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Original Article

Current Trends in the Diagnosis and Evidence-Based Management of Patients with Myeloproliferative Disorders

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ABSTRACT

Myeloproliferative disorders (MPD) are clonal hematopoietic disorders characterized by abnormal clone expansion of haematological progenitor cells, which can lead to thrombosis, bleeding, and/or transformation to leukaemia. Chronic myelogenous leukaemia (CML) is characterised by increasing granulocytic cell proliferation with no loss of differentiation, leading to an increased number of granulocytes and their immature progenitors, with occasional blast cells on peripheral blood film. Polycythaemia Vera (PV) is a disorder of stem cells that presents a total hyperplasia, malignant, and cancerous marrow. Its most prominent feature is an increased absolute red blood cell mass due to uncontrolled red blood cell production, followed by increased myeloid and megakaryocytic production due to an abnormal clone of the haematopoietic stem cells with increased sensitivity to growth factors. Essential thrombocythemia (ET) is defined by a persistent increase in platelet count with a proclivity for thrombosis and haemorrhage. Expansion of megakaryocytes in the cell lineage leads to high platelet count, and the condition is thought to be clonal. Primary myelofibrosis (PMF) results in aberrant megakaryocyte development. Extramedullary haematopoiesis and reactive connective tissues are found in fully mature bone marrow (BM). PMF is linked to uncontrolled megakaryopoiesis as well as atypical, fibrosis, and hypercellularity. Haematological and morphological abnormalities in combinations with mutations (BCR-ABL, CARL, JAK2 or MPL) represent major diagnostic criteria for MPD. The WHO criteria for tumours of the hemopoietic and lymphoid tissues was revised in 2016. Prognostic models rely on clinical and haematological data, but new models with genetic information are being created for clinical trial environments. Management of most patients with MPDs involves treatment or monitoring symptoms associated with presenting disease and/or preventing other events such as thrombosis. Treatment modalities include symptomatic treatments, surgery, therapeutic radiation, therapeutic phlebotomy, therapeutic apheresis, cytoreductive therapy and haematopoietic stem cells transplantations.

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INTRODUCTION

Myeloproliferative disorders (MPDs) are clonal hematopoietic disorders characterized by an increased production of matured myeloid cells and an increased risk of thrombosis, bleeding, and leukemic transformation (Sung-Yong et al., 2020). MPDs includes Chronic myelocytic leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). (Tefferi and Vardiman, 2008). Philadelphia-negative MPD are ET, PMF and PV. These are typical myeloproliferative neoplasms (MPNs). Changes in Janus kinase 2 (JAK2) and receptor of thrombopoietin helps in understanding of MPN pathophysiology. TheJAK2 genetic changes is now target for drug development in addition to being standard criterion for diagnosis (Chul et al., 2015).

Louis Henri Vaquez initially documented PV in a patient with significant erythrocytosis and hepatosplenomegaly in 1892, hypothesising that it was caused by hematopoietic cell proliferation. This is where the history of myeloproliferative disease begins (Vaquez,1892). A group of individuals with splenomegaly and erythrocytosis were then characterised by William Osler as having Vaquez's disease(Osler, 1903). Myelofibrosis was first described and characterized by a German physician; Gustav Hueck. He showed the presence of bone marrow fibrosis and extramedullary haematopoiesis in patients with primary myelofibrosis (PMF)(Heuck, 1879). In 1934, Emil Epstein and Alfred Goedel described essential thrombocythemia (ET) when they understood that patients with thrombocytosis without marked erythrocytosis constituted a distinct clinical syndrome (Epstein and Goedel, 1934). Myeloproliferative disorders, such as chronic myelogenous leukemia, polycythemia vera, essential thrombocythemia, and primary myelofibrosis, are characterized by clonal hematopoietic cell expansion and genetic mutations, which have become the standard diagnostic criteria.

CHRONIC MYELOGENOUS LEUKAEMIA (CML)

Chronic myelogenous leukaemia or chronic myeloid leukaemia is a myeloproliferative disorder characterized by raised proliferation of

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the granulocytic cell line with no loss of the cells capacity to differentiate (Besa, et al., 2021). Accordingly, the peripheral blood cell profile shows raised number of granulocytes and their immature precursors with occasional blast cells. CML progresses through three phases: chronic, accelerated, and blast. During the chronic phase of the disease, mature cells proliferate; in the accelerated phase more cytogenetic abnormalities occur; during the blast phase, immature cells quickly proliferate (Besa et al., 2021).

Majority of patients are diagnosed during the indolent phase (chronic) with subsequently progresses to the more aggressive phase (accelerated and blast) within (3-5) years. CML is caused by a specific genetic mutation resulting in Philadelphia chromosome. CML accounts for 20% of adult leukaemia cases. Middle-aged individual experience the atypical form of CML and rare in younger individuals who present more aggressive type of CMLs. The disorder is rarely new in elderly (Besa et al., 2021).

