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Review Article

Bone Marrow Microenvironment Signalling and Chemoresistance in Acute Myeloid Leukemia

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Summary

Leukaemic blasts sheltering in the marrow niche survive chemotherapy that kills their circulating counterparts. The mechanism has been characterised in unusual detail, the drugs to disrupt it exist and are licensed for other purposes, and after two decades the clinical benefit remains unproven.

Objectives: To review the published evidence on bone marrow microenvironment signalling as a mediator of chemoresistance in acute myeloid leukaemia: which interactions confer protection, how they have been demonstrated, which have been targeted clinically, and why the translation has been slower than the biology predicted.

Material and Methods: Narrative review of mechanistic studies, preclinical models, early-phase trials and randomised evaluations indexed in PubMed and the major haematology journals. Studies were eligible if they characterised a marrow microenvironment interaction contributing to chemoresistance in acute leukaemia, or reported clinical evaluation of an agent targeting one. No new patient data were generated and no patients were recruited; every estimate quoted is one published by the original investigators.

Results: CXCR4 is overexpressed in 25 to 30 per cent of patients with acute myeloid leukaemia, and high expression is associated with poor prognosis. Its ligand CXCL12 is produced by marrow mesenchymal stromal cells and anchors blasts in contact with stroma and extracellular matrix, which generate growth-promoting and anti-apoptotic signals. Stromal co-culture confers chemoresistance in vitro and co-treatment with a CXCR4 antagonist restores chemosensitivity. In murine models, adding a CXCR4 antagonist to cytarabine reduced leukaemic burden and improved survival. Clinical translation has proceeded through a phase 1/2 chemosensitisation study in relapsed and refractory disease and, more recently, a randomised, double-blind, placebo-controlled phase 2 trial in which 128 patients in first remission received high-dose cytarabine with a selective CXCR4 antagonist or placebo.

Conclusion: The mechanism is well established and reproducible across models, and the therapeutic principle remains largely untested at scale. Two decades after the interaction was described, the randomised evidence amounts to a single phase 2 trial of 128 patients.

Abbreviations: AML – Acute Myeloid Leukaemia, ALL – Acute Lymphoblastic Leukaemia, BM – Bone Marrow, BMSC – Bone Marrow Stromal Cell, CXCR4 – CXC Chemokine Receptor 4, CXCL12 – CXC Motif Chemokine Ligand 12, SDF-1 – Stromal Cell-Derived Factor 1, VLA-4 – Very Late Antigen 4, VCAM-1 – Vascular Cell Adhesion Molecule 1, LSC – Leukaemic Stem Cell, MRD – Measurable Residual Disease, HSC – Haematopoietic Stem Cell, PDX – Patient-Derived Xenograft.

Keywords: Acute Myeloid Leukaemia; Bone Marrow Microenvironment; CXCR4; Chemoresistance; Leukaemic Niche

Introduction

Relapse after remission remains the principal cause of treatment failure in acute myeloid leukaemia, and the cells responsible survive therapy somewhere [1,2]. Interactions between leukaemic cells and the bone marrow microenvironment have been proposed as the explanation, with the niche acting as a sanctuary in which blasts receive survival signals unavailable in the circulation [3,4].

Leukaemic stem and progenitor cells anchored in the marrow do more than shelter there. They reprogramme the niche into a leukaemia-supporting and chemoprotective environment, altering the stromal compartment rather than merely occupying it [5,6]. The same

architecture that maintains normal haematopoietic stem cells is co-opted [4,7].

The best-characterised mediator of that interaction is the chemokine receptor CXCR4 and its ligand CXCL12, also known as stromal cell-derived factor 1 alpha [3,8]. Antagonists of this axis exist and one is licensed for stem cell mobilisation, which made the therapeutic hypothesis unusually testable: disrupt the anchorage, mobilise the blasts into circulation, and expose them to chemotherapy [9,10].

This review sets out which interactions confer chemoresistance, how they were demonstrated, what clinical testing has been done, and why the translation has been slower than the mechanistic evidence would suggest.

Material and Methods

Search strategy: PubMed and the archives of the major haematology journals were searched for studies of the marrow microenvironment in leukaemia. Search terms combined acute myeloid leukaemia with bone marrow microenvironment, niche, CXCR4, CXCL12, stromal cell, chemoresistance, cell adhesion-mediated drug resistance, plerixafor and mobilisation. Reference lists of retrieved mechanistic studies and trials were screened by hand.

Eligibility: Studies were included if they characterised a marrow microenvironment interaction contributing to chemoresistance in acute leukaemia, or reported clinical evaluation of an agent targeting such an interaction. Studies in acute lymphoblastic leukaemia are cited where they establish a shared mechanism and are identified as such. Preclinical and clinical evidence are distinguished throughout.

