Cancer Association of South Africa (CANSA)

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Fact Sheet on Polycythaemia Vera

Introduction

Polycythaemia Vera is a slow-growing type of blood cancer in which the bone marrow makes too many red blood cells – it is one of the blood disorders called myeloproliferative neoplasm.

Polycythaemia Vera (PV) may result in production of too many white blood cells and platelets. These excess cells thicken the blood and cause complications, such as a risk of blood clots or bleeding.

'Poly' means many and 'cythaemia' relates to blood cells. It is also sometimes called erythrocytosis, which means too many red blood cells. And it used to be called polycythaemia rubra vera or PCRV.

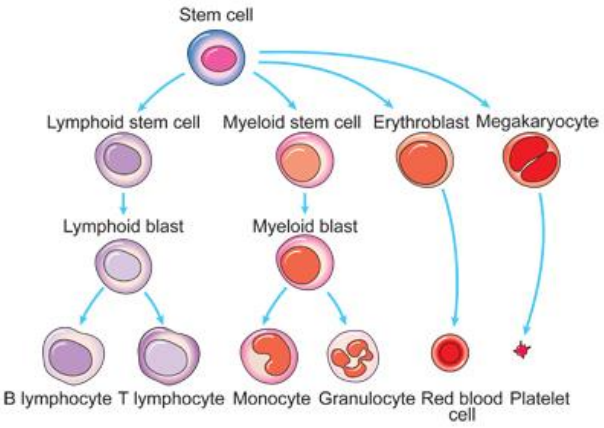

Diagram showing how blood cells are made

Lu, X. & Chang, R. 2020.
"Polycythemia vera (PV) is a myeloproliferative neoplastic disorder involving uncontrolled red blood cell production resulting in elevated red blood cell (RBC) mass. There is often concurrent stimulation of myeloid and megakaryocytic lineages leading to increased white blood cell and platelet production, respectively. The current understanding of pathophysiology involves increased sensitivity to growth factors due to an abnormal hematopoietic cell clone. Signs and symptoms, including headache, dizziness, claudication, thrombosis, are a consequence of increased blood viscosity."

Spivak, J.L. 2019.
"Since its discovery, polycythemia vera (PV) has challenged clinicians responsible for its diagnosis and management and scientists investigating its pathogenesis. As a clonal hematopoietic stem cell (HSC) disorder, PV is a neoplasm but its driver mutations result in overproduction of morphologically and functionally normal blood cells. PV arises in an HSC but it can present initially as isolated erythrocytosis, leukocytosis, thrombocytosis, or any combination of these together with

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splenomegaly or myelofibrosis, and it can take years for a true panmyelopathy to appear. PV shares the same *JAK2* mutation as essential thrombocytosis and primary myelofibrosis, but erythrocytosis only occurs in PV. However, unlike secondary causes of erythrocytosis, in PV, the plasma volume is frequently expanded, masking the erythrocytosis and making diagnosis difficult if this essential fact is ignored. PV is not a monolithic disorder: female patients deregulate fewer genes and clinically behave differently than their male counterparts, while some PV patients are genetically predisposed to an aggressive clinical course. Nevertheless, based on what we have learned over the past century, most PV patients can lead long and productive lives."

Other names for Polycythaemia Vera (PV)

Polycythaemia Vera is also known as:

- Primary polycythaemia
- Polycythaemia rubra vera
- Erythremia
- Splenomegalic polycythaemia
- Vaquez's Disease
- Osler's Disease
- Polycythaemia with chronic cyanosis
- Myelopathic polycythaemia
- Erythrocytosis megalosplenica
- Cryptogenic polycythaemia

Incidence of Polycythaemia Vera in South Africa (PV)

The outdated National Cancer Registry (2017), known for under reporting, does not provide any information on the incidence of Polycythaemia Vera in South Africa.