The clinical presentations of CML are insidious changing as the disease progresses. The disease have3 phases (chronic, accelerated, and blast). Individuals in the chronic phase may present with no symptoms or may display some symptoms including Fatigue, loss of weight, weakness, inability to exercise, mild fever and increased symptoms of hypermetabolism. Other symptoms are increased leucocytes count or spleen enlargement on routine check, early satiety, and reduced food intake from encroachment on stomach resulting from splenomegaly, left upper quadrant abdominal pain from spleen infarction and hepatomegaly (Besa et al., 2021). As the disease progresses, symptoms progress. Progressive disease symptoms include: Bleeding, petechiae, and ecchymoses in the accelerated phase of the disease. Bone pain and fever are associated with the blast phase of the disease. There is decreased Haemoglobin (Hb), low platelet and high basophil with rapid splenomegaly in blast crisis (Besa et al., 2021).

Current Trends in the Diagnosis of CML

Findings in peripheral blood and histology as well as Philadelphia chromasome (Ph1) in BM are key in diagnosis of CML. Diagnosis consists of the full blood count (FBC) BM review and differential Peripheral blood smear (Besa et al., 2021). The FBC and blood smear are frequently used for the diagnosis. Peripheral blood can be used for reverse transcriptase quantitative PCR for BCR-ABL as demonstrated by fluorescent in-situ hybridization for t [9;22] [q34; q11.2]. Bone marrow aspirate, biopsy, conventional cytogenetics, and flow cytometry are utilised to detect BCRABL transcripts that are not picked up by standard BCR-ABL polymerase chain reaction (PCR) and to rule out concealed advanced stage illness. By analysing their phenotypic characteristics, flow cytometry can track the development of lymphoid blast crises. Karyotyping on the other hand may identify additional cytogenetic abnormalities (cytogenetic clonal evolution) (Thompson et al., 2017).

The characteristic features of complete blood count (CBC) are: Leucocytosis (median of 100,000/µL) with a left shift and classic “myelocyte bulge” (more myelocytes than metamyelocytes on blood smear), blasts are cells usually<2%, absolute basophilia is almost common, with absolute eosinophilia in 90% of cases, monocytosis is present but there is no increased in percentage. Absolute monocytosis is more prominent in the unusual presence of advanced stage rather than chronic phase of disease (Thompson et al., 2017).

Platelet count is usually normal or elevated in p190 BCR-ABL type. Blast phase, accelerated phase, and chronic phase are the three stages that are traditionally defined by low platelet counts. Although data from tyrosine kinase inhibitor (TKI) research offered a universally accepted classification, the phases have received variety of meanings. Bone marrow findings of CML include the Ph1, BCR/ABL mutation, increase cellularity, myeloid and progenitor cells, Megakaryocytes are prominent and may be at the increased, Mild fibrosis in the reticulin stain is present (Besa et al., 2021).

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Chronic Myelomonocytic Leukemia (CMML) is a myelodysplastic and myeloproliferative neoplasm that varies from CML in that it has dysplastic features, more pronounced cytopenias, and an increase in monocytes without a significant rise in basophil count. Ph-negative CMML may also exhibit other cytogenetic abnormalities (Thompson et al., 2017). Both Chronic Neutrophilic Leukemia (CNL) and CMML are Ph negative (Thompson et al., 2017). Because of the prominent neutrophilia seen in this kind of CML, CML such as those with a p230 BCRABL alterations, may be misinterpreted for CNL. However, the Ph-cytogenetics chromosomes will clearly distinguish between them. Almost none of these unusual mutations could be detected by a routine PCR. Rarely, isolated thrombocytosis without leucocytosis that mimics ET may be seen in CML patients. A diagnostic clue is often a high basophil count. Cytogenetic and molecular tests that are Ph-positive and BCR/ABL positive will be used to distinguish these instances (Thompson et al., 2017).

Evidence-based Management of CML

There are three goals for treatment of chronic myelogenous leukaemia that undergoes changes in the past 10 years (Besa et al., 2021). They are:

- Achievement of total haeematologic remission and physical examination i.e., absence of organomegaly
- Cytogenetic remission (Ph negative).
- Molecular remission (negative BCR/ABLmRNA)

The clinical phases of CML typically consist of three stages: the chronic phase, during which the disease process is readily treated; the unstable and aggressive course, which is frequently deadly; and the last stage. With hydroxyurea medication, the chronic phase typically lasts two to three years; however, in individuals who benefit from interferon-alfa therapy, it may last up to nine years. Tyrosine kinase inhibitor (TKI) treatment has also significantly increased the length of hematologic and cytogenetic remissions. Majority of patients with chronic phase (CP) of CML who received TKI demonstrated median survival expectancy approaching normal life (Gambacorti-Passerini et al., 2011).

TKIs have improved outcomes in CML. In comparison to imatinib, which has a better PFS, interferon is less successful in terms of rates of CHR, CCyR, and MMR, according to the seminal IRIS research (O'Brien et al., 2003). Allogenic stem cell transplant (alloSCT) was the primary course of treatment for eligible individuals prior to IRIS and interferon therapy. About 50-85%of patients were able to attain long-term disease-free survival as a consequence of the graft versus leukaemia (GVL) effect AlloSCT is usually associated with opportunistic infections and graft versus host disease (GVHD), which result in treatment-related mortality of between 5 and 20% with good compliance in many long-term survivors. AlloSCT is only used in patients with advanced illness and treatment failure since TKI therapy has been so successful in treating patients with these conditions (Thompson et al., 2017).

Imatinib was briefly used in studies that focused on using greater dosages of the medication to enhance outcomes after it was established as the standard treatment for CML (Cortes et al., 2003). Imatinib was used for a brief period of time in studies that looked at using higher dosages of the medication to enhance outcomes after it was established as the standard treatment for CML. In a single arm TIDEL study, which treated patients with 600mg of imatinib per day, it was found that a 400mg dose of imatinib BID was associated with a higher likelihood of cumulative rates of CCyR and MMR. It was also found to be very well tolerated, with 82% of patients maintaining at least 600mg daily, the study showed superior rates of MMR at (1-2) years in patients that can sustain daily averages of 600mg of imatinib for six months (Kantarjian et al., 2004; Jain et al., 2013).

Initial dosages of 800 mg of imatinib were shown to have a high risk of MM at 12 months when compared to 400 mg or 400 mg with interferon alpha. These people get an average daily dose of 628 mg of imatinib because of the medication's

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significant side effects and the high dose. (Hehlmann et al., 2011). This first higher dosage was found to promote quicker MMR achievement. However, there was no EFS or survival advantage connected to 400 mg of imatinib per day (Hehlmann et al., 2011; Thompson et al., 2017). Imatinib and interferon have been used in several randomised studies, with varying degrees of success. Patients who had imatinib together with pegylated interferon alpha 2a or alpha interferon-2b for a year had a significant risk of contracting MMR, according to the French SPIRIT and Nordic groups. However, CCyR did not differ from each other (Preudhomme et al., 2010; Simonsson et al., 2011). Contrary to this finding, the German CML study group demonstrated no differences in rates of CCyR or MMR when pegylated alpha interferon-2b was coupled with 800 mg/d of imatinib compared to imatinib alone (Hehlmann et al., 2011). Poor tolerance of interferon in all studies was reported in addition there is high chances usage stopping with no PFS or survival significance (Thompson et al., 2017).

With a high degree of efficacy, ponatinib is the only TKI that works in individuals with the T315I mutation in ABL1. Since it has demonstrated significant pre-clinical and clinical activity in the context of salvage, ponatinib has been designated as front-line therapy (Cortes et al., 2012). In a randomised phase 3 study, imatinib 400 mg and ponatinib 45 mg achieved equivalent outcomes (Lipton et al., 2014).

Depending on whether the patient has progressed from the chronic phase while using a TKI or is in the Accelerated Phase of CML, different treatment approaches are best. According to Ohanian et al. (2014), 80–90% of patients who have never received therapy will have CCyR while taking TKI, and these patients will have similar EFS and overall survival (OS) to patients who are presenting in the chronic phase and are receiving treatment with 2nd generation TKI. Additionally, individuals who solely meet the cytogenetic clonal evolution criteria for AP fare better than those who meet the hematologic or clinical criteria for AP (Ohanian et al., 2014). On the other hand, 2nd generation TKI trials for patients with imatinib failure and AP disease have shown much lower response rates and worse EFS with increasing relapses (Apperley et al, 2009).

TKIs and alloSCTs are two possible treatments. There are no randomised data to help with TKI dosage or selection. However, non-randomized studies suggest that second-generation TKIs have higher response rates than imatinib (Ohanian et al., 2014), with ponatinib offering perhaps the best result (Thompson 2017).

About 50–60% of individuals receiving therapy for blast crisis phase have myeloid blast phase (MBP), while 20–30% have lymphoid blast phase (LBP). 10–30% of the remaining patients are a mixed group. The purpose of blast phase therapy is to accomplish reversion to chronic phase and then carryout alloSCT +/− post-transplant TKI maintenance (Thompson et al., 2017)

POLYCYTHAEMIA VERA

Polycythaemia Vera (PV) is a disorder of stem cells that present a total hyperplasia, malignant, and cancerous marrow. PV most prominent feature is an increased absolute red blood cell mass because of uncontrolled red blood cell production. This is then followed by elevated white blood cell (myeloid) and platelet (megakaryocytic) production, because of an abnormal clone of the haematopoietic stem cells with increased sensitivity to the different growth factors for maturation. (National Cancer Institute, 2020). PV is a MPD that is associated with a Janus kinase-2 (JAK2) mutation (Lu and Chang, 2021). Silmutaneous stimulation of myeloid and megakaryocytic line leads to increased white blood cell and platelet production. Present understanding of mechanismof PV includes high sensitive to growth factors due to proliferation hematopoietic cell clone. The consequences of blood viscicity produces signs and symptoms of PV (Lu and Chang, 2021).

The aetiology PV is neoplastic proliferation. Abnormal response to growth factors, and the abnormal clonal line interferes with normal lineage proliferation are the consequences

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ofsignalling defect. The JAK2 gene involved with intracellular signalling is mutated in 90% cases of PV (Barbu et al., 2011). There is abnormal karyotype in the hematopoietic progenitor cells in approximately 34% of patients with PV (Lu and Chang, 2021).

The BM of patients suffering from PV contains both normal and abnormal clonal stem cells. Unregulated neoplastic proliferation results in absence of myeloid cells. Changes in JAK2 kinase leads to the signalling defects causing PV. There is valine to phenylalanine substitution at position 617 of the JAK2 gene, or JAK2V617F resulting in constitutively active cytokine receptors (James et al., 2005) seen in almost all patients with PV (Barbu et al., 2011; Spivak and Silver, 2008; Lu and Chang, 2021).

Current Trends in the Diagnosis of PV

The first criteria for the diagnosis of PV were proposed by Polycythemia Vera Study Group (PVSG) in the 1970s. Later, PCR based methods for detecting the JAK2 V617F mutation was introduced. However, paucity of centres doing red blood cell mass measurements, demonstrating an elevated red blood cell mass continues to be a problem (Srikanth and Sara, 2021). PV diagnosis can be established with presence of all three A criteria and also when criteria A1 plus A2 plus any two criteria from category B are present(Srikanth & Sara, 2021).

A Criteria

- Total red blood cell mass of greater than or equal to 36mL/kg in males and greater than or equal to 32 mL/kg in females.
- Arterial oxygen saturation greater than or equal to 92%.
- Splenomegaly.

B Criteria

- Platelet count of more than 400,000/μL
- Leucocyte count of more than 12,000/μL
- Alkaline phosphatase greater than 100 U/L
- Serum vitamin B12 concentration greater than 900 pg/mL with binding capacity of more than 2200 pg/mL

PV is diagnosed based on WHO guidelines. The standards are based on an evaluation of many clinical and lab parameters, such as the JAK2 mutation status and serum erythropoietin (Epo) level (Tefferi, 2011). PV is diagnosed when there is a JAK2 mutation and a low level of serum Epo (Tefferi et al., 2007). In order to identify the few individuals with PV who do not have JAK2 V617F, further mutational investigation for JAK2 exon 12 mutation is necessary when there is no JAK2V617F (Tefferi, 2011). Therefore, although a bone marrow test is not necessary for the diagnosis of PV, individuals who meet the diagnostic criteria for PV may have significant fibrosis in their bone marrow (Tefferi et al., 2007). According to Arber, et al., (2016); the WHO revised guidelines requires either all the three or the first two major criteria plus the minor criterion for diagnosis of PV.

The WHO major criteria for PV diagnosis

- Level of more than 16.5 g/dL in men and of more than 16 g/dL in women. Alternatively, a haematocrit of more than 49% in men and of more than 48% in women, or red cell mass of more than 25% above mean normal predicted value.
- BM biopsy showing myelopenia with pleomorphic, mature megakaryocytes
- Presence of JAK2V617F or JAK2 exon 12 mutation

The minor WHO criterion for PV diagnosis

- Decreased Serum erythropoietin level.

Criterion b may not be necessary in patients who have sustained absolute erythrocytosis. Nevertheless, bone marrow biopsy is the only way to detect initial myelofibrosis that is present in about 20% of patients and may predict a more rapid progression to overt myelofibrosis(Arber, et al., 2016).

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Patients that are positive for JAK2 and their hemoglobin/ hematocrit level is diagnostically equivocal, bone marrow examination is required to distinguish the ET and PV (Tefferi and Barbui, 2015). When JAK2 V617F mutation is absent but the Erythropoitin (Epo)level is low; testing for JAK2 exon 12 and 13 mutations would be necessary for making a diagnosis of PV in the 2-3% of PV patients who are negative for JAK2 V617F mutation. Patients that who are negative for JAK2 mutations and have a normal or high Epo level have secondary erythrocytosis (Srikanth and Sara, 2021).

Evidence-based Management of PV

Polycythemia Vera has no cure currently. Treatment objectives are leaving symptoms and decreasing the potentials of the disorder complexity. There are no preventive majors for transformation of PV to acute leukemia, myelodysplastic syndrome and myelofibrosis, however, substances that increases the risk can be avoided (Tefferi et al., 2018a).

The optimal management is still difficult to make even with findings of the Polycythaemia Vera Study Group (PVSG). However, there are general principles for management of patients with PV. These principles include the following (Streiff et al., 2002; Srikanth and Sara, 2021; McMullin et al., 2015):

- Tailor therapy that matches the clinical needs of the patient; blood, bone marrow, and organomegaly.
- Red blood cell mass can be normalized with phlebotomy (250-500) mL every other day. Smaller volume is removed from elderly and cardiac disease patients.
- Chemotherapy with hydroxyurea can be used to suppress myeloid cells in patients older than 50 years.
- JAK1/2 inhibitor ruxolitinib is approved for treatment of PV in patients resistant to hydroxyurea.
- Patients older than 80 years and those with comorbidity are given Iphosphorus-32.
- Regular examination and treatment to maintain reference haematological parameters.
- Elective surgery is postponed until long term control of the disease is achieved.
- Women of childbearing potentials are treated with phlebotomy.
- Alkylating agents is no more used because of the associated increased incidence of leukaemia and certain types of cancer.
- Hyperuricemiais treated with allopurinol (100-300 mg/d) until remission has been attained.
- Some interferon is considered an alternative to hydroxyurea for some patients. These include (Tefferi et al., 2021): young women of reproductive age, Patients with intolerance of or resistance to hydroxyurea therapy and Patients requiring treatment to reduce their phlebotomy requirement rather than to prevent thrombosis (Tefferiet al., 2021). However, there is also a research that supports the use of interferon alpha as a first-line treatment (Bewersdorf et al., 2021; Srikanth and Sara, 2021).

ESSENTIAL THROMBOCYTHEMIA

Essential thrombocythemia otherwise called essential thrombocytosis (ET). Formerly ET was known as haemorrhagic thrombocythemia (Ashorobi and Gohari, 2021). It is a myeloproliferative disorder of acquired origin that is characterized by continuous elevation of the platelet number with a tendency to thrombos formation as well as bleeding. ET is considered to be a clonal disease arising in a multipotent stem cell(Brière, 2007). JAK2 mutation is the major cause of ET (Tefferi and Pardanani, 2015) and is associated with thrombocytosis and the presence of megakaryocytic hyperplasia in the bone marrow. This increases the potential of venous thrombosis and haemorrhage and

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occasionally the transformed to a blast stage of myelofibrosis (Michiels et al 1999). WHO defines ET as more than 450,000 platelets with the presence of JAK2mutation, Calreticulin (CALR) or myeloproliferative leukaemia virus oncogen mutation, lacking clonal or reactive causes (Tefferi et al., 2018b).

ET and other clonal MPDs (CML, PV, Myelofibrosis) have similar molecular causes that lead to splenic myeloid metaplasia and an over production of mature cells. CML is now simple to identify because to the presence of the ph-positve chromosomal abnormality and evidence of a special molecular marker that disrupts protein kinase BCR/ABL. Despite the recent finding of JAK2 V617F mutation in these subgroups, the mechanism of molecular pathogenesis of MPDs in individuals with PV, ET, myelofibrosis, and myeloid metaplasia of the spleen is still unknown (Kralovics et al., 2005).

Current Trends in the Diagnosis of ET

Due to the lack of a specific molecular marker, additional clinical conditions associated with thrombosis must be checked out in order to diagnose ET. The exclusion criteria were put out by PVSG (Murphy et al., 1997). The WHO has recently recommended a stricter new set of criteria in which a specific megakaryocytopoiesis aberration is present together with additional bone marrow abnormalities (Imbert et al., 2001). Unmistakably, the JAK2 V617F mutation is a new genetic indicator for ph-negative (Kaushansky, 2005; Kralovics et al., 2005; Jelinek et al., 2005; Szpurka et al., 2006). No particular outcome of Ph-negative MPD that is associated with the presence or absence of the V617F mutation is recognised by the PVSG or the WHO. The diagnosis of ET presently comprises:

- There are two compelling, non-specific grounds in favour of a Ph-negative MPD: the JAK2 mutation and the findings of the BM biopsy.
- Ruling out of PV and IMF using their current phenotypic-based definitions (Imbert et al., 2001; Murphy et al., 1997).

