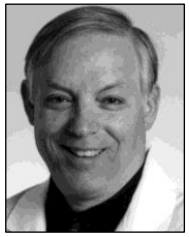
Focus on aggressive polycythemia vera



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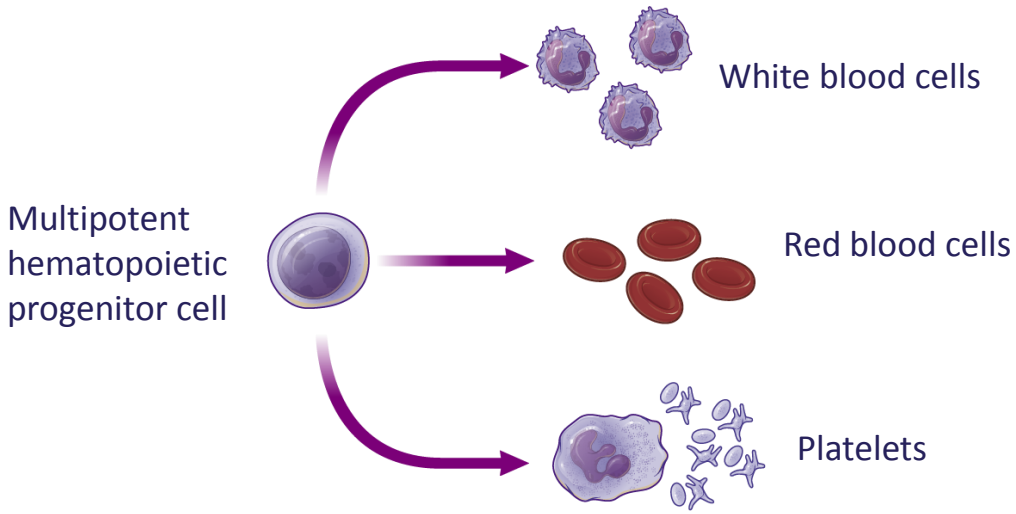
Disclosure

These slides were developed by Incyte Corporation (Wilmington, DE) from an interview with Jerry L. Spivak, MD, conducted in May 2015. Dr Spivak has served as a consultant for Incyte Corporation and was compensated for his participation.

Introduction to polycythemia vera (PV)

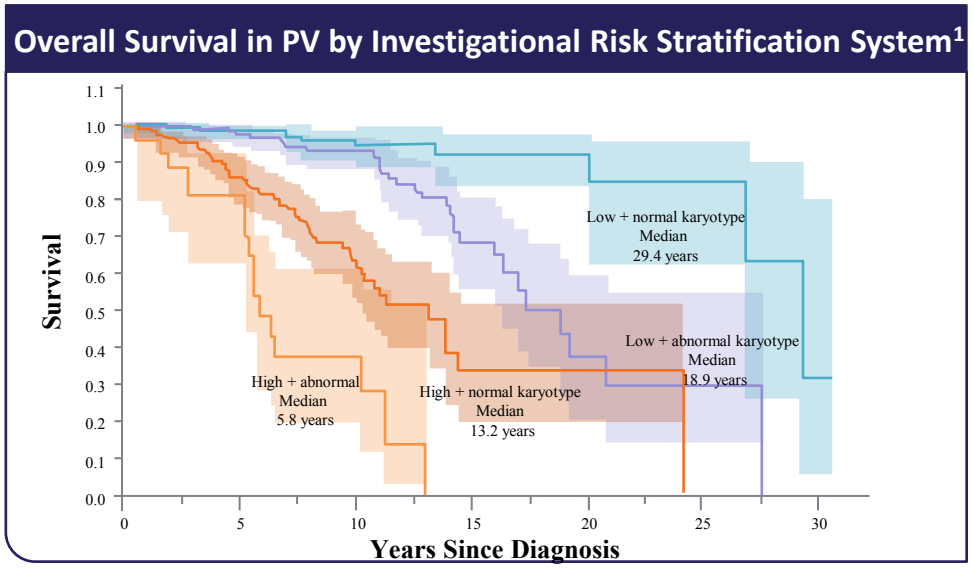
- A clonal disorder involving a multipotent hematopoietic progenitor cell[1]
- Characterized by the accumulation of phenotypically normal red blood cells, white blood cells, and platelets, alone or in combination, in the absence of a definable stimulus[1]



Reference: 1. Spivak JL. *Blood*. 2002;100(13):4272-4290.

