Second, how does imatinib-mediated disruption of pericytes cause such profound vascular depletion and lymphoma regression? In this study, imatinib-mediated inhibition of PDGFRβ signaling in vascular smooth muscle cells caused a significant reduction in activation of PDGFRβ, PDGFRα, and c-kit, as well as the downstream effectors Akt and mitogen-activated protein kinase. Furthermore, imatinib treatment blunted vascular smooth muscle cell expression and secretion of VEGF and transforming growth factor β, which are both important in maintaining the survival, proliferation, and integrity of vascular ECs. The latter findings provide the basis for understanding mechanistically how imatinib-mediated disruption of PDGFRβ-pericytes can cause such profound antiangiogenic effects in the absence of direct targeting of endothelium.

It is worth noting in this study that treatment of mice with 2C5, an anti-PDGFRβ-specific antibody, caused substantial depletion of NG2+ pericytes in human lymphomas in vivo but more modest effects on tumor vascular density and tumor growth in vivo compared with imatinib. This may be explained by the persistence of perivascular CD68+ myeloid cells in anti-PDGFRβ-treated lymphomas, which were otherwise depleted in response to imatinib. The authors postulate that CD68+ perivascular myeloid cells may serve as surrogates to maintain vascular integrity in tumors in the face of targeted depletion of pericytes. As pointed out by the authors, the stronger antilymphoma effects of imatinib compared with the anti-PDGFRβ antibody may reflect the activity of imatinib against a wider range of stromal cell targets, including PDGFRα+ fibroblasts and c-fms+ myelomonocytic cells, as well as via inhibition of c-kit signaling in pericytes.

Taken together, this study provides proof of principle that administration of a TKI can mediate antiangiogenesis in a human lymphoma model via inhibition of PDGFRβ-pericyte function. Importantly, this approach resulted in significant inhibition of human lymphoma growth in vivo. These interesting results provide the basis for more refined consideration of antiangiogenesis as a strategy to attack human lymphomas in the clinic. In that regard, it is also encouraging that the authors observed a differential toxicity of imatinib therapy against the lymphoma vasculature, whereas the vasculatures of organs not involved with lymphoma were not affected. It has been suggested that one reason anti-VEGF therapy has not succeeded in the treatment of patients with lymphoma is that other proangiogenic mechanisms were not disabled via this approach. Targeting the PDGFRβ-pericyte, which regulates multiple pathways involved in the maintenance and proliferation of vascular ECs, represents an attractive strategy to dismantle the lymphoma vasculature and, perhaps, the lymphoma itself.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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CLINICAL TRIALS AND OBSERVATIONS
Comment on Leen et al, page 5113

Antiviral cell therapy: is this the future?

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In this issue of Blood, Leen and colleagues report the first multicenter trial of third-party viral-specific T cells (VSTs) for the treatment of 50 patients with refractory viral infections (cytomegalovirus, adenovirus, and Epstein-Barr virus) after stem cell transplantation. How is this paper different from the other articles on cell therapy for viral diseases published recently in Blood and in other journals? First, it is a multicenter study: the VST lines were generated in vitro at Baylor College of Medicine, but besides being administered at Baylor, the lines were shipped to and used in another 6 participating centers. Second, it is a therapeutic trial (as opposed to a trial using prophylactic treatment); it is the largest study showing therapeutic use of the multi-VSTs developed by the Baylor group. Previous publications by these investigators have shown the prophylactic efficacy of bivirus (adenovirus and Epstein-Barr virus) cell lines in extremely immunocompromised children who had received transplants, but this is the first time that so many patients with a variety of refractory viral infections were treated with the trivirus VSTs. Third, the fear of graft-versus-host disease (GVHD) caused by alloreactivity potentially present in the infused VSTs did not materialize (GVHD developed in only 8 patients, de novo in 2 patients, recrudescence in 6 patients, and grade 3 in only 1 patient), confirming previous observations. However, the most important feature is that the VSTs used were off-the-shelf, only partially HLA-matched cell lines previously generated from third party donors (the degree of HLA matching varied between 1 out of 6 and 4 out of 6 times); suitable cell lines were found for 90% of the screened patients with a small bank of only 32 lines. Finally, the fact that the efficacy was higher than 70% for the 3 viruses targeted and was persistent in 89% of the patients makes it even more compelling. This study clearly gets us closer to a practical therapeutic option for patients with refractory...
viral infections following allogeneic stem cell transplantation.

