benefit without improvements in OS must be considered carefully. This underscores the relevance of the associated MRD study to predict which patients may derive the most benefit from continuing potentially toxic therapy and alternatively those that may be able to cease therapy without compromising disease control.

In the LYMA trial, in contrast, patients were treated with 4 cycles of rituximab-dexamethasone, cytarabine and cisplatin (R-DHAP) followed by ASCT, and responders were randomized to either 3 years of maintenance rituximab or observation.[5] Maintenance rituximab resulted in superior OS compared with observation (4-year OS 88.7% vs 81.4%, P = .041) and did not result in substantial increases in toxicity compared with observation. Appropriate samples were available for MRD analysis in 220 patients from peripheral blood and/or bone marrow aspirate and assessed using a similar methodology to that used by Ferrero et al.[6] MRD status after R-DHAP (pre-ASCT) predicted PFS and OS, and maintenance rituximab improved PFS and OS irrespective of MRD status.[6] A similar patient-specific qualitative molecular MRD approach was built into the Nordic MCL2 study, in which patients treated with chemoimmunotherapy followed by ASCT underwent serial monitoring of peripheral blood and bone marrow aspirate.[7] In this trial, 78 of the 145 patients who underwent ASCT had a molecular marker and 36 developed molecular relapse: 10 of whom had concurrent clinical relapse, and 26 of whom underwent preemptive treatment leading in reinduction of molecular remission in 92% of patients.[8]

It is clear from the work of Ferrero et al and others that assessment of molecular MRD is improving our ability to predict outcome in patients with MCL. However, robust data to support changes in treatment approaches will only be possible if researchers continue to prospectively test MRD-guided decision strategies as a part of trial design as well as prioritizing samples for these critical associated correlative studies. With the potential for further novel, widely applicable and sensitive molecular MRD technologies in the future as well as ongoing trials evaluating well-tolerated and effective agents such as Bruton tyrosine kinase inhibitors, MRD-guided therapy in MCL has the potential to allow deescalation/intensification of therapy to deliver better outcomes for patients.

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TRANSPLANTATION

Comment on Zhu et al, page 1431

GVHD: pDCs providing VIP protection

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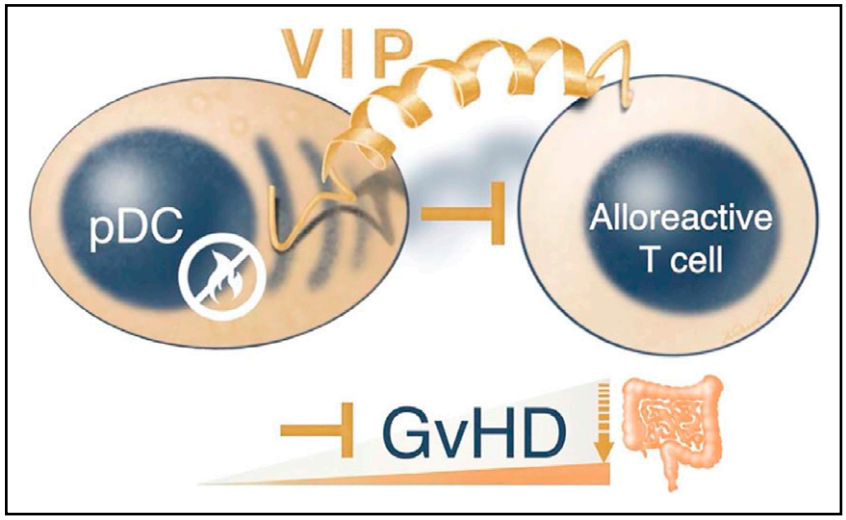
In this issue of *Blood*, Zhu et al[1] have identified vasoactive intestinal peptide (VIP) expression on plasmacytoid dendritic cells (pDCs) as an important mechanism that regulates the alloreactivity of allogeneic T cells and mitigates the severity of acute graft-versus-host disease (aGVHD).