Differential diagnosis of ET

- Platelet count

At first, a platelet concentration of more than 1000 x 109/L was required to detect ET. The most current PVSG criterion is several occurrences of platelet count exceeding 600 x109/L. This diagnosis can now be supported by a platelet count just over 450 x 109/L together with a suggestive clinical presentation (such as erythromelalgia, the incidence of arterial or venous thrombosis), and the availability of positive data in support of a Ph-negative MPD (Chait et al., 2005; Mossuz, 2006). Differential diagnosis of ET involves the elimination of the following:

- Other factors that contribute to a subsequent rise in thrombocytes

It is necessary to rule out secondary thrombocytosis brought on by an iron deficit, malignancy, chronic inflammatory conditions, splenectomy histories, and extended bone marrow regeneration.

- Familial hereditary thrombocytosis

  Familial thrombocytosis is caused by TPO gene mutations, which result in increased TPO levels. In kids with increased TPO levels, thrombocytosis has been reported on several occasions. Testing to determine whether the TPO gene has a loss of function mutation may be prompted by this (Bellanne-Chantelot et al., 2006; Brière, 2007).

- Primary thrombocytosis linked to chronic myelodysplastic syndromes

Characteristics of primary thrombocytosis connected to chronic myelodysplastic illnesses should be checked out when cytogenetic, myelographic, or haemogram results were indicative of myelodysplasia (Imbert et al., 2001; Murphy et al., 1997). The presence of the JAK2 mutation in certain people with myelodysplastic syndromes and sideroblastic anaemia may have justified the distinction between a separate myeloproliferative/myelodysplastic overlap in the

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most current classification of myeloid neoplasia (Kaushansky, 2005; Jelinek et al., 2005). Nonetheless, it may still be feasible to discriminate between these equivocal instances and real ETs, at least in studies that concentrate on long-term evolution or therapeutic evaluation(Brière, 2007).

- Primary thrombocytosis connected to a chronic myeloproliferative disorder that presents differently than ET

The more or less pure thrombocythemia forms of CML that formerly gave birth to the concept of Ph-negative MPD are now easily curable. This is mostly predicated on the identification of BCR/ABL transcripts in peripheral blood as opposed to research on the Philadelphia chromosome in BM cell (Michiels et al., 2004; Brière, 2007).

Evidence-based Management of ET

Prevention of vascular complexity (thrombotic and haemorrhagic events) is the main aim ET treatment. This complexity results in morbidity and mortality (Besses and Alvarez-Larrán, 2016). Strictly based on risk classification, the patient should receive therapy or not. As a result, the treatment plan is determined by the patient's thrombosis risk. When platelets are more than 1000 x 10^9/L, careful consideration should be given to acquired von Willebrand syndrome. Aspirin should not be taken in situations when there are abnormal von Willebrand laboratory results and/or bleeding. Nonetheless, patients with microvascular thrombosis events like erythromelalgia can get aspirin(Ashorobi & Gohari, 2021).

The first line of therapy is cytoreduction. This can be achieved by the use of hydroxyurea. Those who are intolerant or resistant to hydroxyurea can instead utilise anagrelide. Anagrelide prevents venous thrombosis better than hydroxyurea when the two are compared. Busulfan, interferon, radioactive phosphorus, and piproban are further hydroxyurea alternatives. Six weeks after giving birth, pregnant mothers with essential thrombocytosis can receive low molecular weight heparin. Cytoreduction in pregnant women can be achieved with pegylated interferon(Cervantes, 2011). Pregnant patients can also be managed with Plateletpheresis in pregnancy associated with extreme increase in platelet counts (Vannucchi and Guglielmelli, 2017).

PRIMARY MYELOFIBROSIS (PMF)

PMF is an abnormal formation of mostly platelets and granules containing leucocytes in the BM. There is usually formation of blood cells outside BM and connective tissues deposition in advanced PMF (Swerdlow et al., 2008). PMF is associated with uncontrolled formation of platelets, hypercellularity of marrow and fibrosis. Other presentation uncontrolled white and red cells formation as well as anaemia and tears drop cells. There are also spleen enlargement high lactate dehydrogenase and JAK2 aberration. Findings in Differential diagnosis in prefibrotic condition is not always clear due the fact that findings is only high platelet count (Wilkins et al., 2008). Primary or secondary myelofibrosis is associated with clonal hemopoietic stem cell growth, which appears as a stromal pattern, a leuco-erythroblastic blood film, and increased levels of several inflammatory and pro-angiogenic cytokines (John et al., 2012).

Decreased Hb, increased or decreased white cells, decreased, or increased thrombocytes, and formation of blood cells by other organs (other than BM) are the variable features of myelofibrosis. The extramedullary haemopoiesis is the most commonly cause of liver and spleen enlargements. The severe constitutional symptoms include pain, splenic infarction, early satiety, portal hypertension, and dyspnoea. Other features include marrow defect, lung associated hypertension, conversion to leukaemia and early death (John et al., 2012).

