This article, sponsored by Incyte Corporation, is based on an interview with Jerry L. Spivak, MD, conducted in May 2015. Polycythemia vera is an area of active investigation, and controversies surrounding it abound. This article reflects the personal perspective of Dr Spivak.

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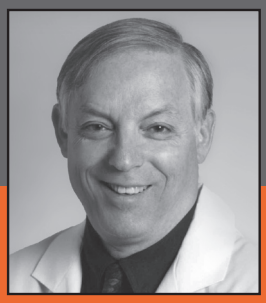

Polycythemia vera:

Focus on aggressive polycythemia vera

Polycythemia vera (PV) is a clonal disorder involving a multipotent hematopoietic progenitor cell characterized by the accumulation of phenotypically normal red blood cells, white blood cells, and platelets. In some patients, transformation to myelofibrosis (MF) with extramedullary hematopoiesis or acute leukemia can also occur. Despite recent progress in the field, several important issues remain controversial; most importantly, how to identify patients with PV at high risk of transformation who would benefit from early institution of therapy, and which therapy would be most appropriate for these patients. A recent study has identified an accurate molecular assay to identify the subset of these high-risk patients with PV.

Using gene expression profiling of circulating PV CD34+ stem cells, investigators were able to distinguish patients with PV in whom the disease is aggressive and associated with increased thrombotic events, increased transformation to acute leukemia, and decreased survival from patients with a more indolent clinical course. Interestingly, these patients dysregulate a set of genes that are also dysregulated in both the chronic and blast phases of chronic myelogenous leukemia (CML).

Identifying aggressive disease

Despite decades of scrutiny, major gaps have remained in our ability to identify prognostic factors in PV—gaps that impede timely institution of therapy. Although median survival in most patients with PV is measured in decades, the disease does not always have an indolent course. A retrospective analysis of a large series of patients with PV found median survival to be 18.9 years from diagnosis,[1] but this median survival included all patients with PV. However, other studies[2,3] have found a subset of patients with PV, between 10% and 15%, with a much lower survival rate, estimated at 5.8 years,[4] an estimate consistent with the median survival in primary myelofibrosis (PMF).[5] In patients with PV who develop MF and extramedullary hematopoiesis, the prognostic criteria employed for PMF (Dynamic International Prognostic Scoring System Plus) can be employed for risk stratification.[6] By this point, however, therapeutic options are limited and generally supportive if bone marrow transplantation is not feasible, because patients with post-PV MF essentially have a form of myelodysplasia and are prone to spontaneous acute leukemia.

Phenotypic variability of PV

What is needed is a way to identify which patients with PV will have an indolent course and which will have an aggressive course before transformation to MF or acute myelogenous leukemia occurs. Importantly, at diagnosis, both types of patients are at risk for the most common PV complications, thrombosis (either arterial or venous) and hemorrhage. PV is the most common myeloproliferative neoplasm because it is the ultimate phenotype of gene mutations activating the JAK-STAT (Janus-associated kinase signal transducers and activators of transcription) signal transduction pathway.[7] Because PV involves a pluripotent hematopoietic stem cell (HSC), it is usually characterized by trilineage hematopoietic cell hyperplasia, but phenotypic variability appears to be the rule rather than the exception with respect to presentation of PV, and the first obligation with respect to institution of the appropriate therapy is accurate diagnosis. The routine use of the complete blood count has increased the identification of patients with PV before hyperproliferation of all 3 blood cell lineages has occurred. Seminal investigations have established that PV can present as isolated erythrocytosis,[8-10] isolated leukocytosis,[11] isolated thrombocytosis,[12,13] or combinations of these 3 (Table 1).[8,14-16] This variability of clinical presentation reflects host genetic diversity in which sex is a major factor.[17,18]

A subset of patients with PV will have median survival consistent with that of PMF, estimated to be 5.8 years.[2-4]

Host genetic diversity is a major factor in the phenotypic behavior of PV.[17,18]

Table 1: Presenting Blood Counts at Time of Diagnosis Document Phenotypic Diversity of PV	
Isolated erythrocytosis	18%[15]
Isolated leukocytosis	Case study[11]
Isolated thrombocytosis	7%-20%[7,19,20]
Erythrocytosis and thrombocytosis	16%-30%[8,14]
Erythrocytosis and leukocytosis	13%-31%[8,14,15]
Erythrocytosis, thrombocytosis, and leukocytosis	40%[15]

PV, polycythemia vera.