Data extraction and handling: Model system, cell source, agent, comparator and reported outcome were extracted as published. Whether a finding derives from cell line co-culture, primary patient samples, a murine model or a clinical trial is stated in every case, because the central question in this field is how far the mechanistic evidence transfers. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 3 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

The principal axis and how many patients it applies to: CXCL12 is produced constitutively by marrow mesenchymal stromal cells and binds CXCR4 on leukaemic cells, facilitating trafficking and homing into the marrow and keeping blasts in close contact with stroma and extracellular matrix that generate growth-promoting and anti-apoptotic signals [3,8]. CXCR4 is a G-protein coupled receptor also expressed on normal haematopoietic stem cells, and the axis is the principal mediator of their homing as well [7,11].

The receptor is overexpressed in 25 to 30 per cent of patients with acute myeloid leukaemia (Figure 1), and a high level of CXCR4 on blasts is associated with poor prognosis [3,12]. Downstream signalling engages several pathways including members of the Src family of non-receptor tyrosine kinases, one of which has been implicated specifically in the crosstalk between leukaemic cells and the niche [6].

The distinction between homing and retention matters for how the axis is targeted. Dependence of human stem cell engraftment on CXCR4 was established in xenograft models before its role in leukaemia was characterised [7], and rapid mobilisation of both murine and human progenitors by antagonism was demonstrated shortly afterwards [11]. The leukaemic application borrowed a mechanism already well described in normal haematopoiesis.

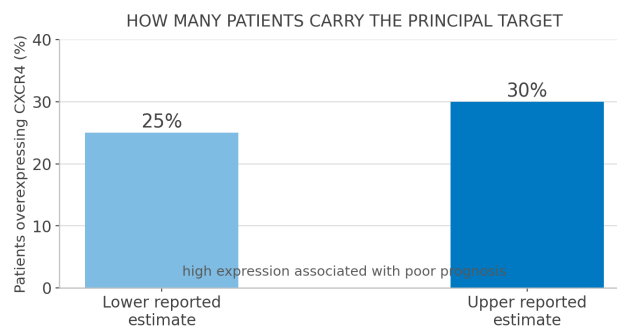


Figure 1: Reported prevalence of CXCR4 overexpression in acute myeloid leukaemia [3,12]

How protection was demonstrated: The core experiment is simple and has been repeated across laboratories. Leukaemic cells co-cultured with marrow stromal cells survive chemotherapy that kills the same cells cultured alone, and adding a CXCR4 antagonist to the co-culture restores chemosensitivity [13,14]. The protection is therefore attributable to the interaction rather than to an intrinsic property of the leukaemic cells.

Work in infant lymphoblastic leukaemia carrying KMT2A rearrangement extended the finding in an informative direction. Stromal co-culture conferred chemoresistance and a CXCR4 antagonist reversed it, and the same group showed that leukaemic cells respond to chemotherapy by upregulating CXCR4, priming themselves to answer stromal CXCL12 [13]. Treatment itself drives cells toward the sanctuary.

In murine models the effect translated. Adding a CXCR4 antagonist to cytarabine in a model of acute promyelocytic leukaemia decreased leukaemic burden and improved overall survival against cytarabine alone [11,15], and CXCR4 inhibition overcame resistance to both kinase inhibitors and chemotherapy in leukaemia models [14]. An antibody antagonist reduced leukaemia development in two patient-derived xenograft models differing in CXCR4 expression, and secondary transplantation showed

leukaemic progenitors had also been targeted [12].

Study	System	Intervention	Principal reported finding
Nervi et al. 2009 [9]	Murine	AMD3100	Chemosensitisation following mobilisation
Zeng et al. 2009 [14]	Preclinical	CXCR4 inhibition	Overcomes resistance to chemotherapy and kinase inhibitors
Uy et al. 2012 [10]	Clinical	Plerixafor with MEC	Phase 1/2 chemosensitisation in relapsed disease
Sison et al. [13]	Co-culture	Plerixafor	Chemotherapy upregulates CXCR4 on leukaemic cells
Kuhne et al. 2013 [12]	Xenograft	Antibody antagonist	Reduced leukaemia in high and low expressing models
Randomised trial [16]	Clinical	Motixafortide	128 patients in first remission randomised

Table 1: Principal studies reviewed, with system studied and the finding as reported by the original investigators

What else the niche provides: CXCR4 is the best studied axis but not the only one. Very late antigen 4 binding to vascular cell adhesion molecule 1 mediates adhesion-dependent survival signalling, and E-selectin on marrow endothelium provides a further anchoring interaction; agents against both have entered clinical evaluation alongside hypoxia-activated compounds (Figure 2) [4,17].

