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Leukaemia Section

Mini Review

Polycythemia vera (PV)

Antonio Cuneo, Francesco Cavazzini

Hematology Section, Department of Biomedical Sciences, University of Ferrara, Corso Giovecca 203, Ferrara, Italy

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Clinics and pathology

Disease

Polycythemia Vera (PV)

Phenotype / cell stem origin

The disease is a chronic myeloproliferative disorder originating from a mutated pluripotent stem cell capable of producing red blood cells, granulocytes and megakaryocytes. In some cases, B-lymphocyte involvement by the clonal proliferation was documented; T-lymphocytes are rarely involved by the malignant process.

Epidemiology

PV is the most common chronic myeloproliferative disorder with a 2-3/100,000 incidence. The prevalence of the disease was 300 cases per one million. The male-to-female ratio is 1.2 and the average age at diagnosis is 60 years.

Clinics

PV must be distinguished from secondary erythrocytosis, and from spurious polycythemia. The diagnosis of PV can reasonably be made in the presence of a raised red cell mass (above 25% above predicted, or hematocrit 0.60 in males or above 0.56 in females), in the absence of causes of secondary erythrocytosis (normal arterial oxygen saturation and no elevation of serum erythropoietin). Some patients may show at diagnosis palpable splenomegaly, thrombocytosis (platelets above 400 x 10^9L), neutrophilia (neutrophils above 10 x 10^9L). Endogenous erythroid colonies usually grow in vitro and serum erythropoietin levels are low. The Presence of JAK2 V617F mutation has an emerging role in the diagnosis of the disease.

Cytology

The bone marrow is hypercellular with normal morphology. Clusterd mature megakaryocytes may be seen. The iron stores are absent. Significant increase of reticulin fibers may be present.

Treatment

Phlebotomy is the mainstay of treatment, aiming at a reduction of hematocrit level to the normal. Low dose aspirin is necessary to reduce the risk of thrombotic complications. Interferon (young patients) or hydroxyurea can be used if cytoreduction is necessary (thrombocytosis, splenomegaly).

Evolution

The disease symptoms are usually related to arterial thrombosis and deep venous thrombosis, which are much more frequent in the untreated patient. 30-40% of the deaths are accounted for by major thrombotic events. Post polycythemic myeloid metaplasia (spent polycythemia) may occur in 5-50% of the patients and these patients are at risk (20-50%) of developing acute leukemia.

Prognosis

A significant prolongation of survival was achieved by modern treatment strategies and a cumulative median survival in excess of 15 years was documented.

Cytogenetics

Cytogenetics morphological

Overall, 25-35% of the patients show a clonal chromosome defect. Only 10-15% of the untreated patients have a clonal aberration, whereas up to 60% of previously treated cases may show a defect. The vast majority of patients studied at disease transformation

harbours cytogenetically abnormal clones. Non-random chromosome aberrations found before treatment include +8, +9, del(13q), del(20q) and gain of 1q. The latter anomaly is frequently seen in the spent phase of PV; a common trisomic region at 1q21-1q32 was identified. These aberrations have little prognostic significance as they are frequently associated with indolent disease. The appearance of sub-clones and/or 5q- may herald disease transformation.

Cytogenetics molecular

a) Fluorescence in situ hybridization (FISH) and molecular studies. Interphase FISH may increase the sensitivity of conventional cytogenetics. Using this technique, additional 9p was shown to represent the most frequent chromosome aberration in PV. Genome-wide screening for loss-of-heterozigosity (LOH) showed the existence of LOH at 9p, 10q and 11q. LOH at 9p is the most frequent defect in PV, where it occur in approximately 30% of the cases and it affects both myeloid and lymphoid cells. LOH at 9p is due to mitotic recombination with uniparental disomy and, hence, it is not detectable by karyotyping and by molecular cytogenetic analysis. The JAK2 gene is located at 9p (vide infra).

b) Janus Kinase JAK2 mutation. A valine to phenylalanine substitution at position 617 (JAK2 V617F mutation) is present in 65-97% of the patients, leading to constitutive kinase activity. The mutation is acquired and occurs at the level of a pluripotent stem cell originating myeloid and lymphoid cells. Mitotic recombination at 9p may lead to the emergence of a clone with JAK2 V617F mutated homozygous cells.

The mutated JAK2 protein binds to the cytoplasmic domain of Epo-R and promotes signalling independent of Epo stimulation. The JAK2 protein is coded for by a gene mapping at 9p and it is activated upon erythropoietin binding to the receptor. JAK2 signalling involves the phosphorylation of several Y residues at the Epo receptor with activation of STAT, MAP kinase PI-3-kinase and AKT. These events lead to survival and proliferation of erythroid progenitors. JAK2 is involved in intracellular signalling following stimulation by IL3, TPO and GM-CSF, and erythroid progenitors in PV are hypersensitive to stimulation by these cytokines.

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