Isolated erythrocytosis: clinical correlates

Isolated erythrocytosis is not a common presentation of PV; it occurs in fewer than 20% of cases.[15] Many of these patients will have a mutation in *JAK2* exon 12, or rarely *LNK*. Thrombosis and hemorrhage, the most frequent serious complications of PV,[21] stem directly from prolonged elevation of the red cell mass or extreme thrombocytosis (platelets >1,000 × 10^9/L).[22] However, it has been our experience that most patients with isolated erythrocytosis alone do well, surviving many decades with few complications. Excess red blood cell production is readily controlled by phlebotomy, which immediately reduces erythrocyte mass and lowers blood viscosity.[23,24] Periodic phlebotomies, monthly initially, can generally maintain hematocrit (Hct) levels of <45% in men and <42% in women,[25-28] while inducing a state of iron deficiency that slows expansion of the erythrocyte mass. An Hct target of <45% has been validated in men, while for women with PV, the Tromsø Study with 26,108 subjects found that women with PV and an Hct of ≥42% had an age-adjusted 1.51-fold higher risk for total venous thromboembolism.[26] A desired side effect of phlebotomy, iron deficiency, is not a liability. Contrary to popular opinion, patients who are iron deficient and have PV do not have an aerobic deficit.[29]

Isolated leukocytosis: clinical correlates

Leukocytosis is an expected event in PV and, while uncommon, isolated leukocytosis can be the presenting manifestation of PV. In 3 large studies, 13% to 31% of patients with PV presented with erythrocytosis and leukocytosis (Table 1).[8,14,15] In the author's opinion, a minor degree of leukocytosis has no clinical significance, and in asymptomatic patients with uric acid >9 mg/dL, it requires no therapy. In some patients, however, substantial leukocytosis occurs in association with splenomegaly. Progressive leukocytosis is a harbinger of extramedullary hematopoiesis or disease acceleration and can thus serve as a guide to disease control following initiation of therapy.

Isolated thrombocytosis: clinical correlates

It is well documented that 7% to 20% of patients (particularly women) present initially with isolated thrombocytosis.[19,20] For this reason, PV should be considered in the differential diagnosis of isolated thrombocytosis. Platelet number alone is not a critical determinant of hypercoagulability in PV at any level, but thrombocytosis is associated with transient microvascular blockage manifested by erythromelalgia[30,31] or a constellation of neurologic symptoms that include intractable migraine.[32] These can be reversed or prevented by aspirin-induced platelet inactivation or a reduction in the platelet count,[33,34] suggesting that both platelet activation and platelet number are important with respect to microvascular events once the red cell mass has been appropriately reduced.[35]

PV should be considered in the differential diagnosis of isolated thrombocytosis.

Erythrocytosis and thrombocytosis: clinical correlates

Approximately 16% to 30% of patients can present with erythrocytosis and thrombocytosis.[8,14] This may be due to involvement of a specific CD34+ progenitor cell[36] that gives rise to only erythrocytes and platelets, or due to the fact that granulocytes can use JAK1 instead of JAK2. Erythroid progenitor cells appear to be more sensitive to *JAK2*V617F than myeloid progenitor cells.[37] Although the progress of PV may vary widely, in our experience, patients presenting with erythrocytosis and thrombocytosis generally have an indolent course. In this regard, it needs to be emphasized that contrary to popular belief, PV and essential thrombocythemia are separate disease entities: Both have different gene expression profiles; CD34+ cell clonal burdens; male-female ratios; expression of *JAK2*V617F, calreticulin (*CALR*), and thrombopoietin (*MPL*) gene mutations; and different natural histories.

Hyperproliferation of all 3 cell lines generally characterizes more aggressive PV.

When PV presents with erythrocytosis, leukocytosis, and thrombocytosis, the diagnosis is rarely in doubt. Surprisingly, the World Health Organization diagnostic criteria for PV ignore the latter 2 cell lineages as well as splenomegaly.[38,39] Approximately

40% of patients with PV present with hyperproliferation of all 3 cell lines.[15] This form of the disease is generally more aggressive and frequently associated with splenomegaly and constitutional symptoms.

Managing risk in PV

PV, a chronic but progressive disorder, has increased proliferation of morphologically normal blood cells as its most visible manifestation, because lineage-committed hematopoietic cells are very sensitive to JAK-STAT pathway activation. However, PV is basically a disorder of stem cell accumulation, not progenitor cell proliferation. The behavior of the transformed HSC is less apparent than the myeloproliferation of lineage-committed cells, but its activity is more central to disease pathology and is myeloaccumulative because its proliferation is not greatly influenced by the JAK-STAT pathway. It is nevertheless possible that activated JAK2 could impact the HSC negatively by damaging DNA, a problem of significant importance because HSCs normally continually acquire new mutations spontaneously with aging.[40,41] Thus, while the early manifestations of PV—thrombosis, hemorrhage, ocular migraine, transient ischemic attacks, erythromelalgia, aquagenic pruritus, acid reflux, gout, and fatigue—represent the consequences of overproduction of mature blood cells together with overproduction of inflammatory cytokines,[42] the later manifestations of the disease—splenomegaly, extramedullary hematopoiesis, MF, bone marrow failure, and transformation to acute leukemia—represent the behavior of the involved HSC. Therefore, long-term risk could be minimized by alleviating the known consequences of myeloproliferation and suppressing HSC accumulation while avoiding agents that can induce additional DNA damage in the involved HSC.

