Philadelphia Chromosome–Negative Myeloproliferative Disorders: An Historical Perspective

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Polycythemia vera is a prototype and also the most common of the four classical myeloproliferative disorders—chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Our understanding of the last three disorders has lagged behind in comparison to our understanding of the molecular basis of CML, which led to the development of the first targeted therapy, imatinib.

Polycythemia vera was described by two giants of medicine, Vasquez in 1892 and William Osler in 1903, who both noted rubor and strokes (and other thrombotic complications) as a manifestation of this disease. As summarized by one of many life-long students of polycythemia vera, Thomas Pearson (who popularized phlebotomy therapy), "The use of leeches and blood letting, which was for centuries the mainstay of therapy in many clinical situations, reflected the importance then attached to having too much blood." This therapeutic approach continues until today; however, recent discoveries and evidence-based medicine question its validity. In the search for validation of this standard therapy, the Framingham Study evaluated hemoglobin concentration and the risk of cerebral infarction; quoting from their report in Stroke in 1972, "Men with hemoglobin values of 15 gm or greater and women with 14 gm or more had twice as many cerebral infarctions as did their cohorts with lower values. The risk of initial development of 82 cerebral infarctions was also strikingly related to antecedent blood pressure status in both sexes and to the cigarette habit in men. When allowance is made for associated blood pressure and cigarette habit—factors found to correlate with both blood hemoglobin values and incidence of cerebral infarction—hemoglobin level had only a modest residual effect, no longer statistically significant." Skepticism about the value of phlebotomy was also recently raised by Italian investigators who, after multivariate analysis of thromboses and risk factors (ECLAP study), found the lack of correlation between hematocrit between 35 to 55 and thromboses in polycythemia vera, similar to previously published studies demonstrated a lack of correlation between hematocrit and thromboses in congenital polycythemic disorders.

The discovery of erythropoietin-independent erythroid colonies and clonal hematopoiesis provided a solid background to our understanding of molecular basis of polycythemia vera. The more recent discoveries of a somatic mutation of JAK2 V617F, exon 12 JAK2 mutations, and somatic mutations of thrombopoietin receptor (cMPL) have not only brought new insights into these non-CML myeloproliferative disorders, but also unique challenges. Unlike tumor-specific bcr/abl inhibitors, early ongoing trials of JAK2 inhibitors have thus far not reproduced the remarkable efficacy and relatively low toxicity of imatinib. Furthermore, there is growing evidence that these mutations, while important in the pathogenesis of these disorders, are not disease-initiating mutations.

Clearly, this story is not over yet, but it is hoped that progress in understanding the three Philadelphia chromosome–negative myeloproliferative disorders will continue at a rapid pace, along with the development of JAK2 inhibitors and other emerging therapies for these disorders.

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