platelet transfusions does not justify subjecting patients to the increased bleeding risks associated with a therapeutic-only platelet-transfusion strategy in any category of patients with hypoproliferative thrombocytopenia. This statement may be particularly relevant considering that these studies were performed in academic medical centers with highly trained staff who were assessing the patients daily for bleeding and using well-defined platelet-transfusion protocols. Furthermore, both trials involved patients 16 years of age or older. In a subset analysis of the PLADO trial data, bleeding rates were significantly increased among children, particularly among those undergoing autologous stem-cell transplantation. These data suggest that results of studies that assess bleeding risks related to platelet transfusion in adults may not be generalizable to children.

Genetically Informed Therapy in Leukemia
Jerald Radich, M.D.

What can we learn from the study of rare diseases? A lot. Chronic myeloid leukemia (CML) occurs in 3 in 100,000 persons, yet it is perhaps the best example of “bench to bedside” medicine in oncology. The discovery of the signature BCR-ABL translocation found in all CML ushered in an era of molecular diagnostics and targeted therapy with tyrosine kinase inhibitors, with treatment implications beyond this rare disease. Similarly, research on the other rare myeloproliferative neoplasms led to the discovery and potential therapeutic targeting of the JAK2 kinase mutation.

In this issue of the Journal, Maxson et al. describe a mutation that appears to play a major role in myeloid cancer. The discovery concerns mutations in the gene encoding CSF3R, the receptor for colony-stimulating factor 3 (previously called granulocyte colony-stimulating factor, or G-CSF) in two rare myeloproliferative neoplasms, chronic neutrophilic leukemia (CNL) and atypical CML. The study warrants attention for the elegance of the scientific approach and the implications for treatment of these rare diseases. Perhaps most important, the study provides an example of the future of target discovery in cancer.

The role of CSF3R in normal hematopoiesis is to regulate neutrophil production in baseline and emergency conditions. Frameshift or nonsense mutations that truncate the cytoplasmic tail of CSF3R are common in severe congenital neutropenia, where they are thought to cause a disruption of normal neutrophil differentiation but allow for an increased proliferative response to CSF3 ligand. When severe congenital neutropenia evolves into acute myeloid leukemia (AML), truncation mutations occur in 80% of patients, sometimes accompanied by an activating point mutation in the proximal membrane domain of CSF3R in addition to the truncation mutation.

CNL and atypical CML are hardly public health menaces; they are so rare that their incidence cannot be estimated. Both are characterized by leukocytosis and a hypercellular bone marrow in the absence of known mutations (e.g., BCR-ABL). Even with standard treatment, the prognosis is bleak, with median survival of 2 to 3 years (death is usually from infection and bleeding). The genetic bases of CNL and atypical CML are unknown.

Maxson et al. performed a series of experiments that first identified a set of novel mutations in CSF3R and then validated the mutation as a legitimate target for kinase inhibition. The first step was the process of screening a variety of approaches to identify therapeutic targets in rare diseases.
of leukemia samples for mutations in the coding region of approximately 2000 genes associated with cancer signaling, including all kinases. This screening showed CSF3R mutations in 16 of 27 patients with CNL and atypical CML (59%); by contrast, the mutation was rare in patients with AML (1 of 92) and other leukemias.

Next, samples with the CSF3R mutation were tested in vitro with chemical kinase inhibitors and small interfering RNA directed against kinases known to be activated by normal CSF3R.8 These studies suggested that different types of CSF3R mutations had differential sensitivity to different therapeutic agents. Frameshift or nonsense mutations that truncated the cytoplasmic tail of CSF3R appeared to deregulate and activate its downstream signaling partners SRC kinase and TNK2 kinase (and thus were sensitive to the multikinase inhibitor dasatinib). Membrane proximal mutations appeared to cause ligand-independent activation of the downstream effector JAK2 and thus were susceptible to the JAK inhibitor ruxolitinib. The authors confirmed the transforming potential and differential drug sensitivity using in vitro colony-forming assays. Finally, the authors treated a patient whose leukemia harbored a CSF3R proximal membrane mutation. As predicted from these studies, the patient had a response to the JAK inhibitor ruxolitinib. The authors confirmed the therapeutic benefit in these rare disorders, this study is important in a broader sense. It shows the power of genetic screening to uncover new potential drug targets and provide a rationale for using drugs that are available for other indications. Notably, the association between the CSF3R mutation and CNL and atypical CML was found in a large sequencing of the “usual suspects” of cancer signaling. Skeptics often deride large-scale screening studies as fishing expeditions, although these are actually an excellent idea if the object is to catch fish. Furthermore, the work went from identification of the CSF3R mutation, through in vitro studies, to a successful clinical application without a murine model. Thus, this study bucks the common notion that one cannot learn anything of significance without engineering a mouse that nature itself could not create.

E. Donnall Thomas, winner (with Joseph E. Murray) of the Nobel Prize in Physiology or Medicine in 1990 for his pioneering work on allogeneic transplantation, often said that medical science did work not by giant breakthroughs but by small, calculated steps. This study shows the potential power of studying a small problem very carefully and is an example of what genetically informed treatment may look like in the near future. This is how we will beat cancer, one gene, one disease at a time.

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**Early-Life Wheezing and Respiratory Syncytial Virus Prevention**

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Wheezing illnesses in preschool children have perplexed clinicians for decades in terms of their differential diagnosis, short-term and long-term treatment, and prognosis with regard to the subsequent development of asthma. Although wheezing illnesses have been described in more...