Signs and Symptoms of Polycythaemia Vera (PV)

For many people, Polycythaemia Vera may not cause any signs or symptoms. However, some people may experience:

[Picture Credit: Polycythaemia Vera]

Itchiness, especially following a warm bath or shower

- Headache
- Dizziness
- Weakness
- Excessive sweating
- Painful swelling of one joint, often the big toe
- Shortness of breath
- Breathing difficulty when you lie down
- Numbness, tingling, burning or weakness in your hands, feet, arms or legs
- A feeling of fullness or bloating in your left upper abdomen due to an enlarged spleen

Arshad, J., Iqbql, T. & Baig, W.S. 2019.
"Polycythemia Vera is a rare myeloproliferative neoplasm usually having ischemic stroke/thrombotic episode as presenting complaint. The patient reported had history of Cerebrovascular accident (CVA) two years back but blood cell counts were normal that time with no Polycythaemia Vera."

Genetics and Inheritance of Polycythaemia Vera (PV)
Mutations in the *JAK2* and *TET2* genes are associated with Polycythaemia Vera. Although it remains unclear exactly what initiates Polycythaemia Vera, researchers believe that it begins when mutations occur in the DNA of a hematopoietic stem cell. These stem cells are located in the bone marrow and have the potential to develop into red blood cells, white blood cells, or blood platelets. *JAK2* gene mutations seem to be particularly important for the development of Polycythaemia Vera, as nearly all affected individuals have a mutation in this gene. The *JAK2* gene provides instructions for making a protein that promotes the growth and division (proliferation) of cells. The JAK2 protein is especially important for controlling the production of blood cells from hematopoietic stem cells.

In rare instances, Polycythaemia Vera has been found to run in families. In some of these families, the risk of developing Polycythaemia Vera appears to have an autosomal dominant pattern of inheritance. Autosomal dominant inheritance means that one copy of an altered gene in each cell is sufficient to increase the risk of developing Polycythaemia Vera, although the cause of this condition in familial cases is unknown.

Putter, J.S. & Seghatchian, J. 2021.
"Polycythaemia vera is one of several classical myeloproliferative neoplasms that may occur in a juvenile onset or late-onset adult forms. It is linked to specific genetic mutations that cause a deleterious elevation in the patient's red cell mass. The discourse on genetics includes an exposé on the molecular biology of the disease and how a shared JAK2 V617F mutation can co-exist among three distinct neoplasms. Concepts of genetics and immunology help define the origin and behaviour of the disease: the tracking of allele burdens of mutations (genetic dosage), the timing or order of acquired mutations, the import of bystander mutations and the onco-inflammatory response; all theories are invoked to explain the progression of disease severity and potential transformational leukaemia. The World Health Organization's diagnostic criteria are accessed to focus on the subtleties of the Hb laboratories and sifting through the challenging listing of differential diagnoses that mimic PV, and our report includes an overview of manual and automated phlebotomy (erythrocytapheresis) procedures, enumerating their clinical indications, significance of temporary phlebotomy resistance and optimizing safety/ efficacy, quality and cost. Stratification of low and high-risk disease distinguishes when to commence chemo-cytoreductive therapy in the high-risk patient to prevent thrombotic complications. Drug resistance is circumvented by artfully switching drugs or using novel drug designs."

Possible Complications of Polycythaemia Vera
Possible complications of Polycythaemia Vera may include:

Blood clots - Polycythaemia Vera causes the blood to be thicker than normal, which can slow the rate of blood flow through the veins and arteries. Increased blood thickness and decreased blood flow, as well as abnormalities in the platelets, increase the risk of blood clots.

Enlarged spleen (splenomegaly) - The spleen helps one's body fight infection and filters unwanted material, such as old or damaged blood cells. The increased number of blood cells caused by Polycythaemia Vera makes the spleen work harder than normal, which causes it to enlarge.

Skin problems **-** Polycythaemia Vera may cause the skin to itch, especially after a warm bath or shower, or after sleeping in a warm bed. Individuals may experience a burning or tingling sensation in the skin, particularly on the arms, legs, hands or feet. The skin may also appear red, especially on the face.

Problems due to high levels of red blood cells - Too many red blood cells can lead to a number of other complications, including open sores on the inside lining of the stomach, upper small intestine or oesophagus (peptic ulcers) and inflammation in the joints (gout).

