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CLINICAL TRIALS AND OBSERVATIONS

Comment on Döhner et al, page 1674

By any other name …

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In this issue of *Blood*, Döhner et al[1] provide a post hoc analysis of data from the QUAZAR trial of oral azacytidine ("oral aza") therapy for patients with acute myeloid leukemia (AML),[2] focusing on the survival impact of *NPM1* and *FLT3* mutations in the context of a flow cytometry–based assay for measurable residual disease (MRD). The analysis indicates that treatment with oral aza conferred a survival benefit regardless of *FLT3* or *NPM1* mutational status, including the favorable (NPM1 mutated/MRD negative) and unfavorable (FLT3 mutated/MRD positive) combinations. *FLT3* and *NPM1* mutations are frequent molecular dance partners that are found in a significant fraction of AML cases, so the demonstration of the efficacy of oral aza in these very common subtypes of the disease make a reasonable case for the real-world applicability of this therapy.

Do we finally have a maintenance therapy for patients with AML? After remission has been achieved and intensive chemotherapy is completed, AML patients and their physicians settle in for a nervous 2- or 3-year vigil, knowing full well that relapse (and death) are very possible, and wishing there was some way to minimize the risk of that relapse. An effective maintenance therapy that can decrease relapse risk has been somewhat of a holy grail for the field. To date, the only maintenance treatment associated with a survival benefit is FLT3 inhibition in the posttransplantation setting.[3,4] Many different maintenance approaches (eg, chemotherapy, immunotherapy, small molecules) have been tried over the decades, but nothing has really emerged. Rashidi et al produced an elegant and exhaustive meta-analysis on this subject in 2016 and rather despondently concluded that there was no substantial evidence for the use of maintenance therapy in AML.[5] They made the salient observation that "the benefit of maintenance seems more apparent after suboptimal induction and consolidation." That comment seems highly applicable to the QUAZAR trial, in which enrolled patients who had achieved remission after intensive induction and a limited amount of consolidation were deemed unfit for further intensive consolidation.

Oral aza as used in the QUAZAR study isn't really maintenance, it is simply ongoing less toxic treatment. In fact, in its approval summary for oral aza, the US Food and Drug Administration (FDA) took pains to point out that this drug did not meet the Agency's definition of a maintenance therapy and labeled it as continuation therapy.[6,7]

What's in a name? Does anyone treating AML even care what type of therapy we call this drug? And how do we best use it to help our patients? Going forward, at least in the United States and likely soon much of the rest of the world, the types of patients who enrolled in QUAZAR are more likely to be treated with the less intensive venetoclax-based regimens rather than 7+3 and intensive consolidation.[8] There probably won't be very many patients who fit into the strict indication in the FDA label.

Label restrictions and definitions notwithstanding, azacytidine has evolved into becoming an essential backbone of treatment for a large and growing fraction of AML patients, and we now have an oral version of the drug, albeit one with very different pharmacokinetics. A resourceful research community can and should go in all sorts of directions with this important new tool. Currently, patients aren't particularly enamored with the concept of treatment with parenteral azacytidine and venetoclax extending indefinitely (eg, for years). Finding some way of using oral aza with venetoclax would seem to be the first order of business. Circling back to FLT3, we know that *FLT3* mutations are associated with shorter responses to the lower-intensity venetoclax regimens,[9] but the combination of FLT3 inhibitors with venetoclax can be rather toxic.[10] The combination of oral aza and an FLT3 inhibitor could be introduced after venetoclax-based induction, and we can call this therapy either maintenance or continuation (or call it a rose …). The list goes on: oral aza plus IDH inhibitor, oral aza plus menin inhibitors, etc. In the current world of AML drug development, the real work often begins *after* a drug is approved.

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HEMATOPOIESIS AND STEM CELLS

Comment on Li et al, page 1686

Forever young: Sphk2 in HSCs, when less is more

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In this issue of *Blood*, Li et al[1] use different mouse models to comprehensively dissect the role of sphingosine kinases (Sphks) in the regulation of hematopoietic stem cell (HSC) function, uncovering that specific loss of Sphk2 expands and functionally rejuvenates HSCs.

HSCs sustain the lifelong production of most adult blood and immune cell lineages. At the apex of the hematopoietic system, HSCs are characterized by their capacity for long-term self-renewal and their ability to differentiate into mature cells.[2] The decline in their regenerative potential is a hallmark of aging, which contributes to the progressive physiological dysfunction and increased risk for age-dependent disorders.[3]

Multiple studies have tried to elucidate potential mechanisms of HSC aging. In this context, heterochronic parabiosis (a rejuvenating intervention where circulatory systems of aged and young mice are surgically connected) can partially reverse some of these phenotypes. However, whether HSCs are responsive/refractory to this approach remains controversial.[4,5] Moreover, the detailed mechanisms mediating its effects are not fully elucidated. Thus, understanding how/why HSCs age is critical to design interventions to prevent, delay, alleviate, or reverse the physiological consequences of aging.

Sphks exist as 2 different isoforms in mammals (Sphk1 and Sphk2), which synthesize sphingosine 1-phosphate (S1P), a bioactive lipid molecule that regulates multiple processes.[6] Genetic abrogation of both kinases is embryonically lethal; however, *Sphk1*-knockout (KO) and *Sphk2*-KO mice are viable and healthy, suggesting functional redundancy between both.[6] In this study, Li and colleagues used a variety of in vitro and in vivo experimental assays to uncover that loss of Sphk2 in the hematopoietic compartment (but not Sphk1) results in expansion of quiescent HSCs without affecting other mature blood cell lineages. Interestingly, loss of Sphk2 is not compensated by increased Sphk1 levels. In addition, even if Sphk2 loss results in decreased S1P levels, the *Spkh2*-KO phenotype is S1P independent, suggesting that Sphk2 catalytic activity is dispensable for these effects.

To assess the long-term functional relevance of Sphk2 deficiency, the authors performed a series of rigorous reconstitution experiments in vivo. Their results demonstrated that *Sphk2*-KO bone marrow cells have enhanced self-renewal potential and increased reconstitution capabilities in a cell-autonomous manner, without compromising linage commitment. Even in conditions that force HSC proliferation and differentiation, such as 5-fluorouracil treatment or lethal irradiation, *Sphk2*-KO mice show significant survival extension, and *Sphk2*-KO HSCs preserve an improved regenerative potential. This is highly relevant because hematological toxicity is one of the main causes for chemotherapy discontinuation in cancer patients. Thus, small molecules pharmacologically targeting Sphk2 might help prevent/treat these adverse events.

The authors further investigated the role of Sphk2 in HSC aging by integrating computational approaches with additional reconstitution assays comparing HSCs from aged and young mice. Consistent with previous results, Sphk2 deficiency prevents the acquisition of age-induced transcriptional signatures in old HSCs, such that *Sphk2*-KO old HSCs present phenotypic and functional characteristics like those observed in young wild-type HSCs. In line with this, old HSCs show higher Sphk2 levels than young HSCs. Functional annotation of genes downregulated in *Sphk2*-KO HSCs suggested reduced oxidative phosphorylation (OXPHOS). Conversely, upregulated genes were involved in the regulation of anaerobic glycolysis. In this context, HSCs are extremely