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## • • • CLINICAL TRIALS

Comment on Fehniger et al, page 1828

# The times they are a-changin'

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The article by Fehniger et al in this issue of *Blood* suggests that lenalidomide at 50 mg daily is a qualitatively different, and potentially useful, therapy for AML.<sup>1</sup>

o date the drug, at 10 mg daily, has found its greatest use in reducing red cell transfusion requirements in patients with lowgrade myelodysplasia (< 10% blasts) and a deletion of the long arm of chromosome 5 (del 5q).<sup>2</sup> Treating 33 acute myeloid leukemia (AML) patients age 60 years or older, none of whom had del 5q, Fehniger et al noted 6 complete remissions (CRs) and 4 CRs with incomplete count recovery (CRi). In contrast to remissions seen after daunorubicin and cytarabine ("conventional treatment"), remissions after lenalidomide occurred without marrow hypoplasia (cellularity < 10%), and there was no apparent relation between achievement of remission and lenalidomideinduced neutropenia. Also, unlike conventional treatment, cytogenetics (ie, intermediate vs "unfavorable" using Southwest Oncology Group/Eastern Cooperative Oncology Group criteria) were not the principal predictor of response. Response was unrelated to age (60-64 years, 65-69 years, or older than 69 years). Rather, there was a striking inverse relation between response and extent of disease, quantified by marrow blast percentage or number of circulating blasts. Extent of disease is typically not a major predictor of response to 3 + 7 but was found by Ades et al to be such in a trial administering lenalidomide to patients with "high-risk" myelodysplastic syndrome (MDS), or AML with up to 30% marrow blasts.<sup>3</sup> Specifically, Ades et al reported a CR in 6 of 29 in patients with less than 20% marrow blasts but only 1 of 18 in patients with 20%-29% blasts who achieved a CR. Because all of these patients had a del 5q and a similar median age to the Fehniger et al study, the higher response rate in the latter (5 of 8 in patients with 20%-30% marrow blasts) likely results from use of a 50-mg rather than the conventional 10-mg dose used by Ades et al.<sup>3</sup> Because more myelosuppression did not seem to translate into a higher response rate, the reason for the dose-response relationship is not immediately obvious. However, the lenalidomide dose-response relation does appear steeper than that seen with conventional treatment; for example, 10 mg vs 50 mg of lenalidomide is comparable to the dose-response relationship of 100 vs 3000 mg/m<sup>2</sup> cytarabine.

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Perhaps the most striking difference with conventional treatment is the seeming lack of a relation (P = .37) between survival and response category (CR vs CRi). For many years response to induction therapy for AML was considered CR or no CR, based on 50-year-old data suggesting that only CR increased survival.4 Walter et al have reported that with conventional treatment, CR was associated with longer survival than CRp (CR with a platelet count  $< 100 000/\mu$ L).<sup>5</sup> Although it seems reasonable to hypothesize that CRi will be associated with shorter survival than CRp given that it appears a lesser response requiring no recovery of neutrophils, large databases are not readily equipped to address the relative value of CRi. And certainly, what is found regarding survival in patients with CR versus CRi receiving conventional treatment may not apply with other therapies, as has been suggested with azacitidine.6 Fehniger et al are careful to note that their ability to detect longer survival with CR than with CRi was limited by patient numbers, and indeed the data in their Table 3 indicate that the median survival for CRi was 8.5 months versus at least 16 months for CR. Because patients are interested in "response" primarily as it affects survival, the survival value of responses less than CR will undoubtedly be further elucidated in the future.

Although lenalidomide is probably qualitatively distinct from conventional therapy, outcomes after its use-as noted by Fehniger et al-do not appear obviously better. While agreeing with the authors that lack of randomization hinders comparison, the CR rate was plausibly lower than might be expected had some of these patients (for example, those age 60-65 years with a normal karyotype) received conventional therapy<sup>7</sup> (or, more recently, escalated doses of daunorubicin8). However, as widely recognized, it is important to move to a more "personalized" approach. In particular, it may be possible to identify patients (eg, those with low blast counts and other, to be discovered, markers) whose survival with 50 mg of lenalidomide is superior to that seen with more conventional therapy.

