Literature Review

An Introduction to Myeloproliferative Neoplasms

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The Philadelphia chromosome negative myeloproliferative neoplasms (MPNs) are a rare group of chronic hematological diseases that are closely related. They arise from one of three disease-initiating driver mutations that cause over-activation of the JAK-STAT pathway resulting in disease of the hematopoietic system. These three MPNs have overlapping clinical and diagnostic features making diagnosis challenging. The World Health Organization (WHO) diagnostic criteria continues to evolve as more advances are made in understanding these complex diseases. As such, prognostic models for risk stratification are also evolving and newer models (e.g., Mutation-Enhanced International Prognostic Score System) incorporate genetic and molecular features. The major and most common complications include thrombohemorrhagic manifestations and progression to acute leukemia. The development of Janus kinase inhibitors has changed the treatment landscape of MPNs, yet treatment options are at this time still limited due to the complexities of these diseases.

Key words: Myeloproliferative neoplasm, polycythemia vera, essential thrombocythemia, primary myelofibrosis.

Introduction

The classical myeloproliferative neoplasms (MPNs) are a group of chronic hematological diseases composed of chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The four classical MPNs are characterized by somatic mutations that occur in the hematopoietic stem cell resulting in excessive and chronic production of mature blood cells.[1] As MPNs are myeloid diseases, the excessive proliferation is restricted to erythrocytes, granulocytes, monocytes, and megakaryocytes.

CML is the only one that is Philadelphia (Ph) chromosome positive and this translocation between chromosomes 9 and 22 results in the BCR-ABL1 gene. The BCR-ABL1 gene is the driver (disease-initiating) mutation in the majority of CML patients and leads to unrestricted hematopoietic stem cell proliferation.[1,2] The other three diseases are Ph negative and are often classified as a group also known as the BCR-ABL1 negative MPNs. They are primarily the result of driver mutations in the Janus Kinase 2 (JAK2), calreticulin (CALR), or myeloproliferative leukemia (MPL) genes.[3,4]

As the focus of this article is on the Ph negative MPNs, any reference to MPN going forward will designate these 3 diseases. PV is characterized by excessive production of cells of the erythroid lineage, ET is characterized by excessive production of cells of the megakaryocytic lineage, and PMF is characterized by bone marrow fibrosis and megakaryocytic proliferation.[1] These diseases have shared clinical, diagnostic, molecular, and pathologic features that will be overviewed in this introductory article and further developed in the following articles.

Accepted: August 24, 2021

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PMF was the first MPN to be described in 1879 followed by PV in 1892 and ET was the last to be formally described in 1934.[5-8] It was not until 1951 that these diseases (including CML) were proposed to be interrelated. Dr. William Dameshek was an American hematologist and was the first to classify the diseases as "myeloproliferative disorders".[2] The term "neoplasm" replaced "disorders" in 2008 to emphasize the clonal nature of MPNs.[9]

Pathogenesis

Discoveries associated with CML (1960s-1990s), such as the Ph chromosome and resulting fusion gene BCR-ABL1, led researchers to question the possibility of undiscovered disease-initiating driver mutations in the Ph negative MPNs.[2] In 2005, research groups identified an acquired mutation in JAK2 gene that is present in more than 95% of patients with PV and over 50% of patients with ET or PMF.[1,10] The second most frequent driver mutation is CALR found in over 25% of patients with ET or PMF.[1,10] The last driver mutation, MPL, is the least frequent and found in over 3% of patients with ET or PMF.[1] About 10% of MPN patients lack a detectable driver mutation (JAK2, CALR, nor MPL) and are denoted as triple negative MPN.[3,11]

These driver mutations over-activate the JAK-STAT (Janus kinase-signal transducer and activator of transcription) signaling pathway which is essential for cytokines and growth factors that regulate differentiation, proliferation and survival of hematopoietic stem cells.[12] Thus, the pathway also plays a role in regulating hematopoiesis. The over-activation of the JAK-STAT pathway leads to impairment of hematopoiesis regulation resulting in various disorders of the hematopoietic system.[11,12] For MPNs, the result is hematopoietic stem cells that are hypersensitive to these cytokines and growth factors resulting in over proliferation of the myeloid cell line.

