## E13. **TREATMENT OPTIONS IN PRIMARY MYELOFIBROSIS.**

*Andrei Colita*
Clinic of Hematology, Coltea Clinical Hospital, Bucharest

Myeloproliferative neoplasms (MPN) are clonal diseases originating in pluripotent hematopoietic stem cells. Clonal expansion leads to increased and abnormal hematopoiesis that produces a group of interrelated syndromes classified according to the predominant phenotypic expression of myeloproliferative clone.

The main entities that are part of NPM are:

- Chronic Myeloid Leukemia
- Polycythemia vera (PV)
- Essential thrombocythemia (ET)
- Myeloid metaplasia with myelofibrosis / Idiopathic; Post PV; post TE

Myeloid metaplasia with myelofibrosis or primary myelofibrosis (MF) is characterized by the association of nonclonale bone marrow stromal reaction (proliferation and fibroblast activation) that causes collagen fibrosis, osteosclerosis, and angiogenesis (processes that are targets of modern therapy) and age of occurrence - in most cases> 60 years. Incidence is 0,5 /100.000/year.

**Characteristics of MF:**

- Clinical: progressive anemia, splenomegaly, cachexia, extramedullary hematopoiesis (HEM)
- Hematological: blood leucoeritroblastic picture, dacriocytes
- Progressive alteration of the quality of life (need for transfusions, compressive signs related splenomegaly and signs of severe hipercatabolism)
- Life Expectancy: 3,5 5 years (> 10 – young patients with good prognosis)
- Causes of death: infection, bleeding, portal hypertension, organ failure, acute leukemia transformation (10-20%)

**WHO diagnostic criteria** (the 3 major and 2 minor criteria must be met)

Major criteria:

1.Presence of megakaryocyte proliferation and atypia, usually accompanied by reticulin fibrosis and / or collagen, in the absence of significant reticulin fibrosis, megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often reduced erythropoiesis (diseasein prefibrotic stage)

2.WHO criteria for PV, CML, MDS or other myeloid neoplasm are not met

3.Demonstrating the existence JAK2617VF or other clonal marker (MPL515WL / K), or in the absence of a clonal marker, excluding secondary myelofibrosis (inflammatory or neoplastic)

Minor criteria:

1. Leucoeritroblastic picture
2. High LDH levels
3. Anemia
4. Palpable splenomegalia

A number of clinical and laboratory parameters were found to be independent prognostic factors that allowed risk stratification of patients with MF: Age> 65 years; Hb <10 g / dl; WBC> 30,000 / l; WBC <4,000 / l; Circulating blasts> 1%; Presence of constitutional signs; Cytogenetic abnormalities; Erythroblasts in peripheral blood > 2%; Platelets <300,000 / l; Splenomegaly ; JAK2 (V617F) / CALR; CD34 + circulating cells.

Based on these prognostic factors several prognostic scores were developed, the most used currently being DIPSS- plus taking into account age, the number of leukocytes and platelets, anemia, transfusion needs, simptimele constitutional karyotype and the percentage of circulating blasts. Based on this score patients are stratified into 4 risk categories (low, intermediate 1 SI2, high) with impact on survival and therapeutic strategy.

**MF treatment possibilities** are represented by:

-Conventional methods that primarily targets improvement of disease symptoms - Supportive and palliative in nature and have no impact on survival

-New methods represented by new agents that target the pathogenic mechanisms of disease and bone marrow transplantation - the only potentially curative method

Conventional Treatment has several components:

1.Substitution - blood products

2.Hipouricemiants + hidration + urine alcalinization

3.Antianemic treatment: Androgens, Corticosteroids, Erithropoietins ,

4.Antiproliferative treatment: Interpheron; citotoxic agentis (Hidroxiurea, Busulfan, 2-Clordezoxiadenosine, Melphalan, 6-Tioguanine, Citosine arabinozid), Anagrelide

5.Reduction of extramedullary hematopoiesis: cytotoxic agents, surgical ablation, radiotherapy

New Therapeutic Methods

1.IMIDs (antiangiogenic activity): Thalidomide; Lenalidomide (cases with 5q deletion)

2.Intracellular signal transduction inhibitors: Imatinib mesilate; JAK2 inhibitors – ruxolitinib, momelotinib, etc

3.Other molecules are under investigation:

- action on intracellular signaling pathways
- hipometilanting agents
- proteasome inhibitors
- new IMIDs
- Anti TNFα agents

4.Allogeneic stem cell transplantation (Allo SCT) - the only therapeutic method that can remove marrow fibrosis and has the potential to cure the disease.

Currently the management of patients with MF depends on prognostic stratification:

- Patients in the low risk category - if asymptomatic are kept under observation; if symptomatic receive conventional symptomatic treatment
- Intermediate-1 Risk - conventional symptomatic therapy or investigational therapy
- Intermediate-2 and high risk : <45 years - myeloablative Allo-SCT; 45-65 years - non-myeloablative Allo-SCT; :> 65 years - investigational therapy

**Important notions:**

- median survival is 5.5 years, but there are wide variations.
- Clinical and hematological presentation - varied according to disease stage
- The main prognostic factors: age> 65 years, presence of constitutional symptoms, Hb <10 g / dL, leukocytosis> 25 x109 / L, blasts in SP> 1%; Some cytogenetic abnormalities
- Based on prognostic factors patients can be stratified into four risk groups
- Risk group stratification is critical in adopting therapeutic strategy.