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Polycythemia Vera – A Myeloproliferative Disorder

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ABSTRACT

Polycythemia Vera (PV) is a myeloproliferative disorder characterized by the uncontrolled proliferation of blood cells, particularly red blood cells, due to mutations, such as the Janus-Associated Kinase (JAK). This condition leads to thickened blood resulting in various clinical manifestations like hypertension, headaches, fatigue, and an increased risk of thrombotic events such as strokes and myocardial infarctions. Over time, PV progresses through stages: the early stage, where symptoms are mild or absent; the advancing stage, marked by increasing discomfort and potential secondary complications; and the spent phase, where extensive scarring of the bone marrow (myelofibrosis) doesn't allow for correct hematopoiesis, leading to cell depletion and anemia. In some cases, PV can progress to acute myeloid leukemia (AML) or myelodysplastic syndrome (MS). Diagnostic criteria for PV include blood tests showing elevated red blood cell counts, bone marrow biopsies indicating excessive blood cell production, and molecular tests detecting JAK2 mutations. Treatment strategies focus on managing symptoms and reducing complications. Phlebotomy is commonly used to reduce hematocrit levels, while cytoreductive agents like Hydroxyurea (HU) and interferon alpha (IFN-α) may be prescribed to reduce cell proliferation. Aspirin and antithrombotic therapies are employed to reduce thrombotic risk. Emerging therapies, such as JAK inhibitors like ruxolitinib offer targeted treatment options. While there is no cure for PV early diagnosis and appropriate treatment can significantly improve long-term prognosis with younger patients and those receiving timely interventions experiencing better outcomes. Advanced cases may require stem cell transplants, which offer the potential for a cure but come with associated risks.

Keywords

Myeloproliferative disorders, Polycythemia vera, Drug Hydroxyurea.

List of Abbreviations

AML: Acute myeloid leukemia, CALR: Calreticulin, COPD: Chronic obstructive pulmonary disease, CBC: Complete blood count, DVT: Deep vein thrombosis, DNA: Deoxyribonucleic acid, EPO: Erythropoietin, EMA: European Medicines Agency, GVHD: Graft versus host disease, GM-CSF: Granulocyte macrophage – colony stimulating factor, HU: Hydroxyurea, IFN: Interferon, IL: Interleukin, JAK: Janus-Associated Kinase, LAP: Leukocyte alkaline phosphate, MPL: Myeloproliferative leukemia, PV: Polycythemia Vera, RNA: Ribonucleic acid, TIA: Transient ischemic attacks, TNF: Tumor necrosis factor, FDA: U.S Food and Drug Administration, WHO: World Health Organization.

Introduction

Polycythemia vera (PV) is a myeloproliferative disorder. Myeloproliferative disorders are considered clonal malignancies of the hematopoietic stem cell [1]. In other words, myeloproliferative disorders are a group of blood cancers where a clonal, or single cell is mutated and causes a line of faulty cells in the bone marrow which leads to too many red blood cells, platelets, or certain white blood cells [2]. Examples of myeloproliferative disorders not including PV are chronic myelogenous leukemia, myelofibrosis with myeloid metaplasia, and essential thrombocythemia [1]. PV is caused by a mutation, 90% being the JAK mutation that leads to bone marrow that is hypercellular with hyperplasia causing an overproduction of mature red blood cells, white blood cells, and platelets [1]. The predominant overproduction is seen in red blood cells.

PV is considered a rare disease. Most people with the disease do not have a family history of the disease, but occasionally, more than one family member with disease is seen. PV is most found in Jews of Eastern European descent compared to other Europeans or Asians. For all populations, "the incidence of PV is approximately 2.8 per 100,000 population of men and approximately 1.3 per 100,000 population of women. The prevalence of PV is approximately 22 cases per 1000,000 people" [3]. In the United States, PV affects about 50 per 1000,000 people in the U.S. The common age for diagnoses is 60-70 years old. PV was first observed clinically by French physician Louis Henri Vaquez in 1892. Eleven years later, additional cases were systematically reviewed and described by William Olser. In 1951 William Dameshek included PV in his classification of myeloproliferative disorders. He believed that all myeloproliferative disorders have genetic origins was validated in 2005 with the discovery of the JAK mutation [4].

To fully diagnose a patient with PV extensive testing is required: a blood test, bone marrow autopsy, and in some cases molecular testing [4]. The chemotherapeutic drug Hydroxyurea (HU) is most used for the treatment of PV. Some patients can be intolerant to or have an inadequate response to HU. Because of this Ruxolitinib, an oral JAK 1/JAK 2 inhibitor was studied for treatment and successfully approved by the U.S Food and Drug Administration (FDA) in December of 2014 and the European Medicines Agency (EMA) in March of 2015 for the treatment of adult patients with PV who are resistant to or intolerant to HU as treatment [6].

While there is no cure for PV, there is success in the use of treatments to ease symptoms and avoid complications. The symptoms of PV do affect the daily lives of patients effected but treatments such as phlebotomy, aspirin, antihistamines, targeted therapies, and other advanced treatments make everyday life much easier [4]. The life expectancy of someone diagnosed with PV is around ten years with proper treatment [1]. Patients with PV are burdened by increased healthcare costs due to an increase in hospital stays, medication, disability leave, and associated thrombotic events [7]. The early detection of PV is important for the avoidance of severe symptoms and reduction of severe complications. Early detection allows for more successful treatments, better quality of life, longer life expectancy, and avoidance of life-threatening complication like a heart attack, stroke, heart failure, and/or angina [1]. Almost all treatments of PV require repeated treatments and management. For example, to reduce the symptom of itchiness, an antihistamine can be taken, but it needs to be taken daily (depending on antihistamine) to ensure therapeutic effect. The same concept is true with the treatment of phlebotomy to reduce the excess number of blood cells especially erythrocytes, which needs to be repeated routinely depending on the severity and progression of disease.

The objectives of this paper include the discussion of pathophysiology of PV including the molecular mechanisms and genetic mutations, hematological changes, and the role of the microenvironment. The discussion of clinical features and diagnosis with the phases of PV, symptoms of PV, and diagnostic criteria. The management and treatment options of PV including phlebotomy and cytoreductive therapy, aspirin and antithrombotic therapy, JAK inhibitors and targeted therapies, and bone marrow transplantation and other advanced options. The prognosis and risk stratification including risk factors and stratification models and long-term outcomes, and lastly, advances in research including emerging biomarkers and genetic research, clinical trials, and new drug development, and challenged in PV research and care.

Discussion

Molecular mechanisms and genetic mutations play a large role in the onset of PV. The JAK mutation causes PV in over 90% of patients. JAK is a cytosolic tyrosine kinase. For PV, the JAK mutation is a gain of function mutation that involves specifically the JAK 2V617F which is a somatic point mutation, the point mutation being a G to T at nucleotide 1849 in exon 14. This point mutation leads to the substitution of valine to phenylalanine at codon 617 [5]. JAK 2 mutations in exon 12 are also seen in patients negative for JAK 2V617F. The JAK 2 mutation associated with exon 14 are seen in 97% of cases of PV caused by the JAK mutation and the other JAK mutations are in 3% of cases of PV caused by the JAK mutation. This finding is a helpful tool used in diagnoses of PV. Studies show that the pathogenic role of Janus-associated kinase 2 mutations originate at the stem cell level which leads to the increase of JAK- STAT activation and the induction of the mutated Janus-associate kinase [5]. When someone is healthy, erythropoietin (EPO) drives the activation of the JAK 2 and downstream STAT signaling erythroid proliferation. When a patient has a mutated JAK 2, it enables the Janus associated pathway to lead to proliferation without the activation form EPO, leading to exaggerated erythroid proliferation [6].

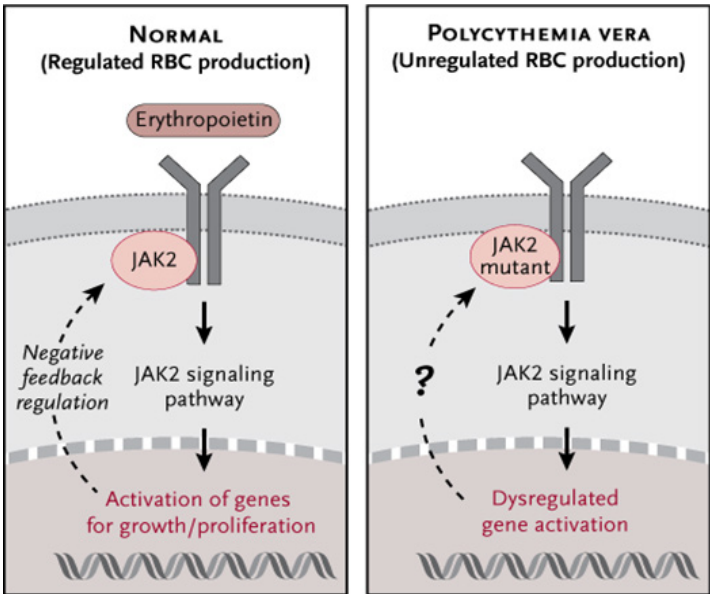

Figure 1: Visual of JAK mutation vs a healthy individual [8].

JAK 2 is also an important signaling piece in thrombopoiesis and granulopoiesis, with patients possessing the JAK 2 mutation commonly experiencing leukocytosis and/or thrombocytosis [6]. Other associated mutations are the Calreticulin (CALR) and

Myeloproliferative leukemia (MPL), and all together, the JAK mutation, CALR, and MPL make up the three myeloproliferative-specific driver mutations [5]. CALR and MPL mutations are rarely seen in patients with PV, as they are not seen congruently with the Janus associated mutation, and they are commonly seen with essential thrombocythemia and primary myelofibrosis. These differences in myeloproliferative disorders are partially caused by cytokine receptors that are activated by the mutation and other confounding mutations [5]. Cytokine activity seen in patients with PV show increases of interleukin (IL) IL-4 and IL-8, granulocyte macrophage–colony stimulating factor (GM-CSF), interferon (IFN-γ), monocyte chemotactic protein–1, and platelet derived growth factor – BB. Tumor necrosis–alpha (TNF-α) and platelet derived growth factor–BB are specifically related to the JAK mutation. PV patients with vascular complications also will present with abnormal concentrations of IL- 12 (p70) and GM-CSF. These cytokine factors may prove as important in future therapeutic research [9]. A study compared healthy individuals and PV patients showed patients exhibit inflammatory profiles compared to healthy subjects (with their statistical significance).

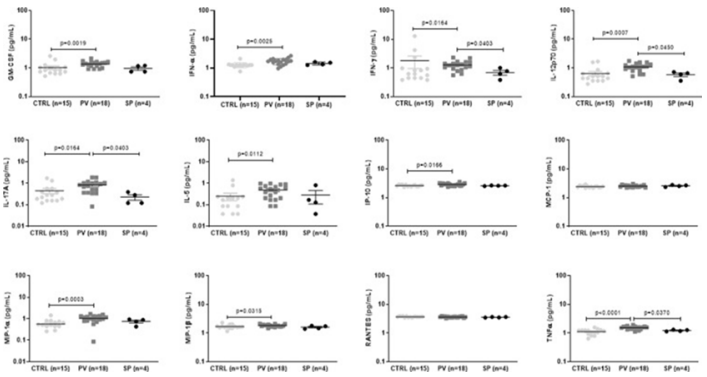

Figure 2: Plasma cytokine levels in healthy individuals, Polycythemia vera patients, and SP patients [10].