There is an aggressive subtype of PV

- One study found a subset of patients with PV with a much lower median survival rate, estimated at 5.8 years[1]
- This is consistent with the median survival in primary myelofibrosis[2]



Risk-stratified survival that considers karyotype in 631 patients with PV.

PV, polycythemia vera.

References: 1. Tefferi A et al. *Leukemia*. 2013;27(9)(suppl):1874-1881. **2.** Tefferi A et al. *Blood*. 2014;124(16):2507-2513.

No guidelines exist for identifying PV with an aggressive course

- Patients with PV who are aged <60 years and have no history of thrombosis are generally considered "low risk"[1]
- This stratification is designed to estimate the likelihood of thrombotic complications in PV, but not survival[1]
- The phenotypic variability of PV provides some clues to outcomes[2]
- In addition, a study using gene expression profiling of CD34+ hematopoietic stem cells was able to accurately identify a subset of patients with aggressive PV[3]

References: 1. Tefferi A et al. *Am J Hematol*. 2015;90(2):163-173. **2.** Spivak JL. Interview. May 20, 2015. Incyte Corporation. Wilmington, DE. **3.** Spivak JL et al. *N Engl J Med*. 2014;371(9):808-817.

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The phenotypic variability of PV

- PV may present as erythrocytosis, leukocytosis, or thrombocytosis, alone or in combination

Presenting Blood Counts at Time of Diagnosis of PV	
Isolated erythrocytosis	18%[1]
Isolated leukocytosis	Case study[2]
Isolated thrombocytosis	7%-20%[3,4]
Erythrocytosis and thrombocytosis	16%-30%[5,6]
Erythrocytosis and leukocytosis	13%-31%[1,5,6]
Erythrocytosis, thrombocytosis, and leukocytosis	40%[1]

PV, polycythemia vera.

References: 1. Szur L et al. *Q J Med*. 1959;28:397-424. **2.** Taylor KM et al. *Leukemia*. 1989;3(6):419-422. **3.** Moliterno AR et al. *Exp Hematol*. 2008;36(11):1480-1486. **4.** Jantunen R et al. *Ann Hematol*. 1999;78(5):219-222. **5.** Berglund S et al. *Eur J Haematol*. 1992;48(1):20-26. **6.** Berlin NI. *Semin Hematol*. 1975;12(4):339-351.

Isolated erythrocytosis in PV

- In our practice, isolated erythrocytosis is seen in fewer than 20% of cases of PV[1,2]
- Excess red blood cell production is readily controlled by periodic phlebotomy, which immediately[3,4]:
  - reduces erythrocyte mass
  - lowers blood viscosity

Threshold for Erythrocytosis[5]

Females: >16.5 g/dL

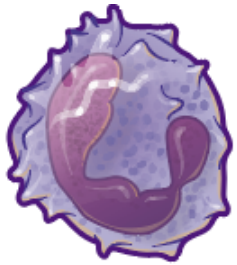
Males: >18.5 g/dL

References: 1. Szur L et al. *Q J Med.* 1959;28:397-424. **2.** Spivak JL. Interview. May 20, 2015. Incyte Corporation. Wilmington, DE. **3.** Segel N et al. *Clin Sci.* 1967;32(3):527-549. **4.** Dameshek W. *Blood*. 1968;32(3):488-491. **5.** Tefferi A et al. *Leukemia.* 2008;22(1):14-22.

Leukocytosis in PV

- While uncommon, isolated leukocytosis can be the presenting manifestation of PV[1]
- In the author's experience, a minor degree of leukocytosis has no clinical significance and requires no therapy in asymptomatic patients with uric acid >9 mg/dL[2]
- Progressive leukocytosis is a harbinger of extramedullary hematopoiesis or disease acceleration and can thus serve as a guide to disease control

Threshold for Leukocytosis[3]



>10 × 10^9/dL

References: 1. Taylor KM et al. *Leukemia*. 1989;3(6):419-422. **2.** Spivak JL. Interview. May 20, 2015. Incyte Corporation. Wilmington, DE. **3.** Barosi G et al. *Blood.* 2013:121(23):4778-4781.