Other blood disorders like acute leukaemia - In rare cases, Polycythaemia Vera may lead to other blood diseases, including a progressive disorder in which bone marrow is replaced with scar tissue (myelofibrosis), a condition in which stem cells do not mature or function properly (myelodysplastic syndrome), or cancer of the blood and bone marrow (Acute Leukaemia).

Cuthbert, D. & Stein, B.L. 2019.
"Polycythemia vera is a Philadelphia-negative chronic myeloproliferative neoplasm, characterized by erythrocytosis, which is unique, compared to essential thrombocytosis and primary myelofibrosis. Though longevity can usually be expected, vascular morbidity is associated with this condition, as well as a propensity to evolve into myelofibrosis (post-PV MF) and acute myeloid leukemia. In addition, patients can have a pronounced symptom burden. Herein, contributors to the symptomatic burden, as well as the thrombotic and transformative tendencies are reviewed. From a symptom perspective, some are explained by cytokine release, others by microvascular complications, whereas certain symptoms can herald disease evolution. Thrombosis has multifactorial contributors, including but not limited to gender, and inflammatory stress; investigators have recently hypothesized that microparticles and Neutrophil Extracellular Trap Formations may add to thrombotic burden. Finally, we examine the progression to post-PV MF as well as leukemic transformation, highlighting well-established risk factors including age and leukocytosis, certain treatments, and the presence of "non-driver" mutations."

Diagnosis of Polycythaemia Vera (PV)
The proposed revised World Health Organization criteria for the diagnosis of Polycythaemia Vera (PV) requires two major criteria and one minor criterion or the first major criterion together with two minor criteria.

Major Criteria
- Haemoglobin of more than 18.5 g/dL in men, 16.5 g/dL in women, or elevated red cell mass greater than 25% above mean normal predicted value.
- Presence of *JAK2* 617V greater than F or other functionally similar mutations, such as the exon 12 mutation of *JAK2*.

Minor Criteria

- Bone marrow biopsy showing hypercellularity with prominent erythroid, granulocytic, and megakaryocytic proliferation.
- Serum erythropoietin level below normal range.
- Endogenous erythroid colony formation *in vitro*.

Other confirmatory findings no longer required for diagnosis include:
- Oxygen saturation with arterial blood gas greater than 92%.
- Splenomegaly.
- Thrombocytosis (>400,000 platelets/mm^3).
- Leukocytosis (>12,000/mm^3).
- Leukocyte alkaline phosphatase (>100 units in the absence of fever or infection).

Several tests are used to confirm the diagnosis of PV and to help the haematologist to understand the condition. The following tests may be needed:

- Full blood count (blood test) - The haematologist may repeat this test for verification if the test was previously done by a General Practitioner
- JAK2 test - The haematologist can test the blood to see if the person has a change (or mutation) called JAK2 V617F mutation. Approximately 98% who have PV have this mutation
- Chest x-ray
- Liver, kidney and urine tests
- EPO test Measurement of your erythropoietin (EPO) level
- Iron, folate and vitamin B 12
- Oxygen Measurement of oxygen levels in the blood
- Abdominal ultrasound - If someone has PV, his/her spleen may be enlarged. This is because in PV the spleen may begin to produce blood cells, and these collect inside the spleen. The ultrasound is a painless test
- Bone marrow biopsy (BMB) - A bone marrow biopsy is a test of one's bone marrow that is done in the hospital. The person will not need stay overnight in the hospital, and will generally just need local anaesthesia. The haematologist will give the patient some medication to prevent pain, and then he or she will extract some bone marrow from the patient's hip bone using a needle. The bone marrow tissue can then be examined in a laboratory so that the haematologist can see how the cells in the bone marrow are functioning

Tefferi, A. & Barbui, T. 2020.
Disease overview: Polycythemia vera (PV) and essential thrombocythemia (ET) are myeloproliferative neoplasms (MPN) respectively characterized by clonal erythrocytosis and thrombocytosis; other disease features include leukocytosis, splenomegaly, thrombosis, bleeding, microcirculatory symptoms, pruritus and risk of leukemic or fibrotic transformation.
Diagnosis: Bone marrow morphology remains the cornerstone of diagnosis. In addition, the presence of JAK2 mutation is expected in PV while approximately 90% of patients with ET express mutually exclusive JAK2, CALR or MPL mutations (so called driver mutations). In ET, it is most important to exclude the possibility of prefibrotic myelofibrosis.
Survival: Median survivals are approximately 15 years for PV and 18 years for ET; the corresponding values for patients age 40 or younger were 37 and 35 years. Certain mutations (mostly spliceosome) and abnormal karyotype might compromise survival in PV and ET. Life-expectancy in ET is inferior to the control population. Driver mutations have not been shown to affect survival in ET but risk of

thrombosis is higher in JAK2 mutated cases. Leukemic transformation rates at 10 years are estimated at <1% for ET and 3% for PV.