PV patients "exhibited increased levels of GM-CSF ($p = 0.0019$), IFN-α2 ($p = 0.0005$), IFN-γ ($p = 0.0164$), IL-12p70 ($p = 0.0007$), IL-17A ($p = 0.0164$), IL-5 ($p = 0.0112$), IP-10 ($p = 0.0166$), MIP-1α ($p = 0.0003$), MIP-1β ($p = 0.00315$) and TNF-α ($p < 0.0001$)", and when compared to SP patients "displayed higher levels of IFN-γ ($p = 0.0403$), IL-12p70 ($p = 0.0450$), IL-17A ($p = 0.0403$) and TNF-α ($p = 0.0370$)" [10].

Hematological Changes in PV

The human body undergoes extreme hematological changes when PV develops.

Although all three hematopoietic lineage cell lines are affected, the primary cell line affected is the erythrocytic. Patients primarily see an increase in hematocrit, hemoglobin, and red cell mass. In the peripheral blood and bone marrow all three cell lineages exhibit increased production. This means that the myeloid stem cell is affected by the disease causing a trilineage effect. It is common to see normoblastic erythroid proliferation, along with a general increase of erythrocytes. A patient's reticulocyte count could show also increase. There can be neutrophilia with a left shift, which means that there is an increase in immature white blood cells, most likely band cells. There may also be basophilia, an increased production in basophils. The erythrocyte distribution width will be increased, and the leukocyte alkaline phosphate (LAP) score is usually elevated. Patients will classically present with thrombocytosis, along with platelets that may have an abnormal shape or function. The bone marrow will be hypercellular, and the bone marrow will also see increased reticulin or fibrosis. The patients iron stores within bone marrow will be depleted. Immature leukocytes and erythrocytes will be found in the blood, and there will also be microcytes, elliptocytes, and dacrocytes/tear drop cells [1]. Erythropoiesis is the human physiological process of replenishing red blood cells in the body, EPO is a hormone primarily released by the kidneys (sometimes by the liver) when the kidneys detect low levels of oxygen (hypoxia) in the blood. It is controlled by a negative feedback mechanism. Erythropoiesis is affected because of the genetic disruptions that affect the cell proliferation of not only erythrocytes, but also leukocytes and thrombocytes, which all lack the negative feedback regulatory response that controls cell proliferation [11]. A problem arising from this mutation and excessive proliferation is a dangerous increase in blood cell viscosity. In PV patients this high blood viscosity leads to two potentially dangerous outcomes. The first is easy blood clotting which leads to a blockage of blood flow through the veins and arteries which can lead to pulmonary thrombosis, myocardial infarction, and/ or stroke. The second is blood flow slowing down in veins and arteries resulting in decreased oxygen which can lead to heart failure or angina. Other problems seen with high blood viscosity are general artery blockages, central nervous system disfunction, renal vein thrombosis, shortness of breath or breathing difficulty, chest pain, claudication or pain when walking that improves with rest, and multisystem organ failure [12].

The body also shows differences in the microenvironment in patients with PV. Most myeloproliferative disorders show a similar microenvironment/stroma response that cause increases in inflammatory cytokines. The bone cell stroma is responsible for the progenitor stem cells present in blood and during the process of hematopoiesis. If the stroma/microenvironment is unhealthy it could promote an inflammatory microenvironment which is not conducive to healthy stem cell production and in late stages of PV, the condition leads to the development of myelofibrosis. Myelofibrosis is the extensive scarring of the bone marrow. This scarring can become so extreme that it eventually affects all the three hematopoietic stem cell lineages, erythroid, myeloid, and megakaryocytic, thus becoming depleted of needed blood cells, while at the same time the hematopoietic system is unable to produce new cells due to this damage [13].

Angiogenesis is also affected by PV. Because of the JAK mutation, there is an increase in angiogenesis. Neovascularization allows for the increase in bone marrow and the angiogenic pathways, specifically via the VEGF/VEGFR pathways are likely involved in the pathophysiology of PV because of the interactions that promote the stimulation cell proliferation and migration of hematopoietic

cells via paracrine and autocrine loops [14]. The endothelial tissue also experiences changes due to PV. Patients present with an increase in endothelial adhesion because of the JAK and increase production of thrombocytes. This increase in endothelial adhesion is what leads to severe complications like pulmonary thrombosis, myocardial infarction, and stroke. This may also be due to the phosphorylation of Lu/BCAM which increase erythroid cell adhesiveness with direct correlation to the JAK gene [15].

Diagnosis, Clinical Features and Symptoms in PV

The clinical features and diagnoses of PV are very important for physicians when diagnosing and subsequently treating the disease. PV is a slow progressing disease so it has distinct stages that can be studies. PV can be broken down into three stages: early PV, advanced PV, and the spent PV. The early PV can be characterized by little to no symptoms up to mild symptoms. The advancing PV stage is characterized by the manifestation of uncomfortable symptoms and potential secondary conditions may arise. The final phase of PV, known as the spent phase, is characterized by the complete takeover of the bone marrow, which leads to mutated cells breaking down and being replaced with fibrotic tissue. When a large portion of the bones marrow is replaced with scar tissue (myelofibrosis), the bone marrow will no longer be able to produce hematopoietic cells of any cell lineage with an overall decrease in the body cell leading to an increased risk of hemorrhaging and conditions like anemia [4]. Following the spent phase other diseases can develop such as acute myeloid leukemia (AML) (about three percent of cases progressing to this point) and myelodysplastic syndrome. AML is an aggressive blood cancer of the bone marrow that migrates into circulation where it metastasizes to other organs and body systems. Myelodysplastic syndrome where cells never fully develop and die early, lowering most blood counts and leading to complication [4]. PV presents a wide range of symptoms, many of which are related to the increased volume and viscosity of the blood. One of the most common symptoms is high blood pressure (hypertension), which occurs due to the thickened blood exerting greater pressure on blood vessels. This can lead to a variety of issues, including headaches and blurred vision, both of which are caused by reduced blood flow to the brain and eyes. Fatigue is also a very common symptoms, as the body struggles to efficiently transport oxygen throughout the tissues due to the increased blood thickness. Another predominant symptom of PV is plethora, which refers to a reddish or flushed complexion caused by the excessive blood volume. This can be accompanied by tinnitus, or ringing in the ears, which results from disrupted blood flow. Many individuals with PV also experience pruritus, an intense itching sensation, often worsened by warm showers, due to histamine release from the increased erythroid cell turnover. In more severe cases, PV can lead to complications such as myocardial infarction or stroke, both of which occur due to the increased risk of blood clots forming in the thickened blood. Deep vein thrombosis (DVT), or blood clots in the deep veins, often in the legs, can also occur, along with transient ischemic attacks (TIAs), which are brief periods of reduced blood flow to the brain that cause temporary neurological symptoms like dizziness or weakness. Other common symptoms include easy bruising and epistaxis, which are nose bleeds, which occur due to the increased tendency for blood vessels to rupture or bleed. Hemorrhaging, or excessive bleeding, may also occur in more severe cases. Hyperuricemia, an elevated level of uric acid in the blood, is common in PV and may lead to the development of gout, causing painful swelling in the joints, often starting in the big toe. Additional symptoms may include night sweats, which are a common sign of systemic illness, and shortness of breath, particularly during physical exertion, that eases after periods of rest, as the thickened blood impairs oxygen circulation. Stomach ulcers are another potential symptom, resulting in abdominal pain, nausea, or discomfort. In some cases, the disease leads to hepatomegaly (enlarged liver) and splenomegaly (enlarged spleen), caused by the body's attempt to manage the excess blood cells.

The spleen may become enlarged as it works harder to filter the increased number of blood cells. Finally, low serum EPO, a hormone that typically stimulates erythroid cell production in response to low oxygen levels, is often observed in PV, and while this isn't a direct symptom, it plays a role in the overall clinical presentation of the disease. Overall, these symptoms reflect the body's struggle to manage the excess blood volume and abnormal blood cell production seen in PV, affecting various systems and organs, and leading to both discomfort and potential serious complications [1]. These symptoms lead to a physician's decision to make certain calls for testing to come to a complete diagnosis.

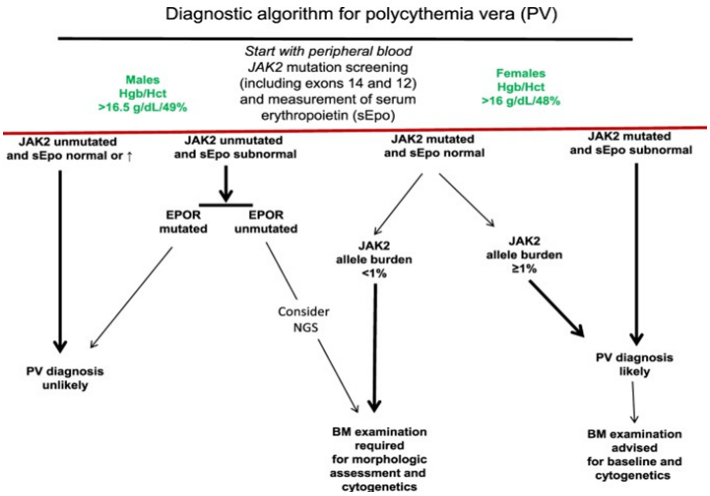

Figure 3: Shows two main avenues that are considered, among other things, when diagnosing Polycythemia vera [5].

The WHO has three diagnostic criteria when diagnosing PV. The first is a blood test to show high erythroid counts. To perform a blood test, the patient will come to the office where a sample of peripheral blood will be taken using a small gauge needle normally from a vein in the arm. The anticoagulated sample will then be sent to the clinical hematology laboratory where a complete blood count (CBC) will be performed [16]. Specific high blood erythroid cell related counts that are looked for are the hemoglobin count, hematocrit levels, and erythroid cell mass or blood volume. The

second criteria is a bone marrow biopsy to see excess of mature megakaryocytes (precursors to blood platelet) or excess of blood in the bone marrow. A bone marrow autopsy, also known as a bone marrow aspiration, is performed following an injection of local anesthetic to the injection site to numb the pelvic bone area, the most common area to conduct this is the posterior iliac crest of the hip. After the area is numbed, the physician will inject a needle into the iliac crest hip area to resect bone marrow tissue. Once a specimen has been obtained, the bone marrow is sent to clinical pathology for histological testing [17]. The third criteria can be met in two ways: molecular testing or blood test. The molecular test is done to confirm the presence of the JAK gene mutation, and the blood test is used to measure the presence of low levels of EPO. Decreased EPO levels is a diagnostic feature manifested in PV. It will always be lower than what one would measure under normal conditions [4]. The molecular testing is performed by taking a blood, tissue, or other body fluid sample like saliva, which is then sent to the molecular biology lab to separate the deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) to check for certain genes, proteins, and/or other molecules that confirms the presence of PV. Molecular testing can also be used as a preventative measure to look for potential development of diseases that could arise in the future. These tests are often performed in congruence with other testing. e.g., bone marrow biopsies to diagnose diseases like cancer [18]. Other essential laboratory testing includes testing for hematocrit, red cell mass, and JAK levels. Hematocrit testing separates the plasma from blood cells to determine if there are too many erythroid cells in circulation. This testing also assists in looking and measuring the erythroid red cell mass, which is a huge indicator of PV if levels are measured above normal. The JAK 2 mutation is a significant indicator of PV present in more than 90% of all cases. The bone marrow biopsy gives clues into the hematopoietic stem cells line over proliferating.

Cytogenetic Analysis in PV

Cytogenetic studies to determine if there are correlations with a positive diagnosis are largely unknown but growing in prevalence. At the time of diagnosis, approximately twenty percent of patients with PV present karyotypic abnormalities. A case study was conducted to further shed light on and kickstart further research into the topic. The case study included 422 patients, 271 in the polycythemic phase, 112 with post-polycythemic myeolofibrosis, 11 in the accelerated phase, and 28 in the blast phase" [19].

Thirty-three patients in the study had abnormal karyotypes, with twenty percent of those patients in the polycythemic phase, and ninety percent of those patients were in the accelerated or blast stage. Patients showed different karyotypic abnormalities depending on what stage of disease they were in. For the polycythemic phase, the isolated del(20q), +8 and +9 were the most common. For post polycythemic myelofibrosis, the del(20q) and +1q were the most common, and for the accelerated and blast phase the complex karyotypes were the most common [19]. Patients with cytogenetic karyotype were more likely to be associated severe cases of disease with reduced survival rates and faster disease progression. It was concluded that different stages of disease showed different karyotypic abnormalities and different karyotypic abnormalities showed different, but all negative effects on progression of disease and survival rates [19].

PV vs Secondary Erythropoiesis

It is important to differentiate PV from other secondary causes of erythrocytosis to ensure proper diagnosis and treatments. Secondary erythrocytosis is the increase erythroid cell mass in peripheral circulation as the result of conditions producing an increase in EPO levels. The stimulated kidneys release EPO due to the detection of decreased oxygen saturation in peripheral circulation. Because of these conditions, it is common for secondary erythrocytosis to be seen in conditions that result in decreased oxygen saturation of the blood. These diseases include but are not limited to severe lung diseases like chronic obstructive pulmonary disease (COPD), birth defects of the heart, high altitude sickness, and carbon monoxide poisoning. Other causes can include kidneys problems like a tumors or cysts in the tumor or a lack of width in the arteries leading to the kidneys, tumors on the brain, liver, or adrenal gland, or genetic disorders like congenital erythrocytosis [20]. PV can be distinguished from diseases like secondary erythrocytosis by conducting a bone marrow biopsy and aspiration along with molecular testing to test for specific genetic mutations like the Janus mediated kinase 2 mutation to improve the understanding how PV develops.

	Polycythemic phase (n=271)	Post-PV MF (n=112)	AP/BP phase (n=39)	Total (n=422)
Normal karyotype	217 (80%)	62 (55%)	4 (10%)	283 (67%)
Abnormal karyotype	54 (20%)	50 (45%)	35 (90%)	139(33%)
Single abnormalities	41 (76%)	29 (58%)	5 (14%)	75 (54%)
- del20q	18	12	1	31
- +9	10	0	0	10
- +8	6	1	1	8
- other single	7	16	3	26
Double abnormalities	9 (17%)	9 (18%)	6 (17%)	24 (17%)
- +1q	4	7	4	15
- other two	5	2	2	9
Complex	4 (7%)	12 (24%)	24 (69%)	40 (29%)
- del5q/-5	0	4	14	18
- del7q/-7	1	2	15	18
- del17p/-17/i(17q)	1	4	9	14

AP/BP: accelerated/blast phase; Post-PV MF: post-polycythemic myelofibrosis.

Figure 4: Cytogenetic abnormalities in patients with Polycythemia Vera [1].

Treatment Plan for PV

After the positive diagnosis of PV, the next step is for the attending physician to create a successful management and treatment plan that matches the specific needs of the stage and severity of the patient's condition. This plan may consist of repetitive phlebotomies to remove around a pint of blood per treatment which results in a lower peripheral hematocrit. The goal hematocrit to reach for patients is below forty-five percent. When treatment is initiated, patients

receive phlebotomy every day until the goal percent is reached, then repeated every four to eight weeks [21]. The clinician may decide to use cytoreductive agents like HU and IFN-γ to treat PV. Cytoreductive drugs are often used for patients who are under the age of sixty that have not experienced any extreme complications from the disease. They are often used when the patient is resistant to phlebotomy, suffer from the symptom splenomegaly, and see significant increases in all three lineages including leukocytes and thrombocytes [22]. This form of treatment can be given orally using HU or by unhealthy injection (IFN-γ) and they are given multiple times a week if not daily. Aspirin and antithrombotic therapies are also commonly used to treat PV. Aspirin can be used because it reduces the narrowed nature of the large and small vessels that causes severe complications. Aspirin works by suppressing the enzyme cyclo-oxygenase in platelets. In turn the platelet type thromboxane A2 production is reduced, and vasoconstriction is reduced due to a lack of aggregation properties. Aspirin is often used in small does to avoid complications and it can be used daily for its therapeutic effects [23]. Although low dose aspirin is seen as successful in reducing the risk of thrombotic events, it is important to be aware of and keep an eye out for important risk factors that lead to thrombotic events in PV patients. Risk factors are common in individuals over or at the age of 60, and they include a history of thrombosis, elevated hematocrit (above forty five percent), and elevated leukocytosis [24]. These risk factors if not severe can be treated with low dose aspirin, but if they become severe of the body becomes resistant to aspirin, cytoreductive therapy is encouraged with HU being the most prestigious first choice for treatment [1,24].

Targeted therapies, also known as molecularly targeted therapies, are commonly used to treat cancers of all types, especially cancers with genetic backgrounds that lead to problems in signal transduction pathways with conformational ligands. Targeted therapies are defined as a type of treatment that used a substance, often a drug, that targets molecules and binding sites that cancers need for effective proliferation of cells. Targeted therapy can work by activating apoptotic pathways, interrupting proliferation sequences, and interrupting signals that help we neovascularization. Some targeted therapies even directly deliver toxic materials or substances that kill the cancer cells. They commonly follow under two categories, monoclonal antibodies, or small molecule drugs [26]. Janus-associated inhibitors are growing in popularity for the treatment of PV. The most popular inhibitor that was successful in trials is Ruxolitinib. Ruxolitinib was approved for polycythemia in 2019 after being approved previously by the FDA and EMA. In healthy individuals, the Janus-associated pathway works as a highly selective ligand that begins the binding of cytokine ligand with a conformation change which brings together two Janus-associated ligands so that they can phosphorylate one another. After autophosphorylation occurs, the transduction of STATS occurs and leads to the proliferation of hematopoietic cells through gene transcription [25]. The medication works by competitively binding to the adenosine triphosphate sites and stopping the signal transduction from taking place which leads to a decrease in cell proliferation.

Ruxolitinib is small molecule drug that should be taken by mouth twice daily for desired effects of the inhibited JAK. It is also sold in a cream form. Possible drug interactions can occur following consumption of grapefruit and St. John's wort. Side effects include possible allergic reactions, anemia, blood clots, myocardial infarctions, infection, stroke, unusual bruising or bleeding, and less severe symptoms that do not require medical attention like diarrhea, headache, muscle cramps, swelling of arms or legs [28]. Another emerging therapy is Rusfertide, although it has not yet been approved by the FDA it has been successful in clinical trials. Rusfertide is used to help lower the hematocrit to below forty-five percent. Rusfertide works by depleting iron stores in the body which in turn stops red blood cell production. The medication depletes iron by imitating the hormone hepcidin. When hepcidin is released, it causes iron levels to go down and in turn, less erythrocytes are produced. If the treatment remains successful, it will eliminate the need for phlebotomy treatments in PV patients. The long-term effects, like whether complications like stroke and myocardial infarctions are reduced is not yet determined because clinical trials have not gone on long enough to give statistical significance.

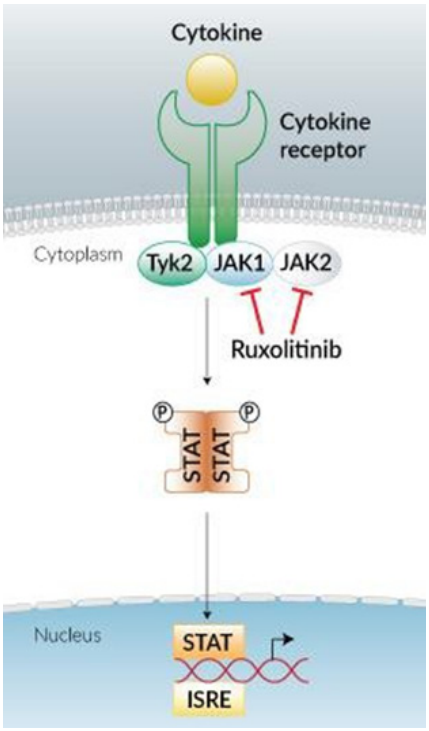

Figure 5: Effect of Ruxolitinib on JAK pathway [27].

Use of Bone Marrow/Stem Cell Transplantation

Bone marrow transplants and other advanced options also exist as an option for PV patients. Stem cell therapy allows for a solution at the route of the problem, the hematopoietic stem cell lines. Patients currently eligible for stem cell transplants are at the end stage of the disease. This consist of extensive scarring of the stroma in the bone marrow, if the patient is at a higher risk for blood clots it may expedite their eligibility. Stem cell transplants can be allogeneic

or autologous. Allogeneic is when there is a donor involved, while in comparison, autologous is defined when the stem cells come from the patients themselves. The large break through with this treatment is that if it is successful, it would be a cure to PV. After a transplant, symptoms of PV will be resolved. The downside of the procedure is that serious complications are possible. These serious complications are catalyzed by the body's rejection of stem cells [30]. When the body rejects stem cells is it is known as graft versus host disease (GVHD). Symptoms of GVHD include skin and gastrointestinal issues like a painful rash and itching, diarrhea, nausea and vomiting, abdominal cramping, and liver failure which leads to jaundice [31].

Assessing prognosis and risk stratification are important for maximizing quality of life and leading to the best chance of remission. When a patient is diagnosed with PV the first step is to assess what stage of disease the patient is in. The diagnostic steps reveal which stage of disease the patient is in. The bone marrow autopsy specifically will reveal the stage of disease based on how much scaring is present in the bone marrow. The hematocrit will also show important signs as to whether thrombosis is a likely complication that will happen in the future. The amount of scarring along with insight from a complete blood count with differential will have tell-tale signs on whether the disease will likely progress into myelofibrosis or leukemia [32]. The international prognostic scoring system is also a good tool for determining prognosis as well. The international prognostic scoring system considers platelet count, presence of blast in bone marrow, age, and hemoglobin level. They judge them in levels of low, intermediate, and high-risk cases.

