

therapy with cladribine, the variability in time to relapse illustrates the necessity to clearly identify those patients potentially requiring more therapy than a single course of this highly effective agent.

This paper also shows the difference in response duration and survival between those achieving a complete remission vs a partial remission following a single course of therapy. These observations highlight the potential advantage of characterizing the quality of bone marrow response achieved following cladribine therapy. As this report shows, patients who relapse have a high salvage rate for second remission. The durability of subsequent remissions declines with repeated therapies. Although current salvage therapy with cladribine is highly effective in achieving a second remission following relapse, optimizing therapy for young patients with this disease in the future will require identification of those at highest risk for early relapse. These individuals may benefit from novel therapy either with combined chemoimmunotherapy or the evaluation of newer agents (eg, specific immunotoxin conjugates, inhibitors of BRAFV600E, or experimental agents directed at targets uniquely expressed in the malignant cells).^{7,8} The introduction of these novel therapies for high-risk younger patients should be conducted in a carefully designed clinical trial rather than being randomly explored in clinical practice.

Despite a commonly held belief that this disease has been “conquered,” there are many unanswered questions deserving of further study.⁹ This disease affords opportunities to explore the biology and importance of minimal residual disease. The bone marrow microenvironment is under investigation in other forms of chronic leukemia as a potential source impacting the ultimate survival of leukemia cells. The substantial variability of response duration in hairy cell leukemia suggests that genomic profiling of the leukemic cells and further exploration of the microenvironment in the bone marrow and spleen may provide a better understanding of relapse and potential improvement in outcome.¹⁰

This study has tremendous value in providing the outcome of a closely followed cohort of younger patients treated in a center with extensive experience with this agent. Although initial studies with cladribine

excluded patients with active infection, there is a need to define how best to approach patients with an active infection who require therapy for their leukemia. Continued surveillance of secondary malignancies will also be important. Considering the prevalence of BRAFV600E mutations in malignant melanoma and thyroid cancer, the finding of this same signature mutation in this rare leukemia would warrant additional epidemiologic studies to understand the relationship of these findings. Exploring novel therapies based upon prognostic subsets, defining optimal management of the infectious and immune-based complications inherent in this disease, and attempting to provide guidance for these complicated patients will require interinstitutional collaborative studies. While the group at Scripps has accumulated enormous experience with this rare disease, this report represents the culmination of 20+ years of follow-up on 88 young patients. Recently, efforts have been made to establish a network of international institutions with special interest in this disease. The Hairy Cell Leukemia Foundation will strive to address questions that will ultimately expedite the development of new therapeutic strategies. Rosenberg and colleagues have made great progress toward improving the quality and quantity of life for patients with this disease. The dramatic responses observed with cladribine inspire the collective institutions dedicated to improving the outcome of these patients by continuing work to ultimately achieve a more durable remission for these young patients seeking a cure rather than control.

Conflict-of-interest disclosure: Dr Grever is a member of the Hairy Cell Leukemia Foundation, an entity mentioned in this commentary. He serves on the Advisory Board and receives no compensation. ■

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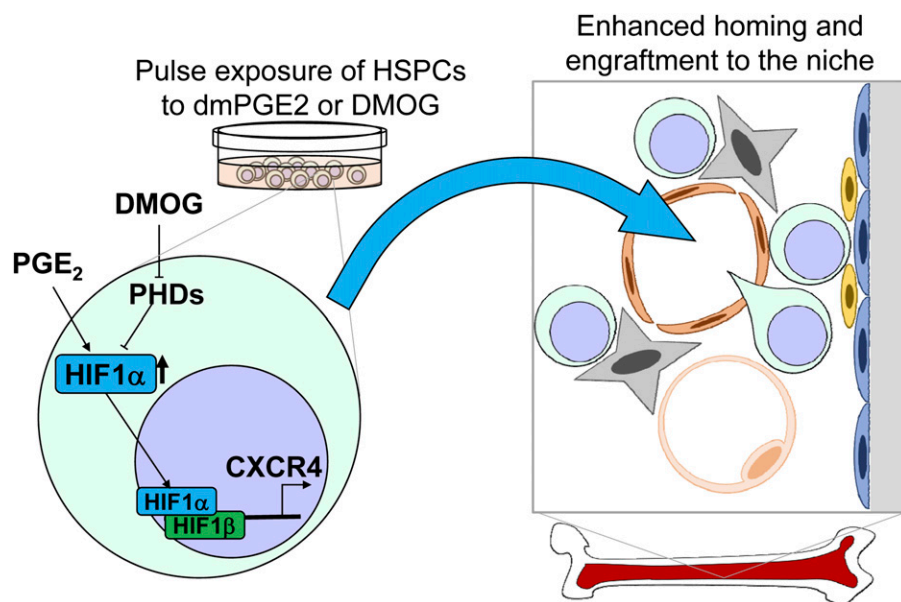
Opening the door for HIF1 α tuning