At diagnosis, the majority of patients with PV will carry only a mutation in *JAK2*[43] or uncommonly in *CALR*.[22] Therapy should avoid inducing further mutations.[44] Alleviation of the symptoms associated with myeloproliferation can be accomplished in most patients by nongenotoxic means, including phlebotomy, to induce a sex-appropriate Hct (45% in men, 42% in women) with periodic phlebotomy to maintain Hct control.[28,45] Aspirin is effective for microvascular events but only if the Hct is controlled. *Helicobacter* infections are common in PV, and hyperuricemia can develop with leukocytosis, but neither leukocytosis nor thrombocytosis has ever been proved to be associated with thrombosis.[46,47] Rather, a very high platelet count can be associated with hemorrhage, although not usually spontaneous, due to catabolism by platelets of high-molecular-weight von Willebrand factor multimers.[48] Thrombocytosis may also be associated with intractable migraine.[32,42] In such instances, as well as with significant aquagenic pruritus, cytoreduction will be necessary. However, in this author's view, if we have learned anything in the last 50 years, it is that no chemotherapeutic agent is safe in PV because every one of them can induce acute leukemia in a disease in which there is already an increased baseline rate of spontaneous acute leukemia.[49] Furthermore, no chemotherapeutic agent can prevent either arterial or venous thrombosis, hinder the development of MF or bone marrow failure, or prolong survival.[49-52] In this regard, hydroxyurea is no different from any other form of chemotherapy that impedes DNA repair.[53,54] Although some studies have arrived at a different conclusion,[55] in the view of this author, the accumulated clinical and research data strongly support the leukemogenicity of hydroxyurea in the myeloproliferative neoplasms.[53,54,56]

The genetics of high risk

Fortunately, most patients with PV do not progress to MF, bone marrow failure, or acute leukemia and can be spared from receiving genotoxic agents, particularly because nongenotoxic therapies are available, if necessary. The important issue now is how to identify those patients with PV who would benefit from early intervention before MF or marrow failure ensues.

It is important to identify patients with PV who may be at higher risk.

A recent study suggests that such patients are identifiable through the use of gene expression profiling.[57] Although next-generation gene sequencing has identified many gene mutations in patients with PV, most do not occur frequently enough to serve as a generalized molecular diagnostic or prognostic marker, and when they do, it is late in the course of the disease. Gene expression, however, serves as the ultimate collective consequence of these various mutations. Although past studies of gene expression in PV could distinguish patients with PV from normal individuals, they provided no prognostic information because most studies were performed with granulocytes, not HSCs. However, by comparing men and women who have PV with their normal sex-specific counterparts, it was found that not only did each group differ from normal counterparts, but gene expression also differed significantly between men and women patients with PV.[57] Most importantly, it was found that the expression of 102 genes was common to both sexes, suggesting that this core group of genes was integrally involved in the pathogenesis of PV.

As few as 10 genes may make it possible to identify high-risk PV

Analysis of the 102 differentially regulated genes revealed the varied involvement of genes in numerous processes, including production of collagen, production of inflammatory cytokines, production of procoagulants, enhancement of HSC expansion, and process of leukemic transformation. Most importantly, the 102 genes could be used to separate patients with PV according to the clinical phenotype (aggressive or indolent) of their disease, and the number of genes required for this purpose could be

reduced to 10. Finally, as proof of principle, it was found that 55 of the 102 core genes in PV were also found to be dysregulated in CML, a disorder due to the constitutively activated kinase BCR-ABL (breakpoint cluster region-Abelson leukemia virus protein), which also activates the JAK-STAT pathway.[57] While not yet translated into clinical practice, these data confirm the different gene expression behavior of men and women patients with PV that fits with the observed differences in their clinical behavior and allowed the genetic identification of 2 clinical forms of PV. Obviously, no single therapy will fit all patients with PV, but those with an indolent form of the disease can be spared exposure to genotoxic drugs, while those with an aggressive form may benefit from early institution of drugs such as pegylated interferon. Chemotherapy should be saved for situations in which potential risks can be balanced by therapeutic benefits.

Recent data suggest the existence of an aggressive form of PV involving dysregulation of some genes that are also involved in CML.

This article reflects the personal perspective of Dr Jerry L. Spivak, who has served as a consultant for Incyte Corporation (Wilmington, DE) and was compensated for his participation in this interview.

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