Thrombosis risk: In PV, two risk categories are considered: high (age > 60 years or thrombosis history present) and low (absence of both risk factors). In ET, four risk categories are considered: very low (age ≤ 60 years, no thrombosis history, JAK2 wild-type), low (same as very low but JAK2 mutation present), intermediate (age > 60 years, no thrombosis history, JAK2 wild-type) and high (thrombosis history present or age > 60 years with JAK2 mutation).

Risk-adapted therapy: The main goal of therapy in both PV and ET is to prevent thrombohemorrhagic complications. All patients with PV require phlebotomy to keep hematocrit below 45% and once-daily or twice-daily aspirin (81 mg), in the absence of contraindications. Very low risk ET might not require therapy while aspirin therapy is advised for low risk disease. Cytoreductive therapy is recommended for high-risk ET and PV, but it is not mandatory for intermediate-risk ET. First-line drug of choice for cytoreductive therapy, in both ET and PV, is hydroxyurea and second-line drugs of choice are interferon-α and busulfan. We do not recommend treatment with ruxolutinib in PV, unless in the presence of severe and protracted pruritus or marked splenomegaly that is not responding to the aforementioned drugs.

New treatment directions: Controlled studies are needed to confirm the clinical outcome value of twice-daily vs once-daily aspirin dosing and the therapeutic role of pegylated interferons and direct oral anticoagulants.

Caponetti, G.C. & Bagg, A. 2019.

"Myeloproliferative neoplasms that include the specific entities of chronic myeloid leukemia, chronic neutrophilic leukemia, polycythemia vera, essential thrombocythemia, and primary myelofibrosis are characterized by the clonal expansion of hematopoietic precursor cells and consequent neoplastic production of mature cells of myeloid, erythroid, and/or megakaryocytic lineage. Genetic studies, encompassing both cytogenetic and molecular testing, play a central and ever increasing role in the assessment of these neoplasms."

Treatment and Management of Polycythaemia Vera (PV)

The long-term risks of Polycythaemia Vera (PV) include leukaemic and fibrotic transformation, which occurs in fewer than 5% and 10% of patients, respectively, at 10 years. Current treatment modalities do not change these outcomes. Instead, treatment for PV is intended to decrease the risk of arterial and venous thrombotic events, which could be approximately 20%.

Iurlo, A., Cattaneo, D., Bceli, C. & Baldini, L. 2020.

"Polycythemia vera (PV) is mainly characterized by elevated blood cell counts, thrombotic as well as hemorrhagic predisposition, a variety of symptoms, and cumulative risks of fibrotic progression and/or leukemic evolution over time. Major changes to its diagnostic criteria were made in the 2016 revision of the World Health Organization (WHO) classification, with both hemoglobin and hematocrit diagnostic thresholds lowered to 16.5 g/dL and 49% for men, and 16 g/dL and 48% for women, respectively. The main reason leading to these changes was represented by the recognition of a new entity, namely the so-called "masked PV", as individuals suffering from this condition have a worse outcome, possibly owing to missed or delayed diagnoses and lower intensity of treatment. Thrombotic risk stratification is of crucial importance to evaluate patients' prognosis at diagnosis. Currently, patients are stratified into a low-risk group, in the case of younger age (<60 years) and no previous thromboses, and a high-risk group, in the case of patients older than 60 years and/or with a previous thrombotic complication. Furthermore, even though they have not yet been formally

included in a scoring system, generic cardiovascular risk factors, particularly hypertension, smoking, and leukocytosis, contribute to the thrombotic overall risk. In the absence of agents proven to modify its natural history and prevent progression, PV management has primarily been focused on minimizing the thrombotic risk, representing the main cause of morbidity and mortality. When cytoreduction is necessary, conventional therapies include hydroxyurea as a first-line treatment and ruxolitinib and interferon in resistant/intolerant cases. Each therapy, however, is burdened by specific drawbacks, underlying the need for improved strategies. Currently, the therapeutic landscape for PV is still expanding, and includes several molecules that are under investigation, like long-acting pegylated interferon alpha-2b, histone deacetylase inhibitors, and murine double minute 2 (MDM2) inhibitors."