Allogeneic hematopoietic cell transplantation (allo-HCT) is a curative therapy for a wide variety of hematologic malignancies as well as some nonmalignant blood disorders. However, about 20% of patients undergoing allo-HCT develop aGVHD, which remains the leading cause of treatment-related morbidity and mortality. Both host and donor immune modulatory mechanisms have been identified that can lessen the severity of GVHD. pDCs are a rare population of cells that mounts potent immune responses against viral infections and are a major source of type I interferons (IFNs). Previously, pDCs were shown to attenuate allogeneic T-cell activation by inducing interleukin 10 (IL-10) expression in regulatory T cells (Tregs)[2] and by the release of type I IFNα/β and indoleamine 2,3-dioxygenase.[3,4] In an elegant article, a team led by Zhu et al identified that expression and release of VIP by donor pDCs regulated alloreactive T-cell activation and GVHD.[1] VIP is an evolutionary highly conserved 28-amino-acid peptide. VIP functions as a neuromodulator and neurotransmitter by binding to VPAC1 and VPAC2 class II G



Donor pDCs can limit alloreactive T cell responses during the initiation of aGVHD. Zhu et al report that donor pDCs control intestinal GVHD via the tiny yet versatile 28-amino-acid VIP.

protein-coupled receptors. Strikingly, VIP fulfills a plethora of physiological functions ranging from vasodilation, smooth muscle contraction and relaxation, and inhibition of gastric acid secretion to modulating epithelial paracellular permeability. Notably, VIP alsoproved to be an anti-inflammatory molecule by regulating Treg release of IL-10 and transforming growth factor β (TGFβ) and promoting Th2 polarization over Th1 differentiation.[5]

Zhu and colleagues investigated how donor pDCs regulate alloreactive donor T cells. They discovered that donor pDC-derived VIP is important for the control of GVHD (see figure). First, they found that human peripheral blood pDCs expressed VIP levels similar to those of mouse bone marrow pDCs. Surprisingly, VIP knockout (VIP-KO) mice showed increased pDC numbers compared with pDC numbers in wild-type mouse marrow. Second, VIP-deficient pDCs were unable to suppress $CD4^+$ and $CD8^+$ T-cell proliferation in vitro, which resulted in higher activated IFN-γ^+, ICOS $^+$, and IFN-γ^+:tumor necrosis factor-alpha (TNF-α^+) T-cell ratios. Third, recipients receiving VIP-deficient pDCs instead of wild-type pDCs developed early intestinal hyperacute GVHD in the small and large bowel, which was usually lethal. Intriguingly, imaging revealed that donor pDCs followed migration patterns similar to those of donor T cells that initially home to secondary lymphoid tissues.[6] This may explain why the research team observed that the immunomodulatory effects of pDCs were transitory and that pDCs predominantly control the initiation of intestinal aGVHD. Limited pDC numbers in GVHD target organs diminished their capacity to control GVHD during the effector phase. Consistent with the severe aGVHD phenotype, VIP-KO pDC recipients' alloreactive donor T cells expanded vigorously and Treg numbers were reduced compared with those of VIP wild-type pDC recipients. The higher inflammatory cytokine levels in VIP-KO pDC recipients indicates that donor pDCs limit (via VIP) the expansion of granulocyte-macrophage colony-stimulating factor (GM-CSF)–producing alloreactive donor T cells that are pathognomonic for intestinal GVHD.[7] Accordingly, these uninhibited donor T cells exhibited strong inflammatory gene signatures of *Fasn*, *Cyclophilin A*, and the GM-CSF regulating transcription factor *Bhlhe40*. Remarkably, although donor pDCs preferentially homed to lympho-hematopoietic tissues, VIP production by donor pDCs did not abrogate graft-versus-leukemia activity of donor T cells in 2 different mouse models.

Considering the versatile nature of VIP, it is unlikely that a single molecular pathway will explain all of the impact of VIP on GVHD. The article by Zhu et al identifies VIP as a key controller of alloreactive T cells. Clearly, this proof-of concept article will also stimulate clinical trials that investigate whether donor pDCs and/or treatment with VIP can protect patients from intestinal aGVHD.

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