Recognizing and treating the patient with high-risk polycythemia vera

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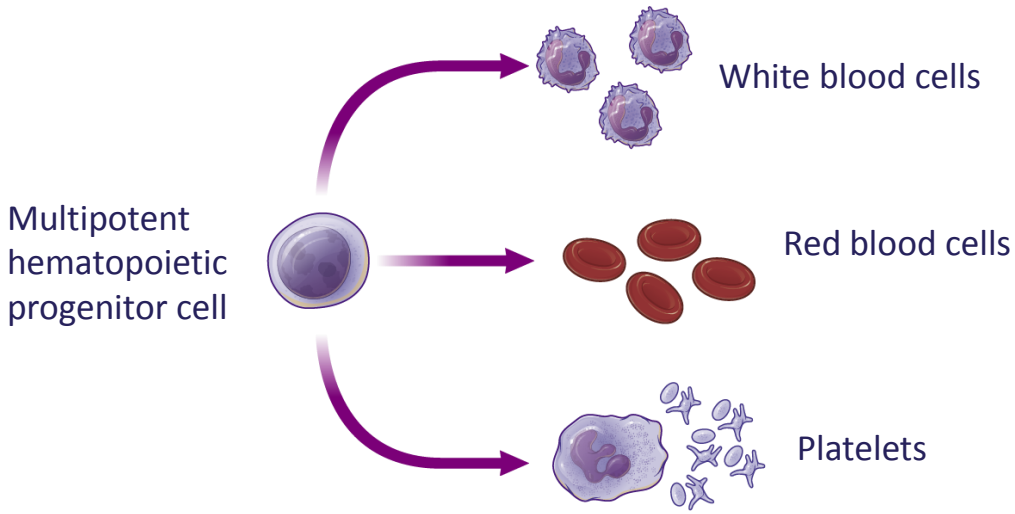
Disclosure

These slides were developed by Incyte Corporation (Wilmington, DE) from an interview with Kim-Hien Dao, DO, PhD, conducted in July 2015. Dr Dao has served as a consultant for Incyte Corporation and was compensated for her participation.

Introduction to polycythemia vera (PV)

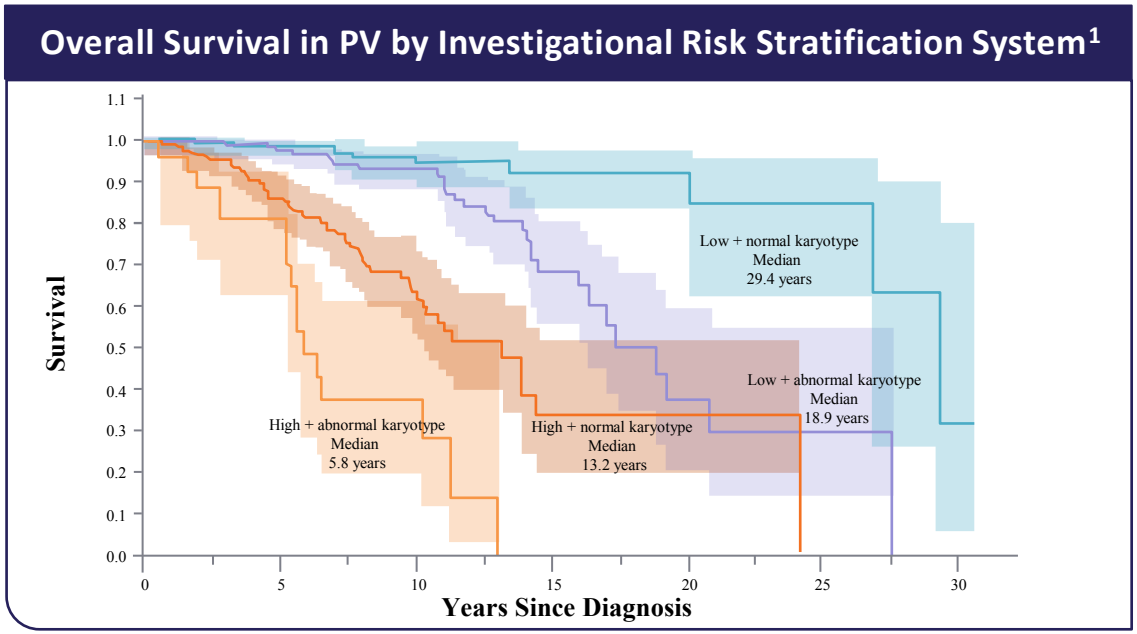
- PV is a chronic clonal myeloproliferative neoplasm characterized by increased red cell mass[1]
- Elevated white blood cell and platelet counts are also common[1]



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

Polycythemia vera may be indolent or aggressive

- Patients may live for decades, but studies have defined 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.

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Conventional factors to distinguish high-risk polycythemia vera

- The current rule of thumb is that patients aged <60 years who have no history of thrombosis are "low risk"[1]
- This stratification is designed to estimate the likelihood of thrombotic complications in PV, but not disease progression or survival[1]
- However, there are many other possible indications that PV may be high risk[2]
- These indicators of inadequately controlled, high-risk disease are not confined to any one phase of treatment and may occur at any time during the course of the disease, ultimately reducing survival[3]

References: 1. Tefferi A et al. *Am J Hematol*. 2015;90(2):163-173. **2.** Dao KH. Interview. July 10, 2015. Incyte Corporation. Wilmington, DE. **3.** Reiter A et al. *Curr Hematol Malig Rep*. 2016;11(5):356-367.

Often underappreciated risk factors

- Suboptimal response to therapy[1]
  - An uncontrolled hematocrit level
  - Thrombotic events
  - Leukocytosis
  - Thrombocytosis
  - Excessive symptoms or complications
  - Increasing spleen size
- Classic cardiovascular risk factors (eg, diabetes)[2]

References: 1. Reiter A et al. *Curr Hematol Malig Rep*. 2016;11(5):356-367. **2.** Dao KH. Interview. July 10, 2015. Incyte Corporation. Wilmington, DE.

Common challenges in controlling polycythemia vera[1]

- Rural patient, no access to a hematologist
- Physician complacency concerning target hematocrit level
- Hematocrit level not monitored closely after diagnosis and not rapidly brought under control
  - Phlebotomy may initially be required frequently, at times every other day
  - The complete blood count should be checked at least every 4 weeks until a steady-state target hematocrit level is achieved
  - Dr Dao's protocol includes initiating phlebotomy immediately to bring the hematocrit level below 45% for men and at 42% for women
  - Many of Dr Dao's patients are resistant to or intolerant of hydroxyurea

Reference: 1. Dao KH. Interview. July 10, 2015. Incyte Corporation. Wilmington, DE.

Case 1: Hydroxyurea failure in an elderly man with depression and an unrelated skin problem[1]

- A 79-year-old man with *JAK2*V617F mutation–positive PV was followed for approximately 5 years without any major constitutional symptoms or past thrombotic events
- He was maintained on hydroxyurea 500 mg 3 times daily and with phlebotomy every 4 to 6 weeks to achieve a target hematocrit level of <45%
- He then developed severe palmoplantar psoriasis and his phlebotomy needs escalated to every 3 weeks
- Therapy for the palmoplantar psoriasis led to severe ulcerations and poor wound healing while on hydroxyurea
- A significant depressive episode and his advanced age suggested caution with the use of pegylated interferons

Reference: 1. Dao KH. Interview. July 10, 2015. Incyte Corporation. Wilmington, DE.

Notes on case 1: Hydroxyurea failure in an elderly man with depression and an unrelated skin problem

- Mucocutaneous problems with hydroxyurea can become a serious problem or dose-limiting issue[1]
  - Hydroxyurea should be prescribed with caution or stopped altogether in the presence of a preexisting wound or skin ulcer, whether it is from:
    - surgery
    - long-standing diabetes
    - an unrelated treatment
  - Approximately 10% of Dr Dao's patients with PV are not candidates for hydroxyurea because of wounds, including surgery and other ulcerative skin issues[1]

In our practice, we are more concerned about the effect of hydroxyurea failure in terms of hematocrit control rather than it being a biomarker for worse disease.[1]

References: 1. Dao KH. Interview. July 10, 2015. Incyte Corporation. Wilmington, DE.

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Notes on case 1: Hydroxyurea failure in an elderly man with depression and an unrelated skin problem

- Warnings and precautions regarding the use of pegylated interferons include[1]:
  - significant depression or other neuropsychiatric disorders
  - history or presence of an autoimmune disease
  - history of significant or unstable cardiac disease
  - retinal disorders
  - hepatic failure

Our facility has also noted that elderly patients are less likely than younger patients to tolerate interferon.[2]

References: 1. Pegasys Prescribing Information. Hoffmann-La Roche, Inc. South San Francisco, CA. **2.** Dao KH. Interview. July 10, 2015. Incyte Corporation. Wilmington, DE

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Case 2: Hydroxyurea failure in a young woman[1]

- A 36-year-old woman presented 8 years ago with ascites and liver enzyme abnormalities during elective preoperative work-up
- She was diagnosed with Budd-Chiari syndrome (hepatic vein thombosis)
- As a result of this complication, often associated with PV, she was tested for the *JAK2*V617F mutation, which came back positive
- She was diagnosed with *JAK2*V617F-positive PV and started on hydroxyurea
- Gastrointestinal upset occurred upon escalation of the dose of hydroxyurea
- Complete blood count revealed erythrocytosis, thrombocytosis, and leukocytosis
- She has been maintained on hydroxyurea while alternating between doses of 1,000 mg daily and 500 mg daily, with phlebotomy every 3 to 4 months
- Her spleen has started to enlarge and phlebotomy requirements have escalated to monthly
- Despite these measures, her hematocrit level remains in the 46% to 48% range

Reference: 1. Dao KH. Interview. July 10, 2015. Incyte Corporation. Wilmington, DE.

Notes on case 2: Hydroxyurea failure in a young woman[1]

- High-risk patient with Budd-Chiari syndrome
  - Few symptoms, but the complete blood count every 4 to 6 weeks indicated a need for phlebotomy
    - Phlebotomy still failed to control the hematocrit level to 42%
    - Gastrointestinal upset ruled out escalation of dose of hydroxyurea
    - Trilineage hyperplasia
    - Enlarging spleen, currently monthly phlebotomy

The patient was averse to injections (eliminating interferon) and requested more information on alternative therapy.[1]

Reference: 1. Dao KH. Interview. July 10, 2015. Incyte Corporation. Wilmington, DE.

New risk factors in polycythemia vera[1]

- New risk factors may be helpful in communicating prognosis to the patient, but in high-risk disease, the goals of therapy remain the same
- These parameters in isolation would not change Dr Dao's disease management. Besides age >60 and prior thrombosis, other high-risk features exist, including:
  - poor hematocrit control
  - cardiovascular risk factors
  - leukocytosis
  - hydroxyurea failure
  - excessive or escalating symptoms
  - enlarging spleen
  - recurrent thromboses

Reference: 1. Dao KH. Interview. July 10, 2015. Incyte Corporation. Wilmington, DE.

Conclusions

- A subset of patients with PV has aggressive disease with outcomes comparable to those of myelofibrosis[1,2]
- In my opinion, it is essential for the hematocrit level to be promptly reduced to a sex-appropriate target, with frequent follow-up until the target is reached[3]
- In rural areas where the patient must be followed by a primary care physician, a hematologist can explicitly communicate the importance and seriousness of strict hematocrit control[3]
- There is no place for complacency with high-risk patients. Patients who have experienced hydroxyurea failure need alternative therapies to reduce the risk for PV-associated complications[3]

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.** Dao KH. Interview. July 10, 2015. Incyte Corporation. Wilmington, DE.

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