Recognizing and treating the patient with high-risk polycythemia vera

Kim-Hien Dao, DO, PhD
Oregon Health & Science University
Portland, Oregon
Disclosure

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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\(^1\)


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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\(^2\)

**Overall Survival in PV by Investigational Risk Stratification System\(^1\)**

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

**References:**

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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\(^3\)


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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)\(^2\)


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Common challenges in controlling polycythemia vera

- 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


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

- A 79-year-old man with JAK2V617F 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


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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\(^1\)

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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.\(^1\)

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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:
  - 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.


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Case 2: Hydroxyurea failure in a young woman

- 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 thrombosis)
- As a result of this complication, often associated with PV, she was tested for the JAK2V617F mutation, which came back positive
- She was diagnosed with JAK2V617F-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


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Notes on case 2: Hydroxyurea failure in a young woman\textsuperscript{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

\textit{The patient was averse to injections (eliminating interferon) and requested more information on alternative therapy.}\textsuperscript{1}


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New risk factors in polycythemia vera

- 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

Conclusions

- A subset of patients with PV has aggressive disease with outcomes comparable to those of myelofibrosis\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{3}


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