Diabetic stem-cell "mobilopathy"

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Hematopoietic stem-cell (HSC) transplantation remains the primary curative treatment for patients with a variety of hematologic cancers. Transplantation of either autologous or allogeneic stem cells requires the acquisition of sufficient numbers of HSCs to ensure rapid and consistent trilineage engraftment, thus minimizing extended periods of pancytopenia after transplantation. Methods to optimize peripheralization of HSCs boost the number of HSCs that can be obtained for transplantation. These methods are based on the use of either cytokines alone (granulocyte colony-stimulating factor [G-CSF] or granulocyte–macrophage colony-stimulating factor [GM-CSF]) or cytokines plus chemotherapy to induce effective egress of HSCs from the bone marrow into the peripheral blood, where they can be collected by means of apheresis. HSCs express CD34 and can thereby be captured and measured by means of flow cytometry.

G-CSF and GM-CSF have been approved by the Food and Drug Administration for autologous and allogeneic stem-cell mobilization, but administration of these cytokines with or without chemotherapy may still result in failure to mobilize sufficient numbers of cells for stem-cell transplantation. A disease state caused by failure to mobilize (“mobilopathy”) results not only in additional cost but also in increased morbidity and even the loss of transplantation as a curative option for some patients. Recently, plerixafor (also called AMD3100), a small-molecule inhibitor of the CXC chemokine receptor 4 (CXCR4)–CXCL12 axis, was approved for stem-cell mobilization and has resulted in a modest reduction in failure rates when combined with G-CSF in patients with myeloma and lymphoma. G-CSF mediates the profound loss of CXCL12-positive osteoblasts and the down-regulation of CXCL12 expressed by nestin-expressing CXCL12-positive abundant reticular and mesenchymal cells. These nestin-positive, CXCL12-positive abundant reticular cells, which in part define the vascular niche, are scattered throughout the marrow but primarily localize adjacent to the vascular sinusoids and are innervated directly and indirectly by β-adrenergic sympathetic nerves. G-CSF induces mobilization of HSCs from the endosteal and vascular niches through its direct effects on certain macrophages and β-adrenergic sympathetic nerves, resulting in the loss of osteoblasts and dramatic down-regulation of CXCL12 in the osteoblasts that remain and in nestin-positive, CXCL12-positive abundant reticular cells. G-CSF also triggers the release of putative and as yet unknown proteases that cleave the multiple tethers (such as CXCL12–CXCR4) that hold the HSCs in these niches. Most HSCs are located in close proximity to nestin-positive, CXCL12-positive abundant reti-
Figure 1. Hematopoietic Stem-Cell Mobilization in the Bone Marrow of Patients with Diabetes.

The bone marrow niche consists of two major elements. The first element is the osteoblastic niche. Osteoblasts express moderate levels of CXCL12 (pink) and bind hematopoietic stem cells (blue circles) that are primarily quiescent. The second element is the vascular niche, which is composed of vascular sinuses; lining endothelial cells; nestin-positive, CXCL12-positive abundant reticular (CAR) cells; β3-adrenergic receptors expressed on CAR cells; sympathetic neurons; and abundant hematopoietic stem cells. As shown in Panel A, the bone marrow microenvironment in patients with diabetes has increased numbers of quiescent hematopoietic stem cells (blue circles) and cycling hematopoietic stem cells (conjoined blue forms) and reduced numbers of osteoblasts and increased numbers of sympathetic neurons and β3-adrenergic receptors. As shown in Panel B, granulocyte colony-stimulating factor depletes osteoblasts and reduces CXCL12 expression in both osteoblasts and CAR cells, resulting in transmigration of hematopoietic stem cells into the vascular sinuses (peripheral circulation). Granulocyte colony-stimulating factor induces a similar reduction of osteoblasts and CXCL12 expression in osteoblasts (white) but no reduction of CXCL12 expression (red) in the marrow of patients with diabetes as compared with normal marrow, resulting in a reduction in transmigration and mobilization of hematopoietic stem cells associated with CAR cells into the vascular sinuses (peripheral circulation).
ticular cells that may, possibly through interaction with CXCL12, maintain the quiescence and stem-cell–like characteristics of HSCs.

Ferraro et al.\(^3\) recently reported that diabetes is a disease that both interrupts the dynamic anatomy of the niche and induces HSC-independent and bone marrow microenvironment–dependent defects in G-CSF–induced HSC mobilization. They first showed, in a small and highly selected cohort of patients undergoing autologous transplantation, that elevated blood glucose and glycated hemoglobin levels are more common in patients in whom HSCs failed to mobilize into the peripheral-blood system. They next observed impaired G-CSF–induced HSC mobilization in mouse models of diabetes. Although the total number and percentages of long-term HSCs in the bone marrow of streptozocin-treated mice (a mouse model of diabetes) were elevated as compared with those of untreated mice, there was no commensurate elevation in levels of circulating HSCs — suggesting a defect in the trafficking of HSCs out of the bone marrow at rest. The preference of HSCs for the bone marrow in mice with diabetes was lost when they were transplanted into healthy mice, further demonstrating that the defect was not HSC-intrinsic but rather was due to the altered bone marrow microenvironment of mice with diabetes.

Consistent with these findings was the observation by Ferraro et al. that normal HSCs homed to the marrow more rapidly and proliferated (in the marrow) more vigorously when injected into mice with diabetes as compared with the behaviors of these cells in healthy mice. Treatment of healthy mice with G-CSF resulted in the expected loss of osteoblasts and in CXCL12 expression in osteoblasts and nestin-positive, CXCL12-positive abundant reticular cells, commensurate with vigorous HSC mobilization. In contrast, treatment of diabetic mice with G-CSF resulted in an expected loss of osteoblasts and down-regulation of CXCL12 expression by osteoblasts, but no change in the expression of CXCL12 by nestin-positive, CXCL12-positive abundant reticular cells, resulting in a dramatic reduction in G-CSF–mediated HSC mobilization (Fig. 1B).

Defects in HSC mobilization after treatment of mice with β\(_3\)-adrenergic receptor agonists as well as studies showing that genetic depletion of osteoblasts in mice with diabetes resulted in complete elimination of any residual mobilization induced by G-CSF all support the authors’ hypothesis that altered G-CSF–induced mobilization in mice with diabetes was due to a defect in the activation of the sympathetic nervous system (in spite of increased numbers of sympathetic nerve fibers in the bone marrow of mice with diabetes). This defect results in a functional blockade of G-CSF–induced down-regulation of CXCL12 in nestin-positive, CXCL12-positive abundant reticular cells, the major CXCL12–expressing resident cells of the vascular niche. The authors suggest that this defect could be overcome with the use of plerixafor with or without G-CSF. Since plerixafor is a weaker mobilizing agent than G-CSF, it is possible but unlikely that it can mediate the successful stem-cell mobilization in the patients with diabetes in whom stem cells fail to mobilize after the administration of G-CSF alone. Only future prospective clinical trials can answer this question.

One can only assume that many groups will now look closely at larger and less selected cohorts of both patients and healthy donors to see whether this preclinical observation holds up clinically. If it does, the use of alternative and optimal mobilization approaches (G-CSF plus plerixafor or G-CSF plus chemotherapy) could be used as early treatment in patients with diabetes to limit the odds of mobilization failure and the number of patients requiring second mobilizations or allogeneic stem-cell transplantation for potentially curative therapy.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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