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European vs. 2015-World Health Organization clinical molecular and pathological classification of myeloproliferative neoplasms

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The BCR/ABL fusion gene or the Ph1-chromosome in the t(9;22)(q34;q11) exerts a high tyrokinase activity, which is the cause of chronic myeloid leukemia (CML). The 1990 Hannover Bone Marrow Classification separated CML from the myeloproliferative disorders essentialthrombocythemia (ET), polycythemia vera (PV) and chronic megakaryocytic granulocytic myeloproliferation (CMGM). The 2006-2008 European Clinical Molecular and Pathological (ECMP) criteria discovered 3 variants of thrombocythemia: ET with features of PV (prodromal PV), "true" ET and ET associated with CMGM. The 2008 World Health Organization (WHO)-ECMP and 2014 WHO-CMP classifications defined three phenotypes of JAK2V617F mutated ET: normocellular ET (WHO-ET), hypercelluar ET due to increased erythropoiesis (prodromal PV) and ET with hypercellular megakaryocytic-granulocytic myeloproliferation. The JAK2V617F mutation load in heterozygous WHO-ET is low and associated with normal life expectance. The hetero/homozygous JAK2V617F mutation load in PV and myelofibrosis is related to myeloproliferative neoplasm (MPN) disease burden in terms of symptomatic splenomegaly, constitutional symptoms, bone marrow hypercellularity and myelofibrosis. JAK2 exon 12 mutated MPN presents as idiopathic eryhrocythemia and early stage PV. According to 2014 WHO-CMP criteria, JAK2 wild type MPL515 mutated ET is the second distinct thrombocythemia featured by clustered giant megakaryocytes with hyperlobulated stag-horn-like nuclei, in a normocellular bone marrow consistent with the diagnosis of "true" ET. JAK2/MPL wild type, calreticulin mutated hypercellular ET appears to be the third distinct thrombocythemia characterized by clustered large immature dysmorphic megakaryocytes and bulky (bulbous) hyperchromatic nuclei consistent with CMGM or primary megakaryocytic granulocytic myeloproliferation.

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Genetic and epigenetic pathways in myelodysplastic syndromes

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Myelodysplastic syndromes (MDS) are a highly heterogeneous group of hematopoietic tumors, mainly due to variable clinical features and diverse set of cytogenetic, molecular-genetic and epigenetic lesions. The major clinical features of MDS are ineffective haematopoiesis, peripheral cytopenias, and an increased risk of transformation to acute myeloid leukemias, which in turn is most likely determined by specific genetic abnormalities and other presenting hematologic features. The risk of developing MDS is relatively higher in some genetic syndromes such as Fanconi anemia and receipt of chemotherapy and radiation treatment. In recent years, a significant progress has occurred and a vast literature has become available including the spectrum of cytogenetic abnormalities, gene mutations relating to RNA splicing machinery, epigenetic regulation of gene expression and signaling pathways associated with MDS pathogenesis, which have provided opportunities to understand the molecular mechanisms as well as employ targeted therapeutic approaches to treat MDS. The cytogenetic abnormalities detected in MDS vary from a single abnormality to complex karyotype not easily amenable to conventional cytogenetic analysis. In such cases, array based high resolution genomic analysis detected abnormalities, which are diagnostic as well as prognostic. The most common driver gene mutations detected in patients with MDS include RNA splicing (SF3B1, SRSF2, U2F1, ZRSR2), DNA methylation (TET2, DNMT3A, IDH1/IDH2), chromatin modification (ASXL1, EZH2), transcription regulation (RUNX1, BCOR) and DNA repair control p53. A small subset of MDS arises due to deregulation of RAS pathway, mainly due to NRAS/KRAS/NF1 mutations. Identification of these mutations and pathways in turn provided opportunities for oncologists to target these patients with specific therapies. Several drugs known to target the spliceosome, oncogenic RAS signalling, or hypomethylating agents have been employed to successfully treat MDS patients.

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