Philadelphia negative chronic myeloproliferative neoplasms diagnosis criteria. Treatment recommendations

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Chronic myeloproliferative neoplasms (MPN) are clonal disorders of pluripotent stem cell. These diseases were first described by W. Dameshek1 in 1951, which included in their group also chronic myeloid leukemia (CML). Currently MPN are reptezentsd by polycythemia vera (PV), essential thrombocythaemia (ET), primary myelofibrosis (PMF) and unclassifiable MPN.

There are some common features of MPN: clonal origin, *JAK2*V617F mutation [2, 3] (which is present in 90% of cases of PV and nearly 60% of ET and PMF), the rising incidence and complications represented by thrombosis, hemorrhage, trend for myelofibrosis and acute transformation. The last classification of MPN was developed by the World Health Organization[4, 5] (WHO) in 2008 (Table 1).

Table 1. 2008 WHO Classification of MPN

1. AML and related precursor neoplasms
2. MDS
3. Myeloproliferative neoplasm (MPN)
- BCR-ABL positive CML
- PV
- ET
- PMF
- CNL
- CEL
- mastocytosis
- Unclassified MPN
4. MDS / MPN neoplasm
- CMML
- JMML
- Atypical CML *BCR-ABL* negative
- Unclassified MDS / MPN napalms
- RARS associated with thrombocytosis
5. Myeloid and lymphoid neoplasm with eosinophilia and abnormalities *of PDGFRA*, *PDGFRB* or *FGFR*1
- Myeloid and lymphoid malignancies with *PDGFRA* rearrangement
- Myeloid malignancies *PDGFRB* rