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Polycythemia Vera Facts

No. 13 in a series providing the latest information for patients, caregivers and healthcare professionals

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Highlights

- Polycythemia vera (PV) is one of a related group of blood cancers known as "myeloproliferative neoplasms" (MPNs) in which cells in the bone marrow that produce the blood cells do not develop and function normally.
- PV begins with one or more acquired changes (mutations) to the DNA of a single blood-forming cell. This results in the overproduction of blood cells.
- Almost all patients with PV have a mutation of the *JAK2* (Janus kinase 2) gene. This mutated gene likely plays a role in the onset of PV. However, its precise role as the cause of the disease is still under study.
- In PV, red cells, white cells and, often, platelets are overproduced. Signs, symptoms and complications of PV result from too many red cells, and often, too many platelets in the blood. The white cell count, especially the number of neutrophils (a type of white blood cell), may also increase, but is not a cause of any significant effects.
- Medical supervision of individuals with PV is important to prevent or treat complications.
- PV is a chronic disease. Although it is not curable, PV can usually be managed effectively for very long periods, even decades. But it may shorten life expectancy in some patients.

Introduction

Polycythemia vera (PV) is one of several "myeloproliferative neoplasms" (MPNs), a term used to group a number of blood cancers that share several features, especially the clonal production of blood cells. All clonal diseases are types of cancer that begin with one or more changes to the DNA in a single cell: the abnormal cells that are in the bone marrow or in the blood are a result of that one mutant cell.

Other MPNs include *essential thrombocythemia* and *myelofibrosis*.

PV results from uncontrolled blood cell production, especially red cells, as a result of acquired mutations in an early blood-forming cell. Because this early cell has the capability to form not only red cells, but also white cells and platelets, any combination of these cell lines may be affected.

This fact sheet about PV provides information about diagnosis, treatment, new treatments being investigated in clinical trials and support resources.

Causes

The cause of PV is not fully understood. Almost all patients with PV have a mutation of the *JAK2* (Janus kinase 2) gene. This mutated gene likely plays a role in the onset of PV. However, its precise role as the cause of the disease is still under study.

Most patients with PV do not have a family history of the disease. However, occasionally there is more than one family member with the disease. PV is more prevalent among Jews of Eastern European descent than other Europeans or Asians. For all races and ethnicities, the incidence (newly diagnosed cases) of PV is approximately 2.8 per 100,000 population of men and approximately 1.3 per 100,000 population of women. The prevalence (estimated number of people in a population with a diagnosis of a disease) of PV is approximately 22 cases per 100,000 people. This prevalence has been shown in several small studies. The average age at which PV is diagnosed is 60 to 65 years. It is uncommon in individuals younger than 30 years.

PV can usually be managed effectively for a long time. People with PV who receive treatment often have a normal or near-normal quality of life. With careful medical supervision and therapy, PV does not usually interfere significantly with everyday activities and employment.

Signs, Symptoms and Complications

The signs, symptoms and complications of PV occur because there are too many red cells, and often, too many platelets in the blood. An increase in the number of white cells does not put the patient at higher risk of infection or cause other significant effects.

Too many red blood cells can make the patient's blood more viscous (thick) so the blood does not flow efficiently. High platelet counts can contribute to the formation of clots (thrombi). Underlying vascular disease, common in older persons with PV, can increase the risk of clotting complications. The clots may cause serious problems, such as stroke, heart attack, deep vein thrombosis or pulmonary embolism. Blood clots occur in about 30 percent of patients even before the PV diagnosis is made. During the first 10 years after a diagnosis of PV, 40 to 60 percent of untreated PV patients may develop blood clots.

Support for this publication provided by Incyte

Some people have few troublesome symptoms and PV may only be discovered when blood counts are done during a periodic health examination. However, people should be aware of the following signs, symptoms, and complications of PV.

- Headaches, excessive sweating, ringing in the ears, visual disturbances, such as blurred vision or blind spots, and dizziness or vertigo (a more severe feeling of motion) may occur.
- Fatigue is common.
- Itchy skin, called "pruritus," especially after warm baths or showers, occurs in some patients.
- A reddened or purplish appearance of the skin, especially on the palms, ear lobes, nose, and cheeks may occur.
- Some patients may experience a burning sensation in the feet.
- An enlarged spleen could cause abdominal fullness or discomfort, this may be confirmed on physical examination or by ultrasound.
- Angina or congestive heart failure may be a harmful effect of the thicker blood and tendency of platelets to "clump" in the coronary blood vessels and lead to clots called "thrombi."
- Gout, a painful inflammation of the joints caused by increased levels of uric acid may occur or become worse.
- Bleeding or bruising, usually minor, occurs in about 25 percent of PV patients.