Is this the future of cell therapy for viral infections? It might well be, if a large-enough cell-line bank could be created. The different strategies to obtain cells with antiviral activity and their potential problems have been reviewed. The 2 competing options are separating the preexisting (and low-frequency) VSTs from donors by a variety of methods or generating them in vitro. The advantage of the first method is that it may be fast; the disadvantage is that sometimes it may be possible for either logistical reasons (donor not available) or technical reasons (VSTs too low to detect or separate). The advantages of the VSTs generated in vitro include obtaining the desired antiviral specificity regardless of preexisting immunity and potentially treating several infections (and maybe even the malignant disease) simultaneously. The disadvantage is time. Even with improved rapid expansion methods, at least 10 days separate the time it is decided that a cell line is needed and the infusion of the VSTs, usually 2 weeks or more. Depending on the clinical situation, time may not be available.

Prebanked, partially HLA-matched VSTs seem to offer significant advantages. If the lack of GVHD is confirmed in further studies, this approach will likely become the preferred first choice because it provides immediate efficacy and does not preclude obtaining cells from the stem cell donors by any of the other 2 methods, although the efficacy of the third-party VSTs seems already very promising.

The only caveat (which may be significant) is whether these VSTs will perform as effectively in the presence of more immunosuppression. The patients included in this study represent a highly selected subset of all of those who went on to have viral infections: patients were excluded if they had active, acute GVHD grades II to IV; had received T-cell-depleting monoclonal agents like anti-thymocyte globulin or alemtuzumab; or were receiving more than 0.5 mg/kg/day of prednisone. Even under these relatively favorable immunologic circumstances, 10 of the 50 patients died of viral infections. In practice, it is common for viral reactivation to occur in the midst of GVHD actively treated with higher doses of steroids and other immunosuppressive agents, which may affect both the efficacy and safety of the VSTs. These concerns, as well as the myriad of immunologic topics brought up by these data (eg, differential effects of the same VSTs on different viruses in different patients, antiviral activity in the absence of detectable circulating antiviral T cells) will be addressed in future trials. After this study, the promise of effective cellular therapy for refractory viral infections seems closer than ever.

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Comment on Covens et al, page 5176

To B1 or not to B1: that really is still the question!

Stuart G. Tangye

In this issue of Blood, Covens et al revisit the contentious area of human B1 cells and provide evidence that human CD20+CD27+CD43+ cells are preplasmablasts, rather than committed to the B1 lineage. It is well-established that 2 populations of B cells—B1 and B2—exist in mice. Decades of research have demonstrated that these subsets can be distinguished from one another according to phenotype, ontogeny, anatomical location, and function. Thus, B2 cells are continually generated from bone marrow precursors and circulate throughout the blood and secondary lymphoid tissues. Follicular and marginal zone B cells both arise from the B2 lineage and can respond to a broad range of T-dependent (TD) and T-independent antigens. B2 cells can undergo class switching, somatic hypermutation, and generate memory cells, thereby potentially providing long-lived antibody-mediated protection against many structurally diverse pathogens. B1 cells, on the other hand, predominate during fetal and neonatal development, self-renew following their generation from stem cells present at these early stages of life, and predominantly localize to peritoneal and pleural cavities. B1 cells are considered innate immune cells that produce the majority of “natural” immunoglobulin M (IgM) and IgA, which is largely encoded by germline immunoglobulin genes. Because of its polyreactivity and ability to recognize large repetitive structures, this natural IgM acts as a first line of defense against pathogens such as encapsulated polysaccharide-expressing bacteria. Subsets of B1 cells also exist that can be delineated by differential expression of CD5. These subsets are also functionally
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