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CLINICAL TRIALS AND OBSERVATIONS

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Venetoclax in AML: aiming for "just right"

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In this issue of *Blood*, DiNardo and colleagues present much-awaited early phase data on the safety and efficacy of using the B-cell lymphoma 2 (BCL-2) inhibitor venetoclax in combination with hypomethylating agents to induce older individuals with acute myeloid leukemia (AML).[1] Remission induction in older or less fit individuals has long required providers, and their patients, to choose between therapies deemed either reasonably effective but toxic ("too hot") or safe but weak ("too cold"). Since early hints of venetoclax activity in AML were first aired, hopes have been building that there might be a middle ground, a "just right" way to induce the typical patient with AML, who is older and may have comorbidities. This well-conducted, multicenter, phase 1b trial, which enrolled 145 subjects >64 years of age and deemed unsuitable for intensive induction, certainly bolsters such hopes, although a few lumps in the porridge should be considered as one digests these data.

First, a little background. Since the 1990s, it has been anticipated that BCL-2 inhibition would have therapeutic relevance in AML.[2,3] Xenograft data showed that upregulation of BCL-2 allows leukemia cells to evade apoptosis. High levels of expression were associated with a worse prognosis.[2,4] An early clinical foray was the addition of a bcl-2 antisense oligonucleotide to intensive chemotherapy; yet a large, randomized cooperative group study found no benefit when compared with traditional induction alone.[5] Venetoclax, a BH3 mimetic and BCL-2 selective inhibitor, initially was deployed in relapsed AML as monotherapy. There was evidence of efficacy: an overall response rate of 19% and particular activity in disease with isocitrate dehydrogenase 1 or 2 mutations.[6] Blockade of MCL-1 by hypomethylating agents was thought to be a way to augment activity and provided rationale for the combination tested here. Although we await clearer evidence of what is happening at the molecular level, the punch line from the current trial is that the combination appears to have synergy.

The authors report impressive results. In this study, 37% of patients achieved a complete remission (CR), and an additional 30% had a CR with incomplete count recovery (CRi). The median overall survival was >17.5 months, although half of the subjects had disease with poor-risk cytogenetics, and the subject's median age was 74 years. Complete response rates with hypomethylating agents alone (the prototype for nonintensive induction) in previous prospective trials generally are in the range of 15% to 20%, and median overall survivals are normally less than a year.[7] Striking to the eye are the tails of the survival curves, with a handful of patients appearing to derive prolonged benefit, although it should of course be noted that azacitadine monotherapy can manifest a similar finding, as seen in a 2010 study of this agent in patients with 20% to 30% bone marrow blasts.[8]

Particularly in a frail population, toxicity of therapy and quality of life (QOL) may be as important as inducing remissions. Outcomes like CRi, partial response, or morphologic leukemia-free state in a patient who will not proceed to transplant and will not be cured, matter most if QOL is sustained or improved. Although QOL data were not collected in this early phase trial, even patients whose remission was incomplete needed fewer red blood cell and platelet transfusions, a gratifying result. Finally, the authors report a low 30-day mortality rate, just 3%. Such may be the result of early disease control, may be the clinical excellence of the centers participating, and may also implicate the overall health of the enrolled subjects. It is hoped that similar safety is seen when this combination is used outside of a trial population.

It is stating the obvious, of course, but a key meta-lesson here is that we, as a field, are not very good at choosing which patients should go on cytotoxic therapies and which patients should be treated with "less-intensive" regimens. Let us put aside the question of disease characteristics for now and focus on patient-related factors. The eligibility criteria state that patients should be "ineligible for standard induction chemotherapy due to the presence of various comorbidities, such as age >75 years, cardiac disease or prior anthracycline use, secondary AML, or high probability of treatment-related mortality." Nevertheless, all patients were required to have adequate hepatic and renal function and an Eastern Cooperative Oncology Group performance status of at least 2. Indeed, the authors report that 21 patients were able to proceed to stem-cell transplantation, something that implies physical durability and fitness. In most AML trials of intensive cytotoxic therapy (ICT), eligibility requires performance status of 0 to 2 and adequate cardiac, renal, and hepatic function, although it is not definitive that any of these features are absolute contraindications for ICT.

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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.

Conflict-of-interest disclosure: L.C.M. served as a consultant to Novartis, Celgene, Incyte, previously held stock in Pfizer, and receives research funding from Jazz Pharmaceuticals. ■

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DOI 10.1182/blood-2018-11-883454

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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

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