In addition to the signs and symptoms above, people with PV are at slightly greater risk than the general population for developing leukemia as a result of the disease and/or certain drug treatments.

Diagnosis

A diagnosis of PV is considered if the patient's red cell count is elevated. Three measures of the concentration of red cells in the blood can be used to diagnose PV: the hematocrit, the hemoglobin concentration and the red cell count. These measurements are included in a standard blood test called a "complete blood count" (CBC). Blood counts are usually measured in a machine that simultaneously measures the hematocrit, hemoglobin concentration and red cell count, and these three measurements closely parallel each other.

For example, in a patient with PV, if a normal hematocrit concentration of 45 percent is increased by one-third to 60 percent, the corresponding normal hemoglobin concentration of 150 grams/liter (g/L) of blood would also be increased by one-third to 200 g/L of blood. The corresponding red cell count would be increased by one-third as well. Thus, for diagnostic purposes, any of the three measurements could be used.

Hematocrit

Generally, the hematocrit concentration is used to diagnose PV and measure the patient's response to therapy.

Hematocrit is the proportion of red blood cells in a volume of blood, usually expressed as a percent or an increase in hemoglobin concentration in the blood. In healthy individuals, hematocrit concentration ranges from about 36 to 46 percent in women and 42 to 52 percent in men.

Other diagnostic features from the results of blood tests that will confirm the diagnosis of PV include

- An elevated white cell count, especially the neutrophil (a type of white blood cell) count
  - The white cell count is increased mildly in most PV patients
  - Usually the increase stays the same and does not progress
- An elevated platelet count, which occurs in at least 50 percent of patients
  - The increase in the platelet count can progress
- The presence of *JAK2* mutation in blood cells
  - Two mutations are seen: *JAK2* V617F (most common) or *JAK2* exon 12 mutation
- An elevated red cell mass
  - Usually only measured if the hematocrit or hemoglobin concentration is not elevated decisively
- Normal or near-normal arterial oxygen saturation
- A low erythropoietin (EPO) assay in the blood
  - Erythropoietin is the principal hormone that stimulates red cell formation in the marrow
  - Blood levels of EPO are usually low in PV patients, but are normal or high in those with secondary polycythemia
  - Secondary polycythemia is discussed briefly on page 4

Marrow Examination

Although not required to make a diagnosis, patients may also have a bone marrow analysis as part of their testing. In PV, marrow contains more than the normal number of cells as a result of the overexpansion of the blood-forming cells and is lacking iron. Chromosome analysis can also be done on marrow cells. The growth of marrow red cell precursors can also be studied to examine their ability to grow in the absence of added erythropoietin.

For more information about bone marrow tests and other lab tests, please see the free LLS publication *Understanding Lab and Imaging Tests.*

Treatment Planning

Treatment decisions are based on the patient's risk for clotting complications (thrombosis). Risks for thrombosis include

- A previous clot or clots
- Advanced age (over 60 years)
- Cardiovascular risk factors, such as high cholesterol levels, diabetes, smoking, obesity or hypertension—all considered additional risk factors for thrombosis

Every patient's medical situation is different and should be evaluated individually by a hematologist/oncologist, a doctor who specializes in treating blood cancers. It is important for you and members of your medical team to discuss all treatment options, including treatments being studied in clinical trials.

For more information about choosing a doctor or a treatment center, see the free LLS publication *Choosing a Blood Cancer Specialist or Treatment Center.*

Treatment

PV is a chronic disease; it is not curable, but it usually can be managed effectively for very long periods. Careful medical supervision and therapy to keep the hematocrit concentration (amount of red blood cells compared with total volume of blood) near normal are important.

