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REVIEW

Advances in stem cell mobilization

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ABSTRACT

Use of granulocyte colony stimulating factor (G-CSF)-mobilized peripheral blood hematopoietic progenitor cells (HPCs) has largely replaced bone marrow (BM) as a source of stem cells for both autologous and allogeneic cell transplantation. With G-CSF alone, up to 35% of patients are unable to mobilize sufficient numbers of CD34 cells/kg to ensure successful and consistent multi-lineage engraftment and sustained hematopoietic recovery. To this end, research is ongoing to identify new agents or combinations which will lead to the most effective and efficient stem cell mobilization strategies, especially in those patients who are at risk for mobilization failure. We describe both established agents and novel strategies at various stages of development. The latter include but are not limited to drugs that target the SDF-1/CXCR4 axis, S1P agonists, VCAM/VLA-4 inhibitors, parathyroid hormone, proteosome inhibitors, Groβ, and agents that stabilize HIF. While none of the novel agents have yet gained an established role in HPC mobilization in clinical practice, many early studies exploring these new pathways show promising results and warrant further investigation.

1. Introduction

Hematopoietic cell transplantation is an important and often life-saving treatment for many hematological malignancies and select solid tumors as means of reconstitution of blood cells following high dose chemotherapy [1–5]. Use of granulocyte colony stimulating factor (G-CSF)-mobilized peripheral blood stem cells (PBSCs) has largely replaced bone marrow (BM) as a source of stem cells for both autologous and allogeneic cell transplantation. In spite of the increased number of CD34+ stem cells obtained after G-CSF mobilization compared to BM harvests, one still needs to obtain a minimum number of CD34/kg ($\sim \geq 2 \times 10^6$) to ensure successful and consistent multi-lineage engraftment and sustained hematopoietic recovery.

The dose of CD34+ cells infused is an important predictor of both neutrophil and platelet engraftment. For autologous stem cell transplantation (ASCT), an optimal CD34+ cell dose which leads to rapid and sustained recovery is thought to be $>5 \times 10^6$/kg [6,7]. On the other hand, 2×10^6 CD34+ cells/kg is accepted as the minimum threshold below which consistent and rapid multilineage engraftment, especially of platelets, may not take place.

For allogeneic stem cell transplants (AlloSCTs), a CD34+ cell dose $\geq 4.2–4.5 \times 10^6$/kg is associated with improved overall survival in the matched unrelated donor setting, without increased risk of acute or chronic graft vs. host disease (GVHD), while higher doses ($>8–14 \times 10^6$ cells/kg) have been associated with increased risk of GVHD [8,9]. Likewise, higher CD34+ cell doses ($>9.1 \times 10^6$) have also been associated with increased risk of chronic GVHD after reduced intensity AlloSCT from HLA-matched siblings [10].

The success of stem cell mobilization is also dependent on both the total dose and the type of chemotherapy as well as radiation administered prior to autologous stem cell collection (Table 1). Studies have identified multiple chemotherapeutic agents which increase the risk of poor stem cell mobilization, including melphalan [11], lenalidomide [12,13], fludarabine [14,15], chlorambucil [16], carmustine [17], hyper-CVAD [18] and DHAP [19].

A limited BM reserve indicated by a low platelet count prior to mobilization [20–23], low bone marrow cellularity [20], baseline low peripheral blood CD34+ numbers [24], and age [25] are other risk factors for poor PBSC mobilization. Diabetes mellitus and impaired glucose tolerance have recently been identified as independent risk factors for poor mobilization [26–28]. The mechanisms underlying these observations remain enigmatic but are thought to be related to a baseline low peripheral CD34+ cell count in these patients [27] and direct alteration of the hematopoietic niche via a sympathetic denervation syndrome associated with diabetes mellitus [28].

2. Bone marrow niche

The BM niche is a highly organized microenvironment which anchors HSCs and regulates their self-renewal, proliferation and trafficking (Fig. 1). Structurally, the niche is formed by supporting cells that engage in direct cell–cell interaction with stem cells and provide chemical signals that support their survival [29,30].

The niche has been subdivided into vascular and endosteal compartments. Within the vascular niche, sinusoidal endothelial cells and

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Table 1
Clinical factors that hinder stem cell mobilization.

Risk factor	Postulated mechanism	References
Increasing age	Age-related reduced HSC reserve	[20,25]
Low BM cellularity	Reflects low HSC reserve	[20]
Low baseline platelet count	Reflects low HSC reserve	[20–23]
Prior chemotherapy	Direct toxicity to HSCs and BM niche	[12–19]
Prior radiation therapy	Direct toxicity to HSCs and BM niche	[11]
Diabetes mellitus/Impaired glucose tolerance	Possible direct alteration of the hematopoietic niche via sympathetic denervation; baseline low peripheral CD34+ cell count.	[26–28]

Abbreviations: HSC, hematopoietic stem cell; BM, bone marrow.

nestin$^+$ mesenchymal stem cells (MSCs) express adhesion molecules such as vascular cellular adhesion molecule 1 (VCAM-1), which binds to HSC receptor α4β1, and stem cell factor (SCF), which binds c-kit on HSC surface. Depletion of nestin$^+$ MSCs increases mobilization of bone marrow HSC toward extramedullary sites and decreases homing of the PBSC to the BM [31]. Nestin + MSCs within the vascular niche associate closely with the adrenergic fibers of the sympathetic nervous system (SNS). Release of SNS neurotransmitters induces metalloproteinase MT1-MMP expression and MMP-2 activity [32], which then mediate the cleavage of important tethers (CXCR4, VLA4, VCAM-1, SCF) holding the HSC in the BM niche, thus promoting HSC egress from the bone marrow [33–35].