Imaging has added a dimension that static assays cannot. Intravital two-photon microscopy of murine calvarial marrow showed that leukaemic cells are migratory, and that chemoresistant myeloid leukaemia cells become less motile rather than more, in contrast to T-lymphoblastic cells studied as a benchmark [18]. Resistance is associated with settling rather than with active evasion.

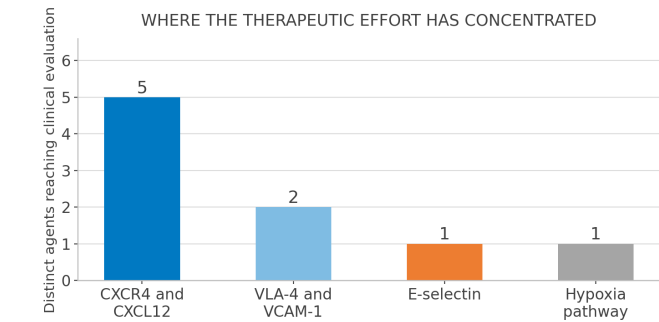


Figure 2: Interactions targeted by agents reaching clinical evaluation [4,17]

What has been tested in patients: The therapeutic hypothesis was first taken into patients through mobilisation. Disruption of leukaemia-stroma interaction with a CXCR4 antagonist produced

massive mobilisation of leukaemic cells into the circulation, and that observation supported the proposal that microenvironment-mediated resistance could be abolished [9,10]. A phase 1/2 study combined plerixafor with salvage chemotherapy in relapsed and refractory disease [10].

More recently the concept reached randomised evaluation. In a double-blind, placebo-controlled phase 2 trial, 128 patients in first remission received high-dose cytarabine with either the selective CXCR4 antagonist motixafortide or placebo, with residual disease measured at single-cell resolution alongside clinical outcome (Figure 3) [16].

Several other antagonists have entered development for either stem cell mobilisation or tumour sensitisation, and an antibody-based approach with additional Fc-mediated cytotoxicity has been characterised preclinically [4,12]. Peptide antagonists designed to interfere with the axis have also been synthesised and tested in vitro [19].

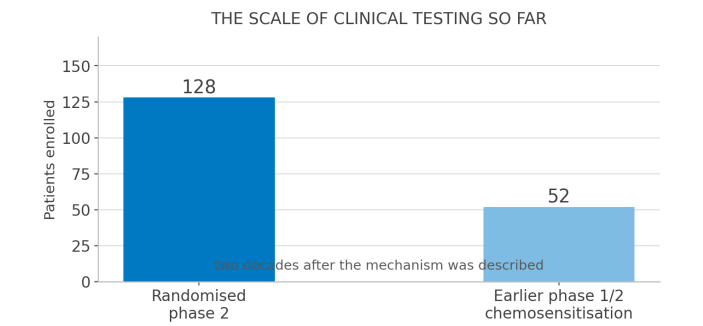


Figure 3: Scale of clinical evaluation of CXCR4 antagonism in this indication [10,16]

Interaction	Mechanism	Stage of evaluation
CXCR4 and CXCL12	Anchors blasts to stroma; anti-apoptotic signalling	Randomised phase 2 [16]
VLA-4 and VCAM-1	Adhesion-mediated survival signalling	Early clinical [4,17]
E-selectin	Endothelial anchoring	Early clinical [4,17]
Hypoxia pathway	Niche oxygen gradient	Early clinical [4]

Table 2: Niche interactions targeted therapeutically and how far each has been evaluated

Where the resistant cells actually sit: Anatomical work localised the problem. Chemotherapy-resistant human leukaemic stem cells were shown to home to and engraft within the endosteal region of the marrow, a specific compartment rather than the marrow generally [20]. That finding gave the sanctuary hypothesis a physical address and made targeting it a coherent proposition.

Adhesion contributes independently of chemokine signalling. Interaction between leukaemic VLA-4 and stromal fibronectin was identified as a decisive determinant of residual disease [21], and reciprocal VCAM-1-dependent activation of NF-kappaB between leukaemia and stroma mediates chemoresistance through a distinct pathway [22]. Two mechanisms operating in parallel is the simplest explanation for why blocking one has produced limited benefit.

The niche also supplies metabolic support directly. Marrow stromal cells transfer mitochondria to leukaemic cells during chemotherapy, and that transfer is protective [23]. A cell receiving functional organelles from its surroundings is being sustained in a way that no chemokine antagonist addresses.

How the target population might be identified: If niche protection matters most for the cells that survive treatment, then residual disease measurement is the natural readout, and it is well standardised in this disease [25]. Leukaemic stem cell frequency measured by flow cytometry at diagnosis independently predicts outcome [24], which offers a candidate enrichment criterion that no trial has yet used.

The randomised trial paired antagonism with single-cell residual disease assessment, which is the right instinct: an intervention aimed at the cells that survive should be evaluated against a measure of those cells rather than against remission rate alone [16,25].

