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MYELOFIBROSIS

Epidemiology and pathogenesis

Myelofibrosis (MF) is a chronic myeloproliferative neoplasm (MPN) that can arise in primary form (MFP) or secondary to previous polycythemia vera (PV) or essential thrombocythemia (ET). This evolution occurs in 10-20% of cases after 15-20 years. The annual incidence of MF is estimated between 0.5 and 1.3 cases per 100,000 persons. The average age at diagnosis is about 70 years. The following driver gene mutations are fundamental in the pathogenesis of MF: JAK2 (55% of cases), CALR (20-30%), MPL (7-10%). Additional mutations in other myeloid genes are also frequent.

Clinical picture

Patients with MF frequently present with constitutional symptoms, fatigue and splenomegaly (secondary to extramedullary hematopoiesis). Cytopenias, such as anemia, can lead to severe clinical consequences. Thrombotic complications are also frequent.

Diagnosis

The diagnostic criteria for MFP have recently been revised by the 2016 WHO classification. A distinction is made between a prefibrotic and a overt form of MFP, based on the degree of marrow fibrosis. Mutations in JAK2, CALR, or MPL are currently among the major criteria for establishing MFP clonality. In their absence, the finding of additional genetic or cytogenetic abnormalities may be useful. Therefore, it is important to always perform cytogenetic analysis and-if possible-gene sequencing on many myeloid genes.
The diagnosis of MFS is based on diagnostic criteria defined in 2008 and requires the presence of a degree of bone marrow fibrosis at least equal to 2.

Prognosis

The median survival of patients with MF is significantly reduced compared to the control population and the risk of evolution into blastic phase is also relevant.
In MFP, at the time of diagnosis it is necessary to use the IPSS score, based on clinical-laboratory variables. Additional myeloid mutations of unfavorable significance have been included in the more recent MIPSS70, to be applied to patients of transplant age, i.e., less than 70 years. Dynamic models, such as DIPSS, are used during MFP follow-up. In MFS, a specific prognostic model, the MYSEC-PM, is used. The outcome of allogeneic transplantation is instead evaluated by the MTSS score.

Treatment

MF treatment depends on the prognostic risk category and on patient's major clinical needs. Only for those few subjects younger than 70 years and with an estimated survival of less than 5 years, allogenic transplant can be considered for curative purposes. Instead, most patients are treated for the management of splenomegaly and constitutional symptoms: the JAK 1/2 inhibitor Ruxolitinib is used for this purpose, with variable and often non-lasting response rates. For patients who do not respond or are intolerant to Ruxolitinib, a clinical trial with alternative drugs (Fedratinib, Bomedestat) or combination between Ruxolitinib and new molecules (e.g., Navitoclax) should be considered. For patients with severe cytopenias, conventional therapies and Ruxolitinib are ineffective, so combinations of the latter with investigational drugs (CPI-0610, Navitoclax, Parsaclisib, Luspatercept) or alternative JAK inhibitors (Momelotinib, Pacritinib) are being under

study. For more information about the hematologic trials available in Varese, please visit the section “Trial Unit” of the Institutional website (https://www.asst-settelaghi.it/ematologia).