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In this issue of *Blood*, Speth et al identify the beneficial effects of a pharmacologic stabilizer of hypoxia-inducible factor-1 α (HIF1 α) for the efficient trafficking of hematopoietic stem and progenitor cells (HSPCs) to the bone marrow niche.¹

Bone marrow transplantation is an effective therapy for various hematologic diseases. However, insufficient numbers of

transplanted hematopoietic stem cells (HSCs) can result in failure of engraftment. Thus, it has long been a dream to robustly enhance



Scheme depicting the effect of HIF1 α on HSPC trafficking during transplantation. Ex vivo treatment of HSPCs with PGE₂ or hypoxia-inducible factor prolyl-hydroxylase inhibitor (DMOG) stabilizes HIF1 α protein. Stabilized HIF1 α translocates to the nucleus with the oxygen-independent subunit HIF1 β to transactivate CXCR4 expression and enhance the homing and engraftment of HSPC to the niche.

the homing efficiency of transplanted HSCs to the bone marrow microenvironment (hematopoietic niche).

Recently, a long-acting prostaglandin E₂ (PGE₂) analog, 16-16 dimethyl PGE₂ (dmPGE₂), was identified as a proliferative agent for HSPCs in a teleost chemical screening. Ex vivo treatment of dmPGE₂ enhanced bone marrow engraftment of HSPCs in murine and nonhuman primate models.^{2,3} The report clearly showed that the PGE₂-guided increase in the homing, survival, and proliferation of HSPCs was at least in part due to enhanced CXCR4 expression⁴; however, the molecular mechanisms underlying these observations remained unclear.

HSCs are maintained in a hypoxic state in which stabilization of the HIF1 α protein governs cell-cycle and metabolic properties.^{5,6} HIF1 α is known to upregulate the expression of CXCR4, an essential receptor for chemokine SDF-1 that not only enhances HSPC retention and homing to the niche but also maintains HSC cell-cycle quiescence (see figure).⁷

Speth et al¹ found that pulse exposure of dmPGE₂ stabilizes HIF1 α in HSPCs. The degree of the stabilization of HIF1 α is comparable to the pulse exposure of DMOG, an inhibitor of hypoxia-inducible factor prolyl hydroxylase that promotes the ubiquitin-proteasomal degradation of HIF1 α protein under normoxic conditions. Pulse treatment

of DMOG increased CXCR4 expression through direct transcriptional activation of a hypoxia-response element on the CXCR4 promoter and enhanced the SDF-1-dependent migration in vitro. In addition, pulse treatment of DMOG enhanced HSPC homing to the niche and improved peripheral blood chimerism after transplantation without alterations in lineage differentiation. The effect of dmPGE₂ on HSPC trafficking was shown to be mediated by the HIF1 α -CXCR4 pathway, because the enhanced homing and CXCR4 expression by dmPGE₂ was clearly cancelled by pharmacologic HIF inhibition or genetic HIF1 α deficiency.

The indication of a PGE₂-HIF1 α -CXCR4 axis demonstrates a crucial mechanism through which low oxygen tension affects HSC function during transplantation. Recent evidence suggests that HSCs maintain their hypoxic state independently of their bone marrow location.⁸ Isolation of HSPCs from their original hypoxic bone marrow microenvironment may downregulate HIF1 α protein expression necessary for efficient homing during transplantation. Thus, in addition to dmPGE₂ pulse exposure of HSPCs, modulation of HIF1 α expression or activity may be a promising tool for better engraftment of HSCs.

Given the fact that the overstabilization of HIF1 α through homozygous deletion of an

E3 ubiquitin ligase for HIF1 α (VHL) or a prolyl hydroxylase for HIF (Phd2) or prolonged HIF stabilizer treatment resulted in the loss of transplantation capacity of HSPCs,^{5,9,10} optimization of HIF1 α stabilization through manipulation of these factors may be beneficial for improving human bone marrow transplantation.

The transcriptional regulation of the HIF1 α expression and stabilization is still under investigation. The work by Speth et al clearly identifies that fine-tuning of the HIF1 α dosage is a promising approach for improving stem cell transplantation. On the other hand, inhibition of HIF1 α is an interesting approach to enhance mobilization of HSCs. Because leukemic stem cells similarly reside in the niche in a quiescent state, techniques to modulate of HIF1 α levels may provide a tool for the elimination of these cells. This paper opens the door for the clinical use of HIF1 α regulation.

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