Treatment goals for the disease are

- To control symptoms
- To decrease the risk of complications

Therapies are aimed at

- Lowering the hematocrit concentration to normal or near-normal values
- Lowering the platelet count if the numbers are high or become high over time
- Decreasing PV-related symptoms

A troublesome symptom that occurs in many PV patients is itchy skin (pruritus). To help prevent pruritus, it is suggested that patients bathe less frequently. Aspirin and antihistamines may help. Other treatment options include light therapy (phototherapy) using psoralen and ultraviolet A light. Interferon alpha or pegylated interferon may be effective.

Patients with low-risk PV are usually phlebotomized (see next section) and given low-dose aspirin. Patients with high-risk PV require medical therapy to decrease hematocrit concentration permanently, which eliminates a need for phlebotomy and decreases the risk of clotting. All patients are given low-dose aspirin.

Phlebotomy

Phlebotomy is the removal of blood through a vein. It is the usual starting point of treatment for most patients. A volume of blood is drawn at regular intervals and the hematocrit concentration is brought down to normal within a period of weeks to months. The procedure used in phlebotomy is identical to that used for donating blood to a blood bank. The immediate effect of phlebotomy is to reduce the hematocrit concentration, which usually results in the decrease of certain symptoms such as headaches, ringing in the ears and dizziness. Eventually, however, phlebotomy results in iron deficiency.

Phlebotomy may be the only form of treatment required for many patients, sometimes for many years. Acceptable disease control may be achieved with withdrawal of a volume of blood every few months. Patients may feel tired after a phlebotomy and need to rest for a short time.

Drug Therapy

Aspirin therapy—Low-dose aspirin should be used to lessen the risk of thrombosis in an artery. It acts by making platelets less likely to adhere to the wall of an artery and clump, or aggregate. Aspirin is given by mouth and the most common side effects include upset stomach and heartburn.

Anagrelide (Agrylin®)—This drug, given by mouth, can be used if platelet numbers are too high. The drug can reduce the rate of platelet formation in the marrow. It does not have an effect on the other blood cells. Patients taking anagrelide may experience side effects including fluid retention, heart and blood pressure problems, headaches, dizziness, nausea and diarrhea.

Antihistamines or related drugs—These drugs may be prescribed to relieve itching and are given by mouth. Side effects include dry mouth, drowsiness, dizziness and restlessness. Some antihistamines can impair a person's ability to drive or operate heavy machinery.

Myelosuppressive drugs (agents that can reduce red cell and platelet production)—In some patients, phlebotomy alone cannot control the overproduction of red cells and can accentuate the overproduction of platelets. Patients who have an extremely high platelet count, complications from bleeding, blood clots or severe systemic complaints and are not responding to low-dose aspirin or phlebotomy, may also be treated with myelosuppressive agents. This drug therapy to suppress the marrow production of red cells and platelets is given instead of phlebotomy.

Hydroxyurea (Hydrea®)—The most commonly used myelosuppressive agent for PV is hydroxyurea, given by mouth. It helps reduce both the hematocrit concentration and the platelet count. Rare side effects are mouth ulcers, change in the sense of taste, skin ulcers or rash. There is some controversial evidence that after long-term therapy hydroxyurea is associated with an increased risk of acute leukemia, so it is frequently avoided as therapy for younger patients. However, it is thought to have much less potential for causing leukemia than some other myelosuppressive agents such as radiophosphorus and alkylating agents, which include melphalan (Alkeran®), busulfan (Myleran®), chlorambucil (Leukeran®) and others. Radiophosphorous and alkylating agents are reserved for patients with short life expectancy.

Ruxolitinib (Jakafi®)—This drug, a Janus-associated kinase inhibitor which is given by mouth, is FDA approved to treat patients with PV who have had an inadequate response to, or are intolerant of, hydroxyurea.

Following interruption or discontinuation of ruxolitinib, symptoms of myeloproliferative neoplasms generally return to pretreatment levels over a period of approximately 1 week. There have been isolated cases of patients discontinuing Jakafi during acute intervening illnesses, after which the patient's clinical course continued to worsen. It has not been established whether discontinuation of therapy contributed to the clinical course in these patients. When discontinuing therapy for reasons other than thrombocytopenia, gradual tapering of the dose of Jakafi may be considered.