Protective mechanism	Evidence	Addressed by CXCR4 blockade?
Chemokine anchoring	Co-culture and murine models [9,13,14]	Yes [9,16]
Endosteal localisation	Xenograft homing studies [20]	Partly [9,20]
Integrin adhesion	VLA-4 and fibronectin [21,22]	No [21,22]
Mitochondrial transfer	Stromal co-culture [23]	No [23]
Quiescent phenotype	Intravital imaging [18]	Unlikely [18]

Table 3: Protective mechanisms attributed to the niche and whether chemokine blockade addresses each

Discussion

The mechanistic case is as strong as such cases get. Stromal co-culture confers chemoresistance, a specific antagonist reverses it, the effect reproduces across laboratories and cell sources, murine models show survival benefit, and patient-derived xenografts confirm that leukaemic progenitors are affected [11,12,13,14]. Chemotherapy itself upregulates the receptor, which supplies a rationale for combining rather than sequencing [13].

Set against that, the clinical evidence is a phase 1/2 study and one randomised phase 2 trial of 128 patients, roughly two decades after

the interaction was described [9,10,16]. That is a striking imbalance between mechanistic confidence and clinical testing, and it deserves explanation rather than restatement.

Why translation has been slow

Three plausible reasons can be distinguished from the literature. The first is that mobilisation is a double-edged intervention: releasing blasts into the circulation exposes them to chemotherapy but also disperses them, and the same axis governs normal stem cell retention, so the therapeutic window is narrow [7,9,11].

The second is that the niche is redundant. If VLA-4, E-selectin and hypoxia each contribute independently, blocking CXCR4 alone may leave sufficient protection intact, which would predict exactly the modest clinical signal observed [4,17]. The third is trial design: chemosensitisation is difficult to demonstrate without a randomised comparison, and until recently none existed [10,16].

What the imaging finding implies

That chemoresistant myeloid leukaemia cells become less motile is not what a simple sanctuary model predicts [18]. A cell actively trafficking to a protected site should remain mobile; a cell that has settled and reduced its metabolic activity looks more like quiescence than like homing.

If resistance is partly a quiescent state rather than only a location, then mobilising cells out of the niche may not be sufficient, because the resistant phenotype travels with them. That reading would explain why an intervention that demonstrably achieves its proximate endpoint, mobilisation, has not straightforwardly produced its distal one [9,18].

Study limitations

The limitations belong to the underlying literature. Most evidence derives from cell line co-culture and murine models, and stromal cell lines do not reproduce the cellular complexity of human marrow [4,13,14]. Patient-derived xenografts improve on this but engraft in a murine niche, so the interaction being studied is cross-species [12]. Intravital imaging is confined to calvarial marrow, which may not represent long bones [18]. Clinical evaluation is limited to one phase 1/2 study and a single randomised phase 2 trial, and the latter enrolled patients already in remission rather than at diagnosis [10,16]. And CXCR4 expression is measured by different methods across studies with no agreed threshold for high expression, which affects the 25 to 30 per cent figure [3,12].

Two gaps deserve naming. No trial has tested combined blockade of more than one niche interaction, which is what the redundancy hypothesis would require [4,17]. And no study reviewed here reports whether patients selected for high CXCR4 expression benefit more from antagonism than unselected patients, which is the obvious enrichment strategy [3,12,16].

Conclusion

The bone marrow microenvironment protects leukaemic cells from chemotherapy through interactions that have been characterised in unusual mechanistic detail. CXCR4 is overexpressed in 25 to 30 per cent of patients and high expression predicts poor outcome; its ligand anchors blasts against stroma that supplies anti-apoptotic signalling; stromal co-culture confers chemoresistance that a CXCR4 antagonist reverses; and murine models show reduced leukaemic burden and improved survival when an antagonist is added to cytarabine. Chemotherapy upregulates the receptor, driving cells toward the sanctuary. Against all of that, clinical evaluation amounts to a phase 1/2 study and one randomised phase 2 trial of 128 patients. The most useful next step is not further mechanistic characterisation but a trial testing whether blocking more than one niche interaction achieves what blocking one has not.

The redundancy argument is testable and specific. Chemokine anchoring, integrin adhesion and mitochondrial transfer have each been shown to protect leukaemic cells, and only the first is addressed by the agents evaluated so far [21,22,23]. If protection is genuinely multiply redundant, a single-axis antagonist would be expected to produce exactly the modest signal that has been observed.

Enrichment offers a second route. Selecting patients by CXCR4 expression or by leukaemic stem cell frequency at diagnosis would concentrate any effect in those most likely to show it, and both measures are available and standardised [12,24,25]. Neither has been used to select for a trial, which given a target present in only a quarter to a third of patients is a notable omission [3].

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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