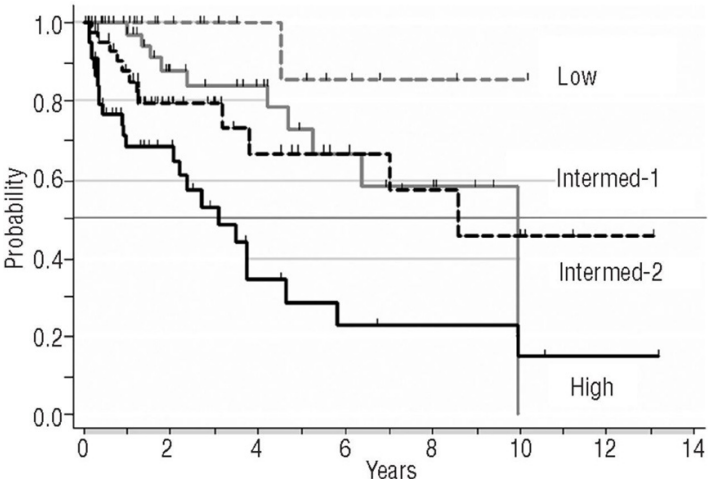

Figure 6: Representation of the international prognostic scoring system for PV [33].

These scorings allow the prediction of progression of disease and if the patient is eligible for certain treatments and what treatments would go best with the patient's particular case. Other factors that are considered are if the patient is over 65, if hemoglobin is low and the platelet count is low (meaning that end stage disease may be present), and presence of circulating blast cells. The prognosis is most positive the earlier the disease is caught and the higher the risk the poorer the prognosis [33]. Although there is no cure for PV because the symptoms and progression of the disease can be managed and slowed, the general long-term outcome is positive. The average age for diagnosis is sixty to seventy years old, but if the patient is younger then they will have a greater outlook. The average survival time after diagnosis is approximately fifteen years. If a patient falls into the younger category (under the age of sixty), then their chance of survival for a longer period goes up. The survival time after diagnosis for a patient under the age of sixty goes up to approximately twenty-five years. Factors other than age that effect the outlook and prognosis of the disease include overall health, weight, presence or absence of certain genetic abnormalities, level of other cell lines (including erythroid, myeloid, and platelet), and if any serious complications have occurred like thrombosis or myelofibrosis [34]. Treatment plays a huge role in the long-term outlook and life expectancy for patients. Research still needs to be done to fully understand the body's reaction if treatment is not given, but there are varying statistics ranging from eighteen months to ten years for survival time without treatment. With the most common cause of death with patients that have PV being blood clots, this is very common in patients that do not receive patients because of the increased viscosity of the blood and number of thrombocytes present in peripheral circulation [34]. If someone does not receive treatment for a considerable amount of time but then seeks out treatment, it is common for them to have progressed to end stages of disease with the development of myelofibrosis or the history of a serious complication. If this is the case, treatments like blood transfusions, medications, and stem cell transplants do exist [34]. The recommendation for the most successful prognosis and long-term outlook is taking the patients doctors regimen properly, staying overall healthy, and considering new medications and stem cell transplants.

Conclusion

PV is a chronic myeloproliferative disorder that affects the body's ability to regulate red blood cell production, leading to an excess of red blood cells in peripheral circulation. PV is a disease with a complex and multifaceted pathophysiology, and it poses problems both in diagnosis and in clinical management. The early stages of PV often show few symptoms, with patients experiencing only mild symptoms/signs, which can make detection difficult. As the disease progresses symptoms increase and complications become more common, leading to death in extreme cases and reduced quality of life. By understanding the underlying mechanisms of PV and the various treatment strategies available, clinicians are better equipped to manage this condition, reduce complications, and improve patients' quality of life. Overall, the main clinical features, pathophysiological changes, diagnostic criteria, and management strategies for PV are important to understand, and emphasizing the importance of early intervention and personalized care are important aspects that need to be implemented in future cases.

The central problem with PV is the uncontrolled proliferation of hematopoietic stem cells, specifically red blood cell progenitors, driven primarily by mutations such as the JAK 2 mutation. This

genetic abnormality leads to the dysregulated signaling of the JAK-STAT pathway, which is central to cell proliferation and differentiation. As a result, there is an overproduction of blood cells, including erythroid cells, myeloid cells, and platelets. The clinical manifestation of PV is largely driven by this overproduction, which causes an increase in blood volume and viscosity. One of the earliest and most common signs is the presence of hypertension, which can lead to other complications, such as headaches, blurred vision, and fatigue. As blood flow becomes impaired due to the increased thickness, organs and tissues may struggle to receive sufficient oxygen, making these symptoms worse. As the disease progresses, more severe manifestations can occur, including splenomegaly, hepatomegaly, and excessive bleeding, such as epistaxis (nosebleeds), easy bruising, and gastrointestinal bleeding. These bleeding complications are often related to the increased viscosity of the blood and the abnormal function of platelets and blood vessels. In addition, the risk of thrombosis is heightened, which can lead to serious cardiovascular events like myocardial infarctions, strokes, and deep vein thrombosis. The relationship between Polycythemia vera and thrombosis is complex, with increased platelet production and enhanced endothelial adhesion contributing to the formation of blood clots. Thrombosis, because of hyperviscosity and elevated platelet counts, remains one of the leading causes of morbidity and mortality in Polycythemia vera patients. Another important aspect of PV is the inflammatory microenvironment within the bone marrow. This microenvironment, which is essential for normal hematopoiesis, becomes unhealthy in PV. The bone marrow stroma, responsible for supporting hematopoietic stem cells, is affected by the inflammatory cytokines and growth factors that increase during the disease. This leads to altered hematopoiesis, often resulting in the development of myelofibrosis in later stages of PV. Myelofibrosis is characterized by the extensive scarring of the bone marrow, which disrupts its ability to produce healthy blood cells. As myelofibrosis progresses, all three blood cell lineages, red blood cells, white blood cells, and platelets, become depleted, leading to anemia, leukopenia, and thrombocytopenia. This phase of the disease, often referred to as the spent phase, significantly worsens the prognosis and can lead to complications such as bleeding and infection.