The prevalence of MF ranges from 0.5-1.5 per 100,000 people, with a median age of 67 years and a gender-neutral distribution. Anaemia, leukopenia or leucocytosis, thrombocytopenia or thrombocytosis, and multi-organ extramedullary haematopoiesis—which frequently results in

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hepatomegaly, symptomatic splenomegaly, or portal hypertension—are among the clinical features of MF that are consistent across all subtypes (Cervantes et al., 2009; Clodagh et al., 2013).

Current Trend in the Diagnosis of PMF

Cytogenetic, molecular, morphological, and clinical manifestations must all be considered in the diagnosis of PMF (Thiele et al., 2008). Moreover, using WHO-adopted criteria, the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) identifies Post-ET MF and Post-PV MF (Barosi et al., 2008). It might be challenging to identify early stages of PMF from ET and myelodysplastic syndrome (MDS) with fibrosis from PMF (Wilkins et al, 2008; Beer et al, 2010; Beer et al, 2011). Moreover, it is demonstrated that a high LDH lacks PMF specificity (Beer et al, 2010). Campbell and Green (2006) therefore developed criteria for the diagnosis of PMF, Post-PV MF, and Post-ET MF (John et al., 2012).

Diagnostic criteria for primary myelofibrosis [proposed by Campbell and Green (2006)] requires A1 + A2 and any two criteria B (John et al., 2012).

Criteria A

- Bone marrow fibrosis ≥3 (on 0–4 scale).
- Pathogenetic mutation (e.g., in JAK2 or MPL), or absence of both BCR-ABL1 and reactive causes of bone marrow fibrosis

Criteria B

- Palpable splenomegaly
- Unexplained anaemia
- Leuco-erythroblastosis
- Tear-drop red cells
- Constitutional symptoms (Drenching night sweats, weight loss >10% over 6 months, unexplained fever (>37·5°C) or diffuse bone pains)
- Histological evidence of extramedullary haematopoiesis

Molecular Investigations for Diagnosis of PMF

- Screening for JAK2 mutation
- In the absence of a JAK2 mutation, BCR-ABL1 rearrangement should be carried out because it excludes PMF when non-specific features are visible on a trephine biopsy (John et al., 2012).
- Negative for JAK2 V617F cases may require MPL W515L mutations test to identify MPL exon 10 mutations.
- Because TET2 mutations only occur in less than 16% of PMF cases, it is not advised to conduct systematic investigations into these mutations.
- Routine screening of this broad gene is not advised because the clinical impact of mutations in other genes, such as IKZF1, CBL, IDH1, ASXL1, SH2B3, IDH2, and NRAS, is unknown (Guglielmelli et al., 2011; John et al., 2012).

Evidence-Based Management of PMF

Allogeneic hematopoietic stem cell transplant was once one of the treatment choices for MF patients (alloHSCT). In MF treatment, hydroxyurea, spleen excision by surgery, radiotherapy, red cell transfusions, erythropoietin, androgens, and immunomodulatory agents (IMiDs), have all been used (Clodagh et al., 2013). Luckily, knowledge of MPNs and the molecular processes behind the MF is quickly growing (Clodagh et al., 2013). Between 50%–60% of individuals with PMF or ET and 90%–95% of those with PV were found to have the Janus kinase (JAK)2 V617F mutation in 2005(James et al., 2005; Kralovics et al., 2005; Baxter et al., 2005; Levine et al., 2005). This finding confirmed dysregulation of the JAK signalling pathway as the primary factor in the pathogenesis of MPDs, which was further supported by the observation that additional mutations in patients with MPNs were found to activate the signal transducers and activators of

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transcription pathway (JAK2 exon 12, MPL, and LNK) (Scott et al., 2007; Oh et al., 2010). Moreover, it resulted in the creation of small-molecule JAK inhibitors, such as the MF drugs; ruxolitinib (Clodagh et al., 2013).

- Despite the lack of published data demonstrating its efficacy and the rarity of overall complete responses, hydroxycarbamide is the most commonly utilized drug. It may take doses greater than 1.5 g/d to have a clinically significant impact. The majority of the time, benefits are visible after 8 to 10 weeks of treatment, although at these levels, adverse effects, particularly substantial cytopenias, may be problematic (John et al., 2012).

- Low-dose melphalan (2–5 mg/three times per week) administered to PMF patients exhibits a response rate comparable to that of hydroxycarbamide with the additional benefit of normalizing spleen size (Petti et al., 2002).

