

# inside **blood** commentary

2 JULY 2015 | VOLUME 126, NUMBER 1

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Comment on Steensma et al, page 9

## Clonal hematopoiesis: a “CHIP” off the old block

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In this issue of *Blood*, Steensma et al propose that we add a new disorder to the spectrum of myelodysplastic diseases (and the myeloid leukemias), which they call clonal hematopoiesis of indeterminate potential (CHIP).<sup>1</sup>

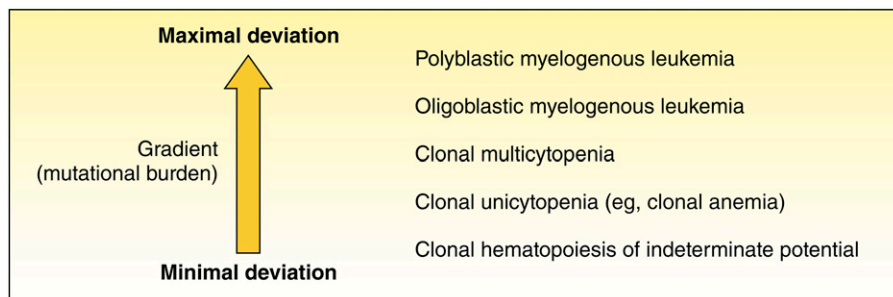
**N**ormal hematopoiesis requires the regulation of 3 principal functions: cell proliferation, lymphohematopoietic stem cell differentiation, and maturation of unipotential progenitors to functional cells. Moreover, unlike many cellular systems, the lymphohematopoietic stem cell is capable of differentiation into 8 myeloid lineages and 3 major lymphoid lineages and, in some cases, further maturation into subsets of those lineages. The requirement for genetic and epigenetic coordination of this process is dazzling and, when something goes awry, accounts for the multiplicity of phenotypes into which we try to pigeonhole the clonal myeloid (and lymphoid) diseases. Despite

these complex matrixes in which abnormalities of proliferation, differentiation, and maturation sum to result in a distinctive phenotype, most cases are classifiable. The diagnostic designation provides the clinician with an image of the likely course, or courses, of the disease and the approach to management, on average. The skill and experience of the physician should determine the approach for an individual patient, given the variability within a specific diagnostic category.

The authors propose that CHIP be used to describe patients with blood cells that contain somatic mutations of genes known to be recurrently mutated in hematologic malignancies in whom the mutant allele

fraction is  $\geq 2\%$ . These persons could have cytopenias that do not meet the criteria for a diagnosis of myelodysplasia, have cytopenias unrelated to myelodysplasia, or have normal blood counts. They liken this category of diagnosis to essential monoclonal gammopathy, so-called MGUS, or, perhaps, monoclonal B-cell lymphocytosis. Their rationale considers that recently applied genomic approaches to hematopoietic neoplasms have identified somatic mutations associated with clonal myeloid (or lymphoid) disorders that may precede development of acute myelogenous leukemia or be found in apparently healthy individuals.<sup>2-4</sup> The frequency of these potentially disease-initiating somatic mutations increases with age, and, although it is not anticipated that most such mutations will result in a myeloid malignancy during a person's lifetime, some will when the cell involved acquires cooperating mutations that lead to clonal evolution and a malignant phenotype.

How would adding CHIP to a diagnostic category improve what we do for patients or offer research opportunities to advance patient care? After all, if the patient has normal blood cell counts, it is unlikely and unwarranted to do genetic studies of blood cells, unless it is part of a population research project. The authors suggest that cytopenias resulting from other causes than a clonal myeloid disease may lead to such genetic probing and that in an older person, an incidental finding of a relevant somatic mutation associated with laboratory findings short of a diagnosis of myelodysplastic syndrome may be misleading. Considering CHIP as a diagnosis may help avoid a misdiagnosis of (overt) myelodysplasia and put the genetic alteration into perspective. They also propose that surveillance akin to that applied to essential monoclonal gammopathy is warranted. Perhaps, most importantly, although not explicitly stated, is the opportunity to consider methods to prevent



A schematic relationship among the disorders that fall under the rubric of myelodysplastic neoplasms. Myelodysplastic disorders are less deviated forms of acute myelogenous leukemia.<sup>7</sup> Here, deviation is considered in terms of loss of regulated processes of proliferation, differentiation, and maturation compared with normal polyclonal hematopoiesis. Mutational burden considers qualitative as well as quantitative oncogenetic contributions to neoplasia. Professional illustration by Patrick Lane, ScEYEnce Studios.