Isolated thrombocytosis in PV

- Occurs in 7% to 20% of patients with PV (particularly women)[1,2]
- PV should be considered in the differential diagnosis of isolated thrombocytosis[3]
- Thrombocytosis in PV is associated with transient microvascular blockage manifested by erythromelalgia[4,5] or a constellation of neurologic symptoms that include intractable migraine[6]
  - These can be reversed or prevented by aspirin-induced platelet inactivation or a reduction in the platelet count[7,8]

Threshold for Thrombocytosis[9]

>400 × 10^9/dL

References: 1. Moliterno AR et al. *Exp Hematol*. 2008;36(11):1480-1486. **2.** Jantunen R et al. *Ann Hematol*. 1999;78(5):219-222. **3.** Spivak JL. Interview. May 20, 2015. Incyte Corporation. Wilmington, DE. **4.** Edwards EA et al. *JAMA*. 1970;214(8):1463-1467. **5.** Michiels JJ. *Semin Thromb Hemost*. 1997;23(5):441-454. **6.** Michiels JJ et al. *Neurology*. 1993;43(6):1107-1110. **7.** van Genderen PJ et al. *Thromb Haemost*. 1995;73(2):210-214. **8.** Rinder HM et al. *Blood*. 1998;91(4):1288-1294. **9.** Barosi G et al. *Blood*. 2013:121(23):4778-4781.

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Erythrocytosis, leukocytosis, and thrombocytosis in PV

- Approximately 40% of patients with PV present with hyperproliferation of all 3 cell lines[1]
  - This form of the disease is generally more aggressive and frequently associated with splenomegaly and constitutional symptoms[2]

References: 1. Szur L et al. *Q J Med.* 1959;28:397-424. **2.** Spivak JL. Interview. May 20, 2015. Incyte Corporation. Wilmington, DE.

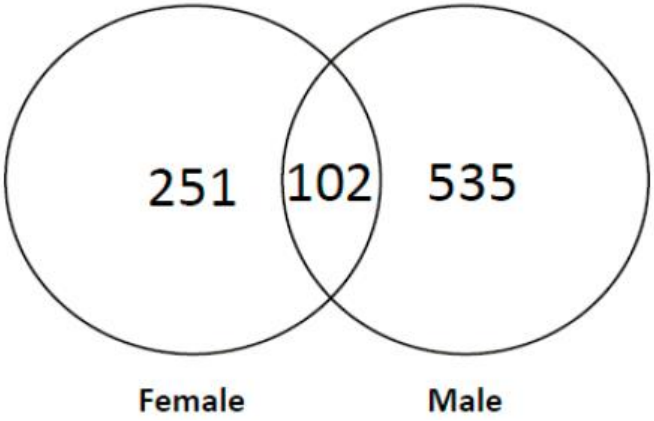
The genetics of high-risk patients

- A study suggests that gene expression profiling may make it possible to identify the subset of patients with aggressive PV[1]
  - These patients might benefit from early intervention before myelofibrosis or marrow failure ensues
- Most previous gene expression studies were performed with granulocytes and provided some diagnostic but no prognostic information
- The new study analyzed gene expression in CD34+ peripheral-blood hematopoietic stem cells using oligonucleotide microarray technology after correcting for potential confounding by sex[1]

Reference: 1. Spivak JL et al. *N Engl J Med.* 2014;371(9):808-817.