Lenalidomide's future in AML almost certainly lies in combination with other agents such as azacitidine<sup>9</sup> or conventional treatment. Indeed, many new anti-AML drugs appear promising in single-arm phase 2 trials such as that reported by Fehniger et al. A very incomplete list includes plerixafor, sapacitabine, voreloxin, suberoylanilide hydroxamic acid(SAHA), AT-406, and bortezomib. It is not immediately apparent which of these is better than conventional treatment. This uncertainty together with the large number of drugs to test will likely sound the death knell for the conventional phase 3 trial, especially when utilizing conventional hazard ratios. Phase 3 trials are ill-suited for a disease as heterogeneous as AML. Both in Europe and recently in US cooperative groups, smaller comparative trials have been explored, under the assumption that the worst false-negative results when a drug is not studied at all.<sup>10</sup> In this way, as in the introduction of qualitatively distinct drugs such as lenalidomide, clinical research in AML is truly in ferment.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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#### • • HEMATOPOIESIS & STEM CELLS

Comment on Leung et al, page 1840

## CD9 phones home with a TEM of its own

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Tetraspanins are small molecule proteins known to impact cellular migration and signaling. In this issue of *Blood*, Leung and colleagues uncover a novel function of the tetraspanin molecule CD9 as a potential mediator of CD34<sup>+</sup> cell homing.<sup>1</sup>

**S** ignaling between CXCR4 and its ligand—stromal-derived factor 1 (SDF-1/ CXCR12)—is clearly important in hematopoietic stem cell (HSC) homing and engraftment, but the precise mediators involved are unclear. Recently, attempts to exploit this axis for benefit in the clinic have led to the development of the CXCR4 inhibitor, plerixafor,<sup>2</sup> and several other similar agents are in development. Given the catastrophe of engraftment failure in hematopoietic stem cell transplantation (HSCT), and the increased rates of such an outcome with cord blood HSCT in adults, attempts to maximize engraftment by enhancing homing are tantalizing.

The use of microarray screening technology in the elucidation of essential mechanistic targets led to many exciting discoveries in the past decade; in this issue, Leung and colleagues explore the role of CD9, a tetraspanin protein found in a screen, as one in a series of genes preferentially induced by SDF-1 in human CD34<sup>+</sup> cord blood cells.

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Cell-surface proteins of the tetraspanin family have 4 transmembrane domains, intracellular N and C termini, and 2 extracellular domains. Tetraspanins are thought to act as scaffold proteins: multimolecular organizers which anchor proteins to one area of the cell membrane thereby forming structures known as tetraspanin-enriched microdomains (TEMs).<sup>3</sup> Tetraspanins are therefore often considered molecular facilitators modulating the activities of their associated molecules depending upon the TEM composition. Interestingly, a TEM formed by CD9 often includes HSC homing proteins B1 integrin,<sup>4</sup> MTI-MMP,<sup>5</sup> and CD26.<sup>6,7</sup>

Leung et al transplanted CD34+CD9cells and whole CD34+ cells (CD9 antibodies used to positively select CD34+CD9+ cells had neutralizing effect and were not used for this reason) into NOD.CB.17-Prkdcscid/J (NOD-Scid) mice, both with and without anti-CD122 antibody. After establishing a clear increase in homing among CD34<sup>+</sup>CD9<sup>+</sup> cells in the bone marrow and spleen of mice 20 hours after transplantation, the authors elegantly put several known pharmacologic inhibitors of the effectors of the SDF-1/CXCR4 pathway to use to suggest a signaling pathway leading to CD9 expression via activation of the transcription factor STAT. Interestingly, phosphatidylinositol 3-kinase was not involved in signaling of CD9 transcription as it is with other factors involved in homing via mediated SDF-1.8

Enhancement of stem cell engraftment has significant clinical relevance in the era of cord blood transplantation. Leung and colleagues are the first to demonstrate that CD9 enrichment improves homing of CD34<sup>+</sup> cells to the bone marrow in the in vivo xenograft assay. It will be interesting to explore potential relationships between CD9 and other SDF-1–induced proteins—regardless of their association with the CD9 TEM—known to impactHSC homing such as CD44<sup>9</sup> and CD26.<sup>6</sup> And, of course, the question remains open as to the effect this improved homing will have on HSC engraftment.

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

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