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.

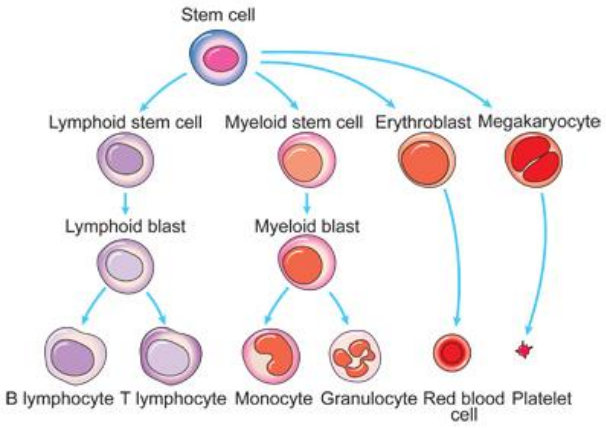

Diagram showing how blood cells are made

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 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."

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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 (2014), known for under reporting, does not provide any information on the incidence of Polycythaemia Vera in South Africa. In providing the incidence figures of Leukaemia in South Africa, The National Cancer Registry (2014) does not make provision for the reporting of the different types of Leukaemia – it also does not differentiate between Acute and Chronic Leukaemia - neither does it provide for different statistics for cases of Adult and Childhood Leukaemia.

According to the National Cancer Registry (2014) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2014. Histological diagnoses means that a specimen was sent to an approved laboratory and that a qualified specialist confirmed a diagnosis of cancer :

Group - Males 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	366	1:598	1,99%
Asian males	8	1:1 041	0,99%
Black males	163	1:1 264	1,47%
Coloured males	54	1:313	1,29%
White males	140	1:225	0,68%

Group - Females 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	258	1:1 069	0,68%
Asian females	12	1:1 607	1,04%
Black females	118	1:2 104	0,73%
Coloured females	36	1:684	0,88%
White females	91	1:363	0,56%

The frequency of histologically diagnosed cases of Leukaemia in South Africa for 2014 was as follows (National Cancer Registry, 2014):

Group - Males 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	81	28	30	46	48	74	39	17

Asian males	1	1	1	1	0	3	1	0
Black males	49	18	19	25	18	20	5	2
Coloured males	12	4	3	5	9	10	8	2
White males	12	5	6	18	18	23	30	11

Group - Females 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	54	30	24	36	37	40	26	10
Asian females	2	1	0	4	0	4	0	0
Black females	28	22	14	19	16	10	4	2
Coloured females	10	2	3	2	5	8	2	3
White females	12	5	5	10	16	16	20	5

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

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.

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-associated complications: pathogenesis, clinical manifestations, and effects on outcomes. *J Blood Med*. 2019 Oct 18;10:359-371. doi: 10.2147/JBM.S189922. eCollection 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

Marton, Simon & Borbémyi, 2016.
"Polycythaemia vera (PV), a condition characterized by blood hyperviscosity due to the expansion of the erythrocyte mass is the most common entity among all Philadelphia chromosome-negative myeloproliferative neoplasms. Arterial and venous thrombotic events are leading determinants of morbidity and mortality but impairment of quality of life due to vasomotor symptoms (erythromelalgia, pruritus) and disease-associated symptoms (tiredness, fatigue, pruritus, night sweats, vision problems, headache, concentration loss, abdominal discomfort, early satiety, fever, weight loss) are also present. The review of polycythaemia vera is actual as the updated WHO 2016 classification of myeloid neoplasms has changed the diagnostic criteria and a new second-line treatment option - JAK1/JAK2 inhibitor ruxolitinib - has been approved for patients who had an inadequate response to or are intolerant of hydroxyurea, which represents a breakthrough in the treatment of this patient population."

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%.

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."

Cingam, S., Glatow-Trujillo, L., Andrisos, L.A. & Arana, Y. 2019.
"Polycythemia vera (PV) is a rare myeloproliferative neoplasm (MPN) associated with significant impairment in quality of life (QoL) due to disease-related symptoms and complications. Assessment of disease burden constitutes standard monitoring of symptoms and response. Conventional treatments for MPN, such as hydroxyurea, phlebotomy, or interferon, have not shown a significant impact in QoL or patient-reported outcomes (PRO). Ruxolitinib (RUX) is a JAK2 inhibitor approved for patients intolerant or resistant to hydroxyurea (HA). We conducted a systematic review of clinical trials of RUX in patients with PV that incorporated PRO measures to evaluate the effects on PRO and QoL. Three randomized Phase 3 studies reported in four publications were relevant for analysis. Although the small number of trials and potential for treatment bias in the review, treatment with RUX was associated with improved QoL and PRO in PV patients intolerant or resistant to hydroxyurea."

Kurtin, S. & Lyle, L. 2018.
CASE STUDY: "Mr. M, a 65-year-old male, presented to his primary care physician with progressive fatigue, difficulty sleeping, and daily headaches for the past 3 weeks. His headaches were not associated with visual disturbances, cognitive deficits, or nausea/vomiting, and he had no history of migraines. He had a history of hypertension and hyperlipidemia, did not smoke, rarely drank alcohol, and had no recent illnesses or hospitalizations. His previous physical examination and laboratory studies 2 years ago were normal. The current physical examination revealed a plethoric yet well-appearing, well-nourished male in no acute distress. His lungs were clear to auscultation bilaterally without wheezes, rales, or rhonchi. He had a regular heart rate and rhythm without murmur. His abdomen was soft, without tenderness, distension, or palpable hepatosplenomegaly. Examination of the extremities was negative for edema. Distal pulses and sensation in the hands and feet were intact and equal bilaterally. Cranial nerves II to XII were deemed intact, and no gross focal deficits were observed. Complete blood count (CBC) revealed a slightly elevated white blood cell (WBC) count (14.6×10^9/L [normal range, 3.9-10.7 × 10^9/L; Wians, 2015]), erythrocytosis (red blood cell [RBC] count, 6.5 × 1012/L [normal range, 4.2-5.9 × 1012/L; Wians, 2015], hemoglobin, 19 g/dL [normal range, 14-17 g/dL; Wians, 2015], and hematocrit, 54.3% [normal range, 41%-51%; Wians, 2015]), thrombocytosis (platelet count, 500 × 109/L [normal range, 150-350 × 10^9/L; Wians, 2015]), and microcytosis (mean cell volume [MCV], 75 fL [80-100 fL; Wians, 2015]), which combined were cause for referral to a hematology/oncology clinic. During his hematology/oncology evaluation, Mr.

M described "never feeling rested" and being unable to sleep with uncertain snoring habits. He was experiencing itching during hot showers yet did not have rashes and had not recently introduced a new soap. He had no family history of blood disorders and no personal history of blood clots. The second CBC and laboratory tests confirmed erythrocytosis (RBC count, 6.5 × 1012/L; hemoglobin, 18.9 g/dL; hematocrit, 54%) and microcytosis (MCV, 75 fL). Serum iron (22 µg/dL [normal range, 60-160 µg/dL]) and ferritin (5 ng/mL [normal range, 15-200 ng/mL]) were suggestive of iron deficiency, serum erythropoietin was 8 mU/mL (normal range, 4.0-18.5 mU/mL), and a Janus kinase 2 (JAK2) mutation analysis was positive for JAK2V617F. Platelet count remained 500 × 109/L and WBC count was 10.2 × 10^9/L."

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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