JAK2 assists with the regulation of growth factors: erythropoietin, granulocyte-colony stimulating factor (G-CSF), and MPL (the thrombopoietin receptor) thus affecting erythroid, granulocytic, and megakaryocytic lines.[3,11] As mutations of JAK2 are found in the majority of MPN patients, the resulting hematological characteristics include erythrocytosis, thrombocytosis and leukocytosis.[11] CALR and MPL mutations expressed in hematopoietic stem cells affect megakaryocytic lineage thus explaining their presence in ET and PMF but rarely found in PV.[11]

Beyond the three disease-initiating MPN driver mutations, additional non-driver mutations are found in many MPN patients. The most common of these mutations affect genes involved in epigenetic regulation, such as the TET2 gene.[3] Other affected genes include those involved in metabolic pathways, signaling cascades and splicing factors. Many of the non-driver mutations may be found in other hematological diseases and malignancies. They are also believed to play a role in disease development such as secondary myelofibrosis and transformation to acute leukemia.[1,3]

Clinical and Diagnostic Findings

MPNs are classified as a rare disease due to the low incidence rates.[6,9] They are often found in middle to advance-aged adults yet can occur in younger populations.[6,9] Clinical findings in MPNs range from asymptomatic to those associated with a debilitating disease thus making management a challenge.[3] The shared clinical features include hypercellular bone marrow, splenomegaly, thrombotic complications, and transformation to acute myeloid leukemia.[4,6] Due to these overlapping clinical features, diagnosis can present a challenge, yet an accurate diagnosis is critical for prognosis and treatment.

As mentioned above, the interrelatedness of the MPNs were described in 1951 by Dr. Dameshek who also referred to them as myeloproliferative disorders. Over the past seven decades, the research and resulting discoveries have guided the classification system as presented in Figure 1. The WHO, in collaboration with the Society for Hematopathology and the European Association for Haematopathology has published the fourth edition of *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* in 2008 and revised this

