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The 2001-2016 World Health Organization vs. European clinical, molecular and pathological and the 2008-2018 clinical, laboratories, molecular and pathological (CLMP): Euro-Asian classification of *JAK2*, *CALR* and *MPL* mutated myeloproliferative neoplasms

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The 2008 World Health Organization (WHO) criteria do not define the prodromal and advanced or masked stages of the myeloproliferative neoplasms (MPN) essential thrombocythemia (ET) and polycythemia vera (PV). Bone marrow biopsy (BMB) has a near to 100% sensitivity and specificity to distinguish thrombocythemia in BCR/ABL positive CML and ET, and the myelodysplastic syndromes in RARS-T and 5q-minus syndrome from thrombocythemia in myeloproliferative disorders (MPD). Bone marrow pathology combined with JAK2, *MPL* and *JAK2* exon 12 mutation detection is a pathognomonic clue to each of the MPNs. Each of the *JAK2* trilinear MPN markers including spontaneous endogenous erythroid colony (EEC) formation, low serum erythropoietin (EPO) levels, and *JAK2* mutations are specific but not sensitive enough to distinguish ET and PV. The combination of *JAK2* mutation and increased erythrocytes (>6x109/L), haematocrit (>0.51 males and >0.48 females) is diagnostic for PV (specificity 100%, sensitivity 95%) obviates the need of red cell mass measurement. About half of WHO-defined ET and MF patients are *JAK2* positive. According to 2008 ECMP criteria, *JAK2* mutated ET comprises three distinct phenotypes of normocellular ET, ET with increased bone marrow erythropoiesis and hyper cellular ET with megakaryocytic granulocytic myeloproliferative without leuko-erythroblastosis. Low vs. high *JAK2* allele and MPN disease burden in heterozygous ET vs. homozygous PV is of major clinical and prognostic significance. *JAK2* wild type *MPL* mutated normocellular ET is the second distinct MPN. *JAK2/MPL* wild type hypercellular ET with primary megakaryocytic granulocytic myeloproliferative (PMGM) is the third distinct MPN. *CALR* mutated ET and MF lack PV features in blood and bone marrow. Pre-treatment bone marrow histology distinguishes JAK mutated trilinear MPN from calreticulin (CALR) and *MPL* mutated MPN. Increase of clustered large pleomorphic megakaryocytes with hyper lobulated nuclei is similar in JAK ET and PV patients. *CALR* mutated thrombocythemia shows characteristic bone marrow features of primary dual megakaryocytic granulocytic myeloproliferative (PMGM) without features of PV. *MPL* mutated thrombocythemia is featured by large to giant megakaryocytes with hyper lobulated stag horn like nuclei in a normocellular bone marrow without features of PV. Increase of JAK2, *CALR* and *MPL* MPN disease burden is related the degree of splenomegaly, myelofibrosis and constitutional symptoms during life-long follow-up. The presence of epigenetic mutations at increasing age predict unfavorable outcome in JAK2, *CALR* and *MPL* mutated MPNs. Low dose aspirin in ET and phlebotomy on top of aspirin in PV is mandatory to prevent platelet-mediated microvascular circulation disturbances. Pegylated interferon is the first line myeloreductive treatment option in prodromal and early stage *JAK2* mutated PV and in *CALR* and *MPL* mutated thrombocythemia. Low dose pegylated interferon in symptomatic is the first myeloreductive treatment of choice to postpone or eliminate the use of hydroxyurea as long as possible.

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