- Immunomodulatory medications: 50 mg/d of thalidomide combined with a reducing dose of prednisolone produced a 33% overall response rate (Mesa et al., 2003), but further follow-up revealed that only 8% of patients experienced a clinical improvement in splenomegaly (Thapaliya et al, 2011). Anaemia (22%) and thrombocytopenia (50%) are among the side effects. Lenalidomide has also been shown to have a 33% response rate in some patients who had not responded to thalidomide therapy in the past (Tefferi et al, 2006b).

- Interferon-alpha preparations that are pegylated or standard are not advised due to their ineffectiveness in reducing spleen enlargement. However, they are myelosuppressive drugs (Tefferi et al., 2001a; Jabbour et al., 2007; Ianotto et al., 2009; John et al., 2012).

- Cladribine; a purine analogue formerly known as 2-chlorodeoxyadenosine, has been demonstrated to minimize clinically significant hepatomegaly and post-splenectomy thrombocytosis as well as clinically significant myelosuppression adverse effects lasting up to 6 months after termination (Faoro et al., 2005).

- JAK inhibitors, the sole treatment examined in the context of randomized clinical trials, may play a future role in the therapy of splenomegaly (Clodagh et al., 2013).

- Surgical management: Splenectomy in the management of MF plays a vital role (Barosiet al., 1993; Tefferiet al., 2000) and the procedure is restricted to carefully selected patients. Patients with significant splenic infarction, severe portal hypertension refractory haemolysis, symptomatic splenomegaly and severe hypercatabolic symptoms can benefit from splenectom. Extensive preoperative evaluation is required to determine if the cardiac, hepatic, renal, metabolic, and haemostatic risks are acceptable (John et al., 2012). TIPS (transjugular intrahepatic portosystemic shunt) is a treatment option for intrahepatic shunt (Angermayr et al., 2002; Wiest et al., 2004; Alvarez-Larran et al., 2005; Doki et al., 2007).

- Radiotherapy is an important option to surgical procedure in patients not fit for surgery and with symptomatic splenomegaly that have platelet count of more than 50×10^9/L (John et al., 2012). Nonetheless, treatment with radiation is symptomatic and only short time lived. A dose of 277 cGy can beto reduce spleen size. Side effect of cytopenias however, was observed and was fatal (Elliot et al.,1998). There was also a study that administered980 cGy with a response rate of 59%of up to 10 months (Bouabdallahet al.,2000). Starting with a low dose of ≤50 cGy one or two times every week while monitoring blood count is recommended due to variable individual sensitivity that cannot be predicted (John et al., 2012).

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The disadvantage is that irradiation does not prevent spleen removal (Bartlett et al., 1995; John et al., 2012). This shows that radiation should not be viewed as an alternative to splenectomy in surgical candidates, together with the small response and operative mortality for the subsequent splenectomy (John et al., 2012). When the peritoneum and pleura are involved with extramedullary haematopoiesis due to ascites and pleural effusions, low dosage radiation therapy is still the preferred course of action (Leinweberet al., 1991; Kupferschmidet al., 1993; Bartlett et al., 1995). When important organs like the liver, brain, and lung are implicated, external beam radiation is also beneficial (Price and Bell., 1985; Landolfi et al., 1988; Tefferi et al., 2001b; Steensma et al., 2002). Recent studies have also demonstrated the effectiveness of low-dose radiation (10–60 cGy) as a treatment for excruciating extremities pain (Neben-Wittich et al., 2010).

CONCLUSION

Haematological and morphological abnormalities in combinations with mutations (BCR-ABL, CARL, JAK2 or MPL) represent major diagnostic criteria for MPD. The WHO categorization of tumours of the haemopoietic and lymphoid tissues was revised in 2016, and that revision serves as the foundation for these criteria. The majority of prognostic models in use today rely on clinical and haematological data. Yet, new models with genetic information are being created for clinical trial environments. A molecular profile of MPDs may also enable the best assessment, response tracking, and medication development that specifically targets the mutant gene.

Individuals suffering from MPDs can live for years without experiencing symptoms and therefore watchful waiting may be a reasonable treatment approach. Management of most patients with MPDs involves treatment or monitoring symptoms associated with presenting disease and/or preventing other events such as thrombosis. Generally, treatments modalities depend on the features of MPDs presented. These modalities include symptomatic treatments, surgery, therapeutic radiation, therapeutic phlebotomy, therapeutic apheresis, cytoreductive therapy and haematopoietic stem cells transplantations.

The JAK1/JAK2 inhibitors have been evaluated for all MPDs with certain degree of success. However, JAK1/JAK2 inhibitors and other cytoreductive agents such hydro-urea are associated with myelosuppressive activity as well as infection and therefore, patients taking these agents should be monitored for their possible side effects.

Management of symptoms and quality of life for MPDs patients is the major goals of treatment. Patients with MPDs can transform to secondary malignancy and therefore should keep to appointments schedules as well as focusing on follow up care.

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