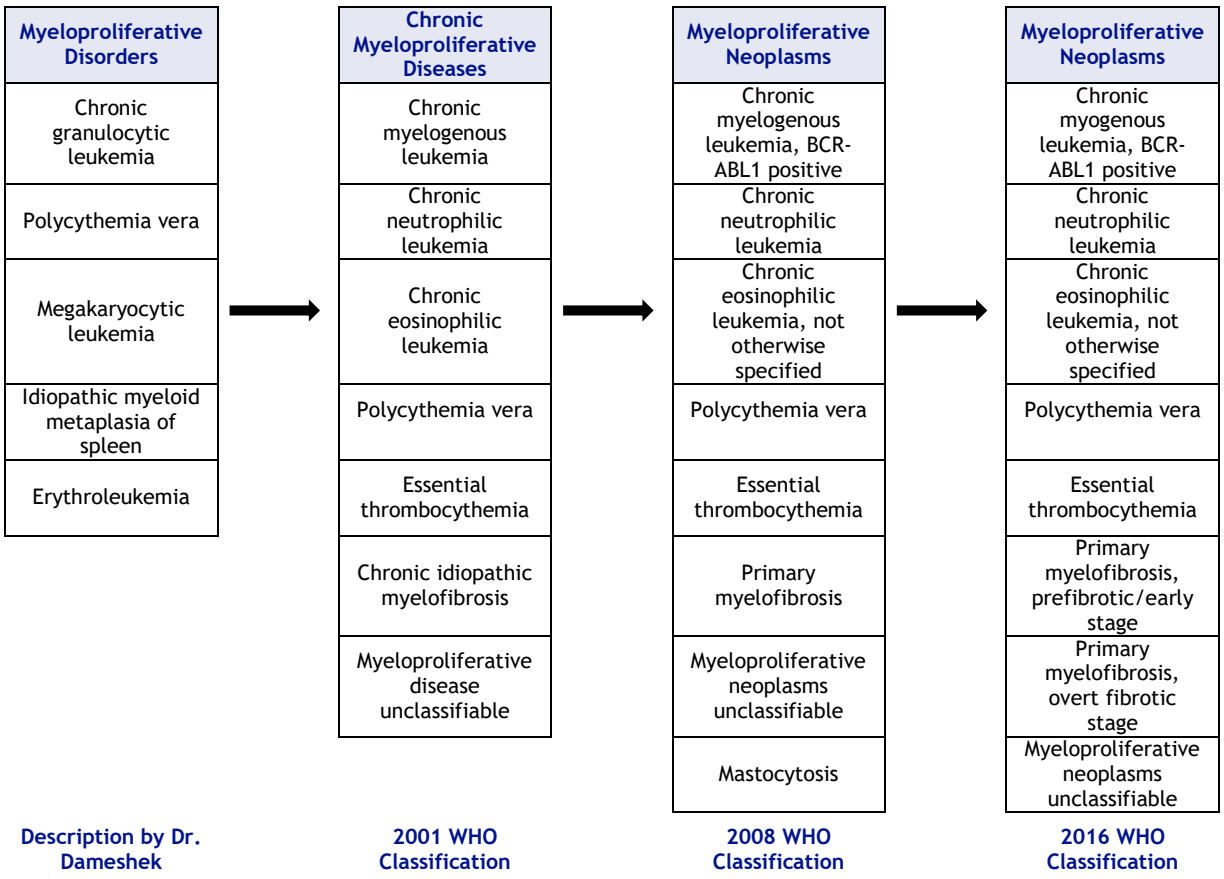

Figure 1. World Health Organization (WHO) classification evolution of myeloproliferative neoplasms. Adapted from Shallis et al. 2020.[2]

edition in 2016. The MPN category was revised due to discoveries of new mutations and one of the major revisions was to subcategorize PMF into prefibrotic or early stage PMF (prePMF) and overt fibrotic stage PMF.[13] This subcategorization is designed to help differentiate ET from prePMF.

PV is characterized by erythrocytosis and is suspected in patients with an elevated hemoglobin or hematocrit, hypercellular bone marrow indicating trilineage proliferation (panmyelosis), and the presence of a JAK2 mutation.[9,14] ET is characterized by thrombocytosis with a platelet count greater than 450 x 10^9/L, bone marrow showing proliferation of the megakaryocyte lineage, and presence of JAK2, CALR, or MPL mutation.[9,14] PMF is characterized by bone marrow proliferation of the megakaryocytic lineage and is accompanied by reticulin and/or collagen fibrosis, and presence of JAK2, CALR, or MPL mutation.[9,14] In addition, cytogenetic abnormalities are found in approximately 30-50% of PMF patients thus cytogenetic analysis contributes to diagnosis and prognosis.[15]

Major complications found in MPN patients include thrombosis, bleeding, and transformation to acute myeloid leukemia. For PV and ET patients, progression to secondary myelofibrosis is another complication of concern.[6] In order to assess the associated risks, multiple prognostic models have been developed specific to each MPN to aid in clinical decision-making.[9] Traditionally these prognostic models for risk stratification have been based on clinical and hematologic parameters however newer models are incorporating molecular and genetic parameters. A more in-depth review of the diagnostic criteria, complications, and prognostic models will be provided in the following articles.

Treatment

Current treatments for MPNs are primarily directed at prevention of complications and alleviation of symptoms as there are no curative drug therapies. For PV and ET patients, treatment has consisted of low-dose aspirin, therapeutic phlebotomy and cytoreductive drugs (e.g., hydroxyurea). As

PMF is associated with anemia, treatment also includes corticosteroids and androgens in addition to cytoreductive drugs.[1,14] The discovery of the driver mutations led to a pivotal moment in the treatment of MPNs, the development of JAK2 inhibitors. Ruxolitinib was the first approved targeted treatment for PMF and has improved symptoms and blood cell counts, and reduced spleen size.[3] Currently several novel drugs and targeted therapies (inhibitors) are being investigated for use in the treatment of MPNs.[16]

Conclusion

The three Ph negative MPNs have overlapping features yet are distinct hematological diseases and are presented in more detail in the following articles. PV is the most common Ph negative MPN with the hallmark clinical finding of an elevated hematocrit. Whereas, PMF has the hallmark findings of bone marrow fibrosis and splenomegaly with a bleak prognosis in comparison to the other Ph negative MPNs.

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