Interferon alfa (immediate-release preparations Intron® A [alfa-2b] and Roferon-A®[alfa-2a] and sustained-release preparations PEG-Intron® [peginterferon alfa-2b] and Pegasys® [peginterferon alfa-2a])—These agents are used to lower the hematocrit concentration. However, they are not used for most patients because, compared to other treatments for PV, they are less convenient to administer (they are given by intramuscular or subcutaneous injection), and may cause troublesome side effects. Some patients experience moderately severe flu-like symptoms, confusion, depression or other complications. Development of sustained-release preparations provides a new option for patients; injections would be weekly, a regimen patients tend to tolerate better (particularly in the case of Pegasys).

For specific drug information, see the free LLS publication *Understanding Side Effects of Drug Therapy*, www.LLS.org/drugs and the Food and Drug Administration (FDA) drug information website at www.fda.gov/drugs/resourcesforyou/consumers/default.htm.

Special Considerations

Untreated patients with PV have increased risk for bleeding complications after surgery. Thus, if surgery is needed for any reason, treatment should be put in place to bring the hematocrit to a normal concentration before surgery.

Some PV patients have disease progression despite treatment. After years of disease, their cells undergo further changes and no longer overproduce red cells. For a time, the red cell count may stay near normal without treatment or it may drop below normal, resulting in anemia. The spleen may become further enlarged. The marrow may become fibrous or scarred, reducing its ability to make red cells and platelets. This condition of the marrow is called "myelofibrosis" or more precisely, post-polycythemia vera myelofibrosis. The platelet count may fall to low levels. Immature white cells may be released from the marrow into the blood. Treatment for myelofibrosis is described in the free LLS publication *Myelofibrosis Facts*.

PV can also transform into other blood cancers such as acute leukemia or myelodysplastic syndromes, but this is a very uncommon occurrence.

Secondary Polycythemia

Secondary polycythemia (also called "secondary erythrocytosis") is not a myeloproliferative neoplasm. It may occur as a result of four principal situations: (1) ascent to high altitude, (2) diseases that lead to low oxygenation of the blood, (3) tumors that secrete the hormone erythropoietin (e.g., kidney tumors) or (4) inherited disorders that result in overproduction or exaggerated action of erythropoietin. Secondary polycythemia is limited to overproduction of red cells. In the case of high altitude or heart and lung diseases that lead to low blood oxygen content, secondary polycythemia is a physical response that the body makes to improve the oxygen-carrying capacity of the blood.

Talking to Your Doctor About Side Effects of Treatment

Management of side effects is important. If you have any concerns about your side effects, talk to your doctor to get help. Most side effects are temporary and resolve when treatment is completed.

The individual side effects of specific drugs are discussed in the treatment section on pages 3 and 4.

Treatments Undergoing Investigation

Patients are encouraged to explore, and enter if they are eligible, clinical trials. Clinical trials test new drugs and treatments, many of which are supported by LLS research programs, before they are approved by the FDA as standard treatments.

Clinical trials are carefully controlled research studies, conducted under rigorous guidelines, to help researchers determine the beneficial effects and possible adverse side effects of new treatments. Clinical trials are designed to be accurate and very safe. Patient participation in clinical trials is important in the development of new and more effective

treatments for PV and may provide patients with additional treatment options. Patients interested in participating in clinical trials are encouraged to talk to their doctors about whether a clinical trial would be appropriate for them. For more information about clinical trials, see the free LLS publication *Understanding Clinical Trials for Blood Cancers* or visit www.LLS.org/clinicaltrials.

A current research approach under investigation includes the possible genetic origin of MPNs. There is a theory that MPNs may occur in families; if so, they are a group of genetic diseases passed on from one generation to another. This idea is being studied to discover if abnormal genes cause MPNs.

We encourage you to contact an Information Specialist and visit www.LLS.org for more information about specific treatments under study in clinical trials.

Treatment Outcomes

The likely outcome of a disease, called the "prognosis," varies in patients with PV. Each patient's risk factors, which affect his or her prognosis, are evaluated individually. In people with PV, median survival approaches or exceeds 20 years. Some people may survive longer after diagnosis, perhaps achieving a near-normal life expectancy. It is important to know that outcome data can show how groups of people with PV responded to treatment, but statistics cannot determine how any one person will respond. For these reasons, patients are advised to discuss survival information with their doctors.

Acknowledgement

LLS gratefully acknowledges

Ruben A. Mesa, MD
Chair, Hematology
Professor of Medicine
Mayo Clinic
Scottsdale, AZ

for his review of *Polycythemia Vera Facts* and his important contributions to the material presented in this publication.