Cuglielmelli, P., Vannucchi, A.M. 2020.
"Polycythemia vera (PV) and essential thrombocythemia (ET) are myeloproliferative neoplasms characterized by increased rate of cardiovascular events, a varying burden of symptoms, and an intrinsic risk of evolution to secondary forms of myelofibrosis and acute leukemia; however, survival is only modestly reduced in most instances. In the last few years, following the description of driver mutations in JAK2, MPL and CALR, the diagnostic criteria for PV and ET were revised, making the identification of very early stages feasible. Scores for identifying patients at different risk of thrombosis were refined, and they largely guide therapeutic decisions. Treatment is therefore mainly focused on reduction of thrombosis risk, control of myeloproliferation, improvement of symptomatic burden, and management of disease-associated complications. New drugs recently entered the clinical arena, with the promise to improve overall patients' management. However, evidence of a disease-modifying potential is largely missing and represents a still unmet clinical need."

Tremblay, D. & Mascaranhas, J. 2020. **Purpose of review:** Polycythemia vera is a myeloproliferative neoplasm characterized by increased erythrocyte count, thrombotic potential, and transformation to myelofibrosis. Older patients and those who have a history of thrombosis require cytoreductive therapy, most commonly with hydroxyurea. Other currently available therapies include pegylated interferon alfa-2a and the JAK1/2 inhibitor ruxolitinib. However, there are limitations to these agents, including potential detrimental adverse effects. In this review, we will describe current therapeutic options for the treatment of PV and then detail new agents with available clinical trial data.
Recent findings: A number of novel investigational therapies including MDM2 inhibitors, histone deacetylase inhibitors, and long-acting pegylated interferon alfa-2b are in various stages of clinical development with encouraging efficacy data. The therapeutic landscape for patients with PV is expanding. Novel agents are in development that not only reduce the thrombotic potential but also act directly on the malignant PV clone with the intention of significantly modifying disease progression.

Bose, P. & Verstovsek, S. 2019.
"Polycythemia vera (PV) and essential thrombocythemia (ET) are both classic, relatively indolent, chronic Philadelphia-chromosome-negative (Ph^-) myeloproliferative neoplasms (MPNs) characterized by elevated blood counts, thrombotic as well as hemorrhagic tendencies, a variety of symptoms, cumulative risks of progression to myelofibrosis and transformation to acute myeloid leukemia over time, and long survival. Molecularly, PV is more homogenous, being driven by *JAK2* mutations in virtually all cases, while ET can be *JAK2-, CALR-*, or *MPL*-mutated, as well as 'triple negative'. Recent targeted next-generation sequencing efforts have identified other, nondriver gene mutations, some with prognostic relevance. Prevention of thrombotic and

hemorrhagic complications continues to be the major focus of management, although symptoms are increasingly being recognized as a relatively unmet need, particularly in ET. Thrombotic risk stratification in PV is still based on age and history of thrombosis, while in ET, the additional contribution of *JAK2 V617F* to thrombotic risk is now well established. The associations of leukocytosis with clotting risk (in both conditions) and mortality (in PV) have drawn increased attention with the availability of ruxolitinib as a second-line treatment in PV. Similarly, there is a renewed interest in interferons with the emergence of ropeginterferon alfa-2b as a potential new frontline treatment option in PV. Drug development is more difficult in ET, the most indolent of the classic Ph^- MPNs, but ruxolitinib is being studied. Triggering apoptosis *via* the p53 pathway through pharmacologic inhibition of human double minute 2 (and synergism with interferon) is a new, promising therapeutic strategy."

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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