Dysregulated genes in men and women with PV

Number of dysregulated genes in PV



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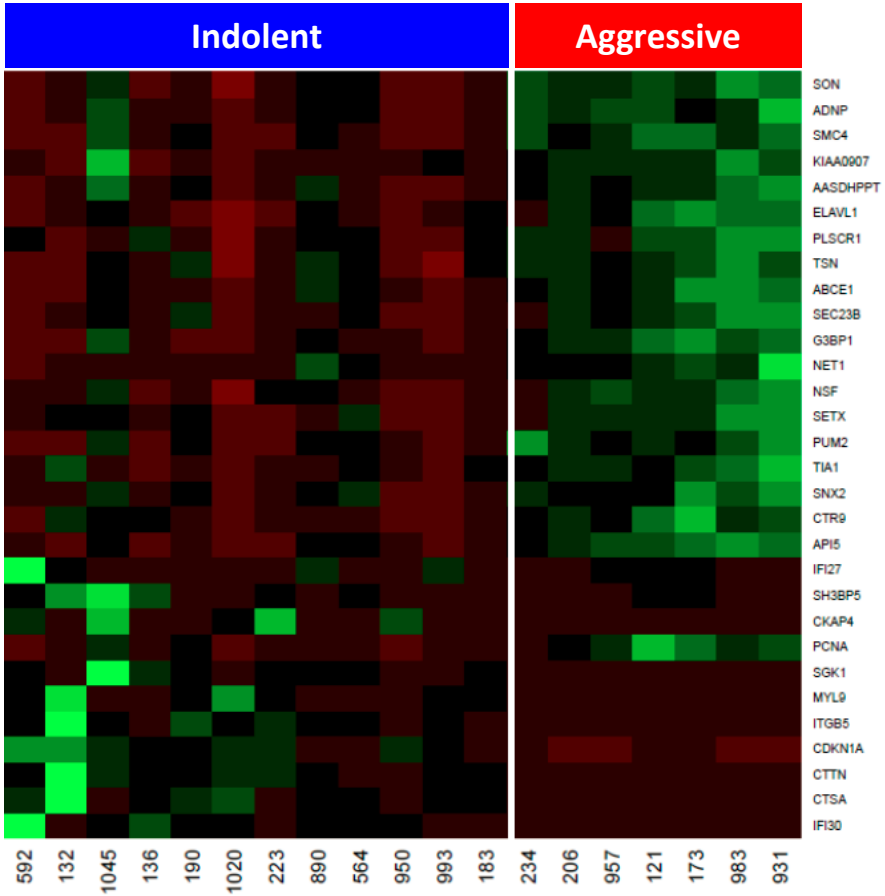
- Men with PV had twice as many upregulated or downregulated genes as women with PV, but there was a core of 102 genes that were consistently dysregulated in the disease process[1]
- 55 of these 102 genes are also dysregulated in chronic myelogenous leukemia[2]

PV, polycythemia vera.

Reference: 1. Spivak JL et al. *N Engl J Med.* 2014;371(9)(suppl):808-817. **2.** Spivak JL et al. *N Engl J Med.* 2014;371(9):808-817.

Prediction of aggressive vs indolent PV

- These 102 core genes were used to identify a subset of patients with increased thrombotic events, increased transformation to acute leukemia, and decreased survival[1,2]
- The number of genes required for distinguishing indolent from aggressive PV could be reduced to 10[1,2]



References: 1. Spivak JL et al. *N Engl J Med.* 2014;371(9):808-817. **2.** Spivak JL et al. *N Engl J Med.* 2014;371(9)(suppl):808-817.

Conclusions

- The course of PV may span decades, but a subset of patients has aggressive disease with outcomes comparable to those of myelofibrosis[1,2]
- No guidelines exist to identify PV that is aggressive with respect to splenomegaly, leukemic or fibrotic transformation, or survival
- In some cases, the type(s) of cell(s) overexpressed may provide some clues to outcomes[3]
- A study using gene expression profiling of CD34+ hematopoietic stem cells was able to accurately identify the subset of patients with increased thrombotic events, increased transformation to acute leukemia, and decreased survival[4]

References: 1. Tefferi A et al. *Leukemia*. 2013;27(9)(suppl):1874-1881. **2.** Tefferi A et al. *Blood*. 2014;124(6):2507-2513. **3.** Spivak JL. Interview. May 20, 2015. Incyte Corporation. Wilmington, DE. **4.** Spivak JL et al. *N Engl J Med.* 2014;371(9):808-817.

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