clonal progression. Indeed, clonal progression is a major cause of morbidity and mortality among patients with hematopoietic neoplasms. Among the most important research directions we could foster is the development of agents that can stabilize minimally deviated neoplastic clones (see figure). The use of (putative) demethylating agents in clonal cytopenias and oligoblastic leukemia is a rudimentary effort to stabilize a chronic or subacute myeloid neoplasm. Therapists hope that by reversing methylation the result may be the reexpression of normal genes previously silenced.

In the management of myeloid malignancies, we are often confronted with the battle between the neoplastic clone and polyclonal normal hematopoiesis. The remission-relapse pattern of acute myelogenous leukemia is a classic example of such competition.<sup>5</sup> The good guys lose too often. It is unclear, in specific biologic terms, how a single mutated cell can gain hegemony over the multiple normal clones that constitute polyclonal hematopoiesis. Stem cell niches are a focus of attention. Although some work has been conducted on this process, we are largely in the dark, and it should be a major direction of our research. Today, ablation is our therapeutic approach in most cases. When we first tried this approach with newly developed chemotherapeutic agents in the 1940s, it was not known that normal residual stem cells were present in the marrow, a critical element in the application of ablative chemotherapy, before the advent of allogeneic hematopoietic stem cell transplantation. In those early days, the importance of transient remissions and the restitution of normal blood counts was the evidence that they provided that normal hematopoiesis could be reestablished. Later, the presence of residual normal stem cells in the marrow of patients with myelogenous leukemia was established using semisolid and liquid culture techniques. Fortunately, in most cases, if suppression of malignant hematopoiesis can be achieved (usually minimal 3-log kill in acute myelogenous leukemia), the restitution of polyclonal hematopoiesis occurs with some frequency. Unfortunately, the return of monoclonal, malignant hematopoiesis often follows, especially in older patients who are the most frequently affected.

Of course, we could effect a clinical cure if we could convert a moderately or maximally deviated myeloid neoplasm to CHIP

(see figure). That approach could provide the greatest potential for progress. Developing models to study stable, metastable, and progressive clonal hematopoietic neoplasms and the ability to prevent their progression is an important research direction.<sup>6</sup>

The paper by Steensma et al has several virtues. It raises an important consideration, the diagnosis of CHIP, at a time when genetic profiles of hematopoietic cells are becoming de rigueur and cautions us against the misinterpretation of a clonal somatic mutation in the absence of a phenotype sufficient to make an accurate diagnosis. It provides an opportunity to reinvigorate the concept of developing a reversible reaction: converting severely or moderately deviated neoplasms back to minimally deviated neoplasms or stabilizing a minimally deviated neoplasm. The latter action could be equivalent to a cure. Not an easy task, but worthy of the application of someone's genius. It also provides an economical discussion and review of important recent genetic findings in the clonal myeloid neoplasms, and it provides insights into the diagnosis of myelodysplastic syndromes. It should be read by hematologists who want to be informed on these matters.

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

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## ● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Saußebe et al, page 42

# Living with CML: is death no longer the end (point)?

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In this issue of *Blood*, Saußebe et al demonstrate, in a study based on 1519 chronic myeloid leukemia (CML) patients, that death may be a flawed end point for the assessment of tyrosine kinase inhibitor (TKI) efficacy because, in the current era, CML patients more often die with their disease than because of it.<sup>1</sup>

**T**he basic tenet of trial design when evaluating new cancer therapies is that having surrogate markers of good response that correlate with favorable long-term outcomes is appropriate and pragmatic, but that the ultimate test for a new therapy is to establish improved survival. This study suggests that survival may not be the gold standard end point, at least when it comes to trials of TKIs in CML. Because, for the

majority of patients, CML is now a chronic condition maintained by regular TKI therapy,<sup>2</sup> improvements in survival have become increasingly difficult to demonstrate, requiring large studies and very long follow-up. This study found that the most powerful predictor of survival for CML patients in the large German CML Study IV trial<sup>3</sup> was a composite measure of comorbidities (the Charlson comorbidity index)<sup>4</sup> at diagnosis rather than