In addition to these interactions, the binding of stromal derived factor-1 (SDF-1, also known as CXCL-12) to its receptor (CXCR4) on HSC plays a key role in the HSC retention within the bone marrow [36]. SDF-1 is produced predominantly by reticular cells termed CXCL-12 abundant reticular cells (CARs) [37] but also by nestin$^+$ MSCs and osteoblasts [38].

The endosteal niche is located closer to the trabecular or cortical bone and is composed of osteoblasts and osteoclasts. Osteoblasts produce several factors, including angiopoetin 1 (Ang-1), which promotes tight adhesion of HSCs to the niche [39], and thrombopoietin (TPO), which has been shown to mediate HSC quiescence [40]. Recent studies have also described the importance of niche macrophages in the expression of various HSC retention factors, including CXCL-12 [41–43].

HSC maintenance, proliferation, differentiation, and egress is a balanced process achieved through tight homeostatic neural and hormonal regulation. The release of progenitor cells from the bone marrow to the peripheral blood occurs constitutively at a very low level [44] but is amplified at times of stress [45].

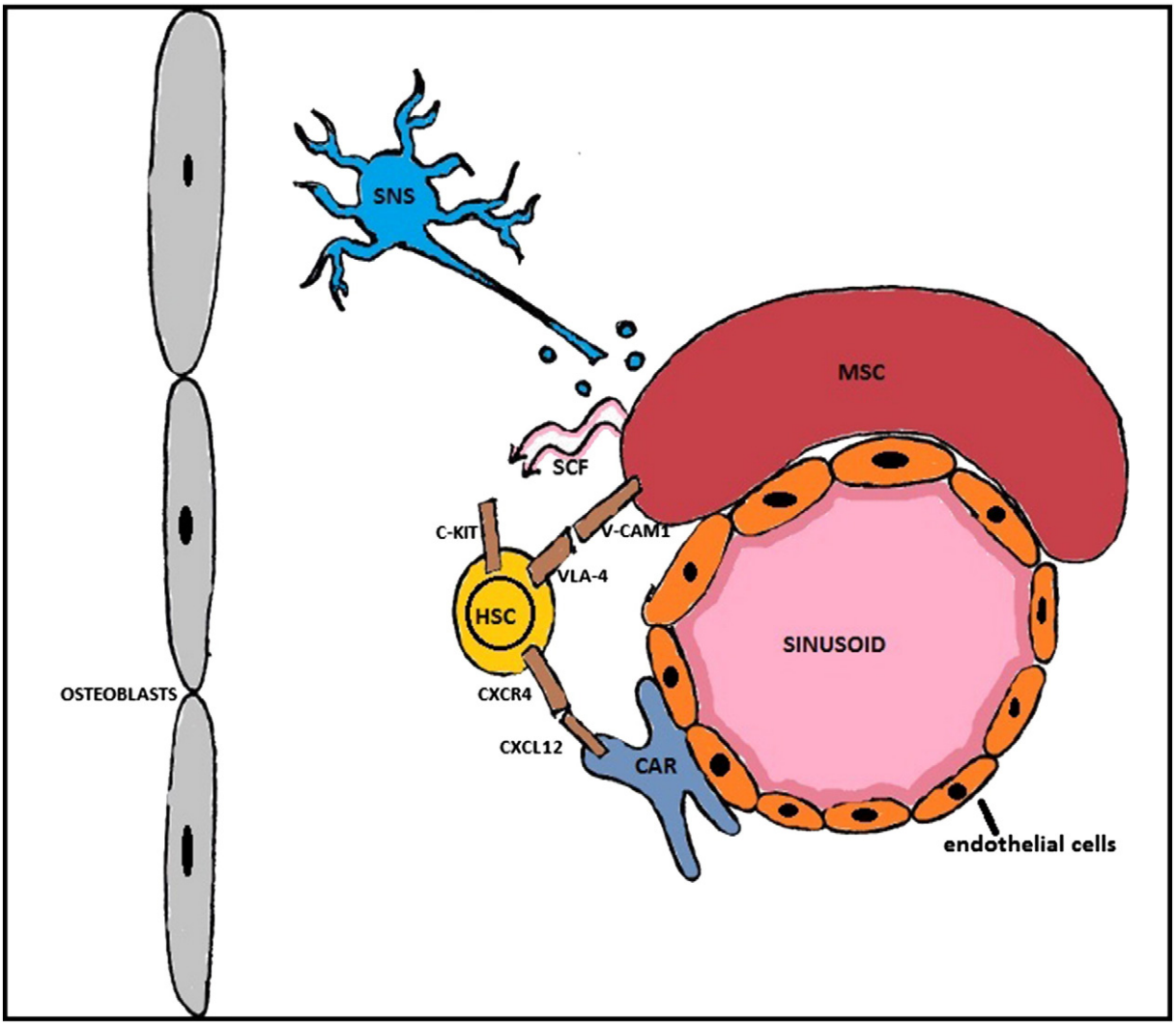

Fig. 1. Bone marrow niche. Abbreviations: CAR: CXCL12 abundant reticular cells; HSC: hematopoietic stem cell; MSC: mesenchymal stem cell; SCF: stem cell factor; SNS: sympathetic nervous system; V-CAM1: vascular cellular adhesion molecule 1; VLA-4: very late antigen-4.