2020 Clinical, Laboratory, Molecular and Pathological (CLMP) criteria for diagnosis and new treatment options of JAK2^{V617F}, JAK2 exon 12, CALR and MPL^{515} mutated Myeloproliferative Neoplasms: From Dameshek to Vainchenker, Kralovics, Tefferi and Michiels 1940-2020

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The JAK2^{V617F} mutated trilinear myeloproliferative neoplasms (MPN) is featured by clinical phenotypes ranging from essential thrombocythemia (ET), prodromal polycythemia vera (PV), erythrocythemic PV, classical PV, masked PV and PV complicated by splenomegaly and myelofibrosis (MF). The JAK2^{V617F} mutation load increases from below 30% in ET to above 50% in PV and further increases to 80% to 100% due to mitotic recombination of chromosome 9p from heterozygous into heterozygous homozygous and homozygous (9p loss of heterogeneity: 9pLOH) in PV and MF. Bone marrow histology of clustered increase of large pleomorphic megakaryocytes (M) with hyperlobulated nuclei are similar in JAK2^{V617F} normocellular ET, prodromal PV and classical PV. Bone marrow cellularity sequentially increases in JAK2^{V617F} mutated ET and PV due to erythromegakaryoytic (EM) and trilinear erythron-megakaryo-granulocytic (EMG) proliferation.

Two main variants of megakaryocytic leukemia (Dameshek 1951) or ET with platelet counts around 1000x109/L and no features of PV include MPL^{515} and CALR mutated thrombocythemia. Bone marrow histology in MPL^{515} thrombocythemia is featured by megakaryocytic myeloproliferation (M) of large to giant megakaryocytes with hyperlobulated staghorn like nuclei in a normocellular bone marrow. Bone marrow histology of CALR thrombocythemia is characterized by megakaryocytic (M) myeloproliferation of large to giant immature megakaryocytes in a normocellular bone marrow followed by primary dual megakaryocytic granulocytic myeloproliferation (PMGM). Natural history and life expectancy of JAK2^{V617F}, MPL^{515} and CALR mutated MPN patients are related to the response to treatment, the degree of anemia, splenomegaly, myelofibrosis and constitutional symptoms. Epigenetic mutations at increasing age predict unfavorable outcome in adanced stages of JAK2^{V617F}, CALR and MPL mutated MPN. Low dose aspirin in JAK2^{V617F}, MPL^{515} and TPO mutated ET and phlebotomy on top of aspirin in prodromal and classical PV will prevent platelet-mediated microvascular and major thrombotic events (Sticky Platelet Syndrome). Pegaylated interferon (IFN) in JAK2^{V617F} ET and PV and IFN or anagrelide in CALR and MPL^{515} mutated thrombocythemias without features of PV are first line treatment options for the control of platelet count to prevent thrombohemorrhagic complications and for the control of MPN disease burden and spleen size to improve survival and quality of life. Ruxolitinib deserves a better place in the treatment of hypercellular PV to reduce MPN disease burden in symptomatic hypercellular PV before significant marrow fibrosis and splenomegaly do occur.