We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has chapters throughout the country and in Canada. To find the chapter nearest to you, visit our website at www.LLS.org or contact:

The Leukemia & Lymphoma Society
3 International Drive, Suite 200
Rye Brook, NY 10573
Contact an Information Specialist at (800) 955-4572
Email: infocenter@LLS.org

LLS offers free information and services for patients and families touched by blood cancers. The following lists various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team's knowledge and skills.

Consult with an Information Specialist. Information Specialists are master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please:

- Call: (800) 955-4572 (M-F, 9 a.m. to 9 p.m. EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org
- Visit: www.LLS.org/informationspecialists

Free Information Booklets. LLS offers free education and support publications that can either be read online or downloaded. Free print versions can be ordered. For more information, please visit www.LLS.org/publications.

Información en Español (LLS information in Spanish). For more information, please visit www.LLS.org/espanol.

Telephone/Web Education Programs. LLS offers free telephone/web education programs for patients, caregivers and healthcare professionals. For more information, please visit www.LLS.org/programs.

Online Blood Cancer Discussion Boards and Chats. Online discussion boards and moderated online chats can provide support and help cancer patients reach out to others in similar circumstances and share information.
For more information, please visit www.LLS.org/chat and www.LLS.org/discussionboard.

LLS Chapters. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), in-person support groups, and other great resources. For more information about these programs or to contact your chapter, please:

- Call: (800) 955-4572
- Visit: www.LLS.org/chapterfind

Clinical Trials (Research Studies). New treatments for patients are ongoing. Patients can learn about clinical trials and how to access them. For more information, please:

- Call: (800) 955-4572 to speak with our LLS Information Specialists who can help conduct clinical-trial searches
- Visit: www.LLS.org/clinicaltrials

Advocacy. LLS enlists volunteers to advocate for policies and laws to speed new treatments and improve access to quality medical care. For more information, please:

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy

Other Resources

Cancer*Care*

www.cancercare.org
(800) 813-4673

Cancer*Care* provides free professional support services to anyone affected by cancer: people with cancer, caregivers, children, loved ones and the bereaved.

Cancer Support Community (CSC)

www.cancersupportcommunity.org
(888) 793-9355

CSC strives to optimize patient care by providing essential but often overlooked services including support groups, counseling, education and healthy lifestyle programs. CSC provides emotional and social support through a network of more than 50 local affiliates, 100 satellite locations and online.

MPN Advocacy and Education International

www.mpnadvocacy.com

MPN Advocacy and Education International is dedicated to providing the knowledge, support, and resources patients will need as they adjust to living with an MPN through educational symposia in several cities each year, website access, free webcasts of each program, collateral materials, and direction to people, resources and other organizations that can help.

MPN Education Foundation

www.mpdinfo.org

The MPN Education Foundation provides information, education and support and looks to advance research and develop drugs to improve the quality of life and care of patients with myeloproliferative neoplasms (MPNs). The foundation provides patient and doctor conferences and facilitates patient participation and accrual in clinical studies and surveys.

The MPN Research Foundation

www.mpnresearchfoundation.org

The MPN Research Foundation is a nonprofit organization whose primary mission is to promote, fund and support the most innovative and effective research into the causes, treatments and potentially the cure of essential thrombocythemia, polycythemia vera and myelofibrosis. The organization also provides information and support to people who have myeloproliferative neoplasms.

The Myeloproliferative Disorders Research Consortium (MPD-RC)

www.mpdrc.org

The MPD-RC is an international, multi-institutional nonprofit consortium funded by the National Cancer Institute. It is set up to coordinate, facilitate and perform basic and clinical research on Philadelphia chromosome-negative myeloproliferative neoplasms (Ph-MPNs).

The National Organization for Rare Disorders (NORD)

(800) 999-6673/(203) 744-0100
www.rarediseases.org

NORD is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research and service.

The National Cancer Institute (NCI)

(800) 422-6237
www.cancer.gov

The National Cancer Institute, part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer, including polycythemia vera (PV). The NCI also provides a clinical-trial search feature, the PDQ® Cancer Clinical Trials Registry, at www.cancer.gov/clinicaltrials, where PV patients can look for clinical trials.

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