resulted in increased toxicity in the patients (NCT02882321) (117).

4.6 SDF-1/CXCR4 axis

This signaling axis is essential in the BM homing of leukemic cells, rendering it a desirable target for therapeutic intervention and several compounds have been developed to neutralize it, including Plerixafor [Mozobil – approved for clinical use – (118)], BL-8040, LY2510924, and Ulocuplumab. In myeloid neoplasia, therapeutic blockade of the SDF-1/CXCR4 axis led to leukemic cell peripheral mobilization and increased sensitivity to chemotherapy in pre-clinical models (119–122), spurring the clinical investigation of this pathway. Plerixafor treatment in AML patients demonstrated safety and tolerability (NCT00512252, NCT01319864) (149, 150), and its combination with chemotherapy (NCT00906945 and NCT01435343) (151, 152), hypomethylating agents (NCT01352650) (153) and signaling inhibitors (NCT00943943) (154) yielded promising results regarding leukemic blast reduction and peripheral mobilization. Other strategies, like BL-8040 and LY2510924 (CXCR4 inhibitors) and Ulocuplumab (Anti-CXCR4 antibody), have also undergone clinical evaluation and demonstrated favorable safety profiles, tolerability, reduced leukemic burden, and increased peripheral blast mobilization (NCT01838395, NCT02652871, and NCT01120457) (155–157).

5 Conclusions

Several seminal discoveries unveiled the significant roles of the BM; it is also a crucial supportive microenvironment for the proliferation and survival of leukemic cells (6). The interactions between the leukemic cells and the BM microenvironment are complex, and this symbiosis facilitates the expansion, thriving, and evasion of chemotherapeutic cytotoxic effects by the leukemic blasts. The therapeutic approach in myeloid neoplasia, particularly AML, is evolving, with increasing consideration given to the interactions between leukemic cells and the BM.

Here, we discussed several BM targets currently under evaluation in clinical trials (Table 1), with promising results combined with standard therapy. Such therapeutic strategies include adhesion molecules, BM fibrosis, and the SDF-1/CXCR4 axis. These clinical studies should be reinforced and expanded to more extensive clinical trials and other myeloid malignancies like CML and MPN.

In sharp contrast, targeting other BM components, like vasculature and bone remodeling, yielded disappointing results with very dismal patient responses and associated toxicity. These results underscore the importance of carefully evaluating these targeting strategies, the molecular targets, and even the drug design.

Nonetheless, it is expected that shortly, some of the most promising targets will receive approval from regulatory agencies like the FDA and EMA, thus integrating into the arsenal available to clinicians. Such integration will enhance the outcomes and prognosis for patients with leukemia, particularly in the AML context.

Finally, it is crucial to continue expanding the therapeutic options in myeloid neoplasia by identifying novel BM microenvironmental components and elucidating their significance in leukemic cell expansion.

Author contributions

CS: Writing – original draft, Writing – review & editing. RC: Writing – original draft, Writing – review & editing. AA: Writing – review & editing. BC: Conceptualization, Funding acquisition, Investigation, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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