inhibit apoptosis. They also observed that Maraviroc treatment prevented reactive thrombocytosis in a mouse model of acute inflammation. Thus for the first time, Machlus et al demonstrate that a platelet-derived cytokine, CCL5, may have a direct stimulatory effect on platelet production by bone marrow MKs that induces a more rapid response than steady-state regulation via TPO (see figure, panel C).

This observation comes close on the heels of a recent report by Nishimura et al[9] describing the potent thrombopoietic effects of another inflammatory/immune modulator. Using in vivo 2-photon imaging of murine MKs, they characterized normal platelet production via shedding from proplatelets and then examined the effects of treatments that induced acute immune-mediated platelet loss (injection with anti-CD42b antibody) or acute inflammation (thioglycolate injection). Both treatments caused a rapid and dramatic increase in platelet production, largely attributed to the inducement of some MKs to undergo a previously unobserved mode of development dubbed "MK rupture." This process produces platelets that are larger than normal but otherwise fully functional (see figure, panel D). Via a series of in vitro and in vivo experiments, Nishimura et al demonstrated that MK rupture can be triggered by high circulating levels of IL-1α, which is released by many cell types (but is much less abundant than CCL5 in platelets) in response to damage and infective/inflammatory stress.[9]

The recent discoveries reported by Machlus et al and Nishimura et al provide novel insights into the potential of the thrombopoietic system to rapidly increase platelet production in response to physiologic stress. These newly revealed regulatory and developmental aspects contribute to a complex emerging picture of platelet production, and they also point to previously uncharacterized links to pathologic processes such as inflammation and infection that are likely to be highly relevant to understanding and treating platelet count fluctuations.

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● ● ● TRANSPLANTATION

Comment on Kanate et al, page 938

# Might haplo "be the (better) match"?

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In this issue of *Blood*, in a registry study by Kanate et al of reduced-intensity conditioning allogeneic blood or marrow transplantation (BMT) outcomes for lymphoma, HLA-haploidentical (haplo) transplantation with posttransplantation cyclophosphamide (PTCy) is associated with similar rates of relapse and survival as HLA-matched unrelated donor (MUD) transplantation but lower rates of grades III to IV acute and chronic graft-versus-host disease (GVHD).[1]

Just over 2 decades ago, haplo BMT was plagued by unacceptable rates of GVHD, graft failure, and nonrelapse mortality.[2] Therefore, MUDs were the major alternative donor source for the majority of patients who required BMT but lacked a matched sibling donor. However, modern approaches have facilitated haplo BMT, including T-cell–depleted "megadose" $CD34^+$ allografting, granulocyte colony-stimulating factor–primed T-cell–replete allografting with intensive pharmacologic GVHD prophylaxis, and T-cell–replete allografting with PTCy-based GVHD prophylaxis.[3] Over the last couple of years, a growing body of literature has emerged from multiple groups in the United States and Europe indicating that haplo BMT using PTCy results in outcomes on par with those using HLA-matched donors.[4-6] A recent comparison of BMT outcomes for acute myeloid leukemia showed equivalent survival but less acute and chronic GVHD for haplos with PTCy compared with MUD allografts.[6] In 2008, investigators at the Johns Hopkins Hospital and the Fred Hutchinson Cancer Research Center presented the first lymphoma-specific evidence suggesting that haplo BMT with PTCy results in outcomes comparable if not superior to those seen with MUD and matched related donors for patients with Hodgkin lymphoma.[7] However, a large-scale, lymphoma-specific study comparing haplo BMT with PTCy to other alternative donor platforms has not been performed until now.

Kanate et al present the outcomes of >900 reduced-intensity BMTs for Hodgkin and non-Hodgkin lymphoma, demonstrating that haplo BMT with PTCy results in lower rates of grades III to IV acute and chronic GVHD and similar rates of relapse, overall survival, and nonrelapse mortality compared with MUD platforms with or without antithymocyte globulin (ATG). Although there are inherent limitations of this registry study given its retrospective nature, including differences between cohorts in patient and disease characteristics, rates of prior autografting, and graft source (marrow vs peripheral blood), the study nonetheless serves as an informative comparison between 2 major alternative donor sources, as well as an analysis of the influence of ATG on MUD

BMT outcomes. ATG use among MUD BMTs did not significantly improve survival outcomes or reduce rates of acute GVHD, although chronic GVHD risk was reduced. Furthermore, MUD BMT with ATG was associated with higher risk of nonrelapse mortality, with many of these deaths due to infectious complications or GVHD. By contrast, death due to GVHD or infection among patients receiving haplo BMT with PTCy was rare. These findings further support previous work demonstrating the overall low toxicity of haplo BMT with PTCy, as well as its favorable performance in many regards compared with MUD BMT. The much higher percentage of non-Caucasian recipients in the haplo cohort illustrates the contrast between the limited donor options within the registry for minorities and the availability of haplo options for nearly every patient who requires BMT.

Despite the haplo cohort having higher disease risk index scores overall, which recent literature would suggest should correspond to inferior outcomes,[8] overall survival and relapse rates were comparable to those for both MUD BMT cohorts. These similar relapse rates suggest that graft-versus-lymphoma activity is not abrogated by the low rates of GVHD seen with PTCy.

Nonetheless, within both the haplo and MUD cohorts, relapse remained the major cause of treatment failure. BMT in its present form fails to cure a significant percentage of patients with lymphoma. However, the encouraging results with haplo donors presented by Kanate et al offer support for innovative future transplant studies in lymphoid malignancies. Low-toxicity approaches such as the PTCy platform are more conducive to the application of novel antilymphoma therapies, of which many have emerged in recent years. The low rates of GVHD, infection, posttransplantation lymphoproliferative disorder, and nonrelapse mortality with PTCy make treating post-BMT relapse a possibility for a greater percentage of patients.[3] Furthermore, donor selection factors other than degree of HLA match can be explored with the PTCy approach to try to improve outcomes for lymphoma patients requiring BMT.[9]

Although it once was important to "be the match," mounting evidence suggests that haplo BMT with PTCy is making transplant more accessible and less toxic while performing equally well in controlling lymphoma compared with MUD allografting. However, given that relapse remains a significant problem irrespective of the type of transplant, investigations integrating transplant with novel therapies, including monoclonal antibodies, small molecule inhibitors, immune checkpoint blockers, chimeric antigen receptor-modified T cells, and antigen-specific T cells, are urgently needed.[10]

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