Neovascularization is also an important feature of PV. The increase in angiogenesis in the bone marrow, likely mediated by pathways like VEGF/VEGFR, reflects the body's attempt to compensate for the abnormal blood flow caused by increased blood viscosity. This neovascularization contributes to the development of further complications, including thrombosis and the formation of new, potentially unstable blood vessels. The clinical progression of PV is often categorized into three distinct stages: the early stage, the advancing stage, and the spent phase. In the early stage, the disease may remain asymptomatic or only show mild symptoms, making it difficult to diagnose. As the disease advances, more noticeable symptoms, such as fatigue, pruritus (itching), and plethora (reddish or flushed complexion), may develop. During this phase, patients are also at higher risk for thrombosis, which can lead to life-threatening complications such as stroke or heart attack. The spent phase, which is marked by the replacement of bone marrow with fibrous tissue and the depletion of blood cell production, presents the most severe form of PV. In this phase, patients may experience extreme fatigue, anemia, and bleeding complications. This stage is also associated with an increased risk of developing acute myeloid leukemia or myelodysplastic syndrome, both of which are associated with poor prognosis and a reduced life expectancy. To effectively diagnose PV, it is crucial to differentiate it from other forms of erythrocytosis, such as secondary erythrocytosis. Secondary erythrocytosis occurs when EPO levels are elevated due to external factors such as chronic hypoxia, kidney disease, or tumors. In contrast, PV is characterized by the autonomous overproduction of erythroid cells due to JAK2 mutations and the absence of elevated EPO levels. The diagnostic criteria established by the World Health Organization (WHO) rely on blood tests, bone marrow biopsies, and molecular testing to identify the characteristic JAK2 mutation and low EPO levels. Once diagnosed, PV can be staged based on clinical symptoms, bone marrow findings, and the presence of complications such as myelofibrosis or thrombosis.

The management of PV focuses on controlling the production of blood cells and preventing complications such as thrombosis, bleeding, and organ damage. One of the most common treatments is phlebotomy, which is used to reduce blood viscosity by removing excess red blood cells. This treatment is typically initiated early in the disease to lower hematocrit levels and reduce the risk of clotting. In addition, cytoreductive agents, such as HU and interferon alpha, are used to target the abnormal proliferation of blood cells. These agents are particularly useful for patients who are resistant to phlebotomy or those with more severe symptoms. HU is commonly prescribed for patients under sixty who have not developed major complications, while IFN-γ is often used in younger patients or those who are pregnant. Aspirin therapy is another cornerstone of PV management, especially in reducing the risk of thrombotic events. By inhibiting platelet aggregation and reducing vasoconstriction, low-dose aspirin can help prevent the formation of blood clots in high-risk patients. For patients at risk of developing more severe complications, targeted therapies such as JAK2 inhibitors, particularly ruxolitinib, have shown promise in clinical trials. Ruxolitinib works by inhibiting the JAK-STAT signaling pathway, which is central to the abnormal proliferation of blood cells in PV. By blocking this pathway, ruxolitinib can reduce the production of blood cells and improve symptoms, particularly in patients with splenomegaly or myelofibrosis. Stem cell transplantation is another option for patients with advanced disease, particularly those who are experiencing severe myelofibrosis or other complications. Stem cell transplants, either autologous or allogeneic, offer the potential for a cure by replacing the defective hematopoietic stem cells with healthy ones. However, the risks associated with stem cell transplantation, including GVHD, make it a treatment option reserved for patients in the later stages of the disease.

The prognosis for PV varies depending on the stage of the disease, the presence of complications, and the effectiveness of treatment. Patients diagnosed early and treated appropriately can

expect a relatively normal lifespan, with many living for 15-25 years post-diagnosis. However, without treatment, the disease can progress rapidly, and survival rates are significantly reduced. The development of myelofibrosis, AML, or other severe complications leads to a poorer prognosis and may require more intensive treatment, such as stem cell transplants or intensive chemotherapy. PV is a complex and multifactorial disease that requires a comprehensive approach to diagnosis and management. While the disease can be asymptomatic in its early stages, timely intervention is critical to prevent complications and ensure the best possible outcome for patients. Advances in molecular therapies and targeted treatments, along with the development of more personalized care strategies, have significantly improved the outlook for many PV patients. Early detection, regular monitoring, and appropriate treatment are essential for managing PV and preventing the progression to more severe stages, thereby enhancing both the quality of life and survival prospects for patients. Continued research into the genetic and molecular mechanisms of Polycythemia vera holds the potential for even more effective treatments in the future, ultimately providing hope for a cure by focusing on personalized care and optimizing treatment regimens, clinicians can help manage the progression of PV and improve the long-term health of patients.

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