Could these patients have undergone classical induction? If so, then the benchmarks by which we judge success might be significantly different. Intensive chemotherapy, even in patients >65 years, can produce decent CR rates for older patients, especially those without features of poor-risk disease.[9] Perhaps the appropriate comparator arm in the randomized study would be intensive chemotherapy, where the advantage of avoiding anthracyclines, maintaining QOL, or being able to undergo therapy as an outpatient might be unveiled. Comparing "just right" with "too cold," rather than with "too hot," means we have not really solved the clinical conundrum of which regimen to choose for our patients.

In addition, should this combination prove effective, why limit its use to patients over a certain age or those who are less than perfectly fit? I am not the first to make this argument,[10] but studies like this shine a light on the inadequacies of our study paradigms. When choice of therapeutic intensity pivots on arbitrary age cutoffs or unproven markers of fitness, we reinforce a culture in which fit patients are not included in studies of novel agents and older patients do not receive the benefits, such as they are, of cytotoxic therapy.

None of this should detract from the deserved enthusiasm surrounding the results presented here. New options for this population, and all patients with AML, are badly needed. Future data from larger numbers of patients and from randomized trials may well cement this regimen as a new standard of care, perhaps irrespective of patient suitability for ICT.

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TRANSPLANTATION

Comment on Paz et al, page 94

BCL6 inhibition: a chronic GVHD twofer

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In this issue of *Blood*, Paz and colleagues demonstrate that the small molecule 79-6 is able to treat and even reverse lung injury attributable to experimental chronic graft-versus-host disease (cGVHD) by targeting B-cell lymphoma 6 (BCL6), a transcriptional regulator of T follicular helper (Tfh) cells and germinal center B cells.[1]

cGVHD represents the major cause of late morbidity and nonrelapse mortality after allogeneic hematopoietic transplantation, affecting ~10% to 70% of patients depending on donor characteristics and transplant conditions.[2] Corticosteroids are the mainstay of treatment of cGVHD, further increasing the risks of infections and other side effects that substantially impair quality of life.[3] New therapeutic strategies are sorely needed to reduce these complications and improve the well-being of transplant patients who have been cured of their primary disease.

Studies in recent years using experimental models and patient samples have highlighted the role of B cells as well as donor T cells in cGVHD pathogenesis.[4] The B-cell-targeting agent rituximab has been tested as an alternative to corticosteroids or in conjunction with them for treatment of cGVHD.[5,6] Some results are promising, particularly for treatment of skin involvement, but unfortunately, the results are less promising for visceral disease.[7] In 2017, the US Food and Drug Administration (FDA) approved ibrutinib for treatment of cGVHD. This was a major step forward for the field, as this was the first FDA-approved therapy for cGVHD. However, an important caveat is that the study based on which ibrutinib was approved primarily enrolled patients with skin and mouth disease, and there was relatively little visceral involvement. Out of 42 patients, the liver was involved in only 3, and the lungs were involved in only 2.[8] New treatment options for visceral disease thus remain an important area of unmet need in cGVHD.

Using experimental mouse models of cGVHD, Paz and colleagues identified BCL6 as a new target for therapeutic intervention in cGVHD. Targeting BCL6 could provide an appealing approach for inhibiting pathologic B cells and T cells in cGVHD, as BCL6 has been described to

be crucial for both Tfh-cell and germinal center (GC) B-cell development and function.[9,10] Importantly, the authors have performed due diligence with their experimental models, testing their hypotheses in mouse models demonstrating multiorgan fibrosis, collagen deposition, and antibody deposition, as well as abnormal pulmonary physiology indicative of cGVHD. The authors show here that absence of *bcl6* in either T cells or B cells reduced development of lung injury in their cGVHD model.

After assessing *bcl6* deficiency at the time of transplant, a model for studying cGVHD development and prevention, the authors then examined a cGVHD treatment model by administering the BCL6 inhibitory compound 79-6 in the setting of established lung cGVHD. Administration of 79-6 post-transplant to mice with active cGVHD significantly reduced splenic GC B cells and collagen deposition in the lungs. Most importantly, and most impressively as well, 79-6 treatment in mice with active cGVHD significantly reversed the abnormal lung physiology as indicated by decreased resistance and increased compliance.

Although these results are promising for treatment of pulmonary cGVHD manifestations, administration of 79-6 did not significantly alter disease progression in liver or colon or in a sclerodermatous model of skin cGVHD. It is also notable that although genetic deficiency of *bcl6* in either the donor T-cell or donor B-cell compartment pretransplant prevented both GC B-cell and Tfh-cell expansion post-transplant, treatment of active cGVHD with 79-6 resulted in a substantial reduction in splenic GC B cells only without impacting the number of Tfh cells. The results highlight the importance of cross talk between these two populations in cGVHD pathogenesis, while also suggesting that GC B cells may either be the more relevant population or perhaps an easier population to control once cGVHD has been established. Interestingly though, although treatment with 79-6 did not reduce the total number of Tfh cells, an increase in the ratio of T follicular regulatory (Tfr) cells to Tfh cells was observed in some mice after treatment, suggesting that administration of 79-6 may be able to induce an expansion of Tfr cells in mice with active cGVHD.

Overall, the findings presented by Paz and colleagues represent an exciting step forward in developing a new treatment for cGVHD with lung involvement, as well as generating new insights into cGVHD pathogenesis. It will be very interesting for future studies to expand on, validate, and translate this work, testing if 79-6 can also be effective as cGVHD pharmacologic prophylaxis and delving deeper into the molecular mechanisms underlying its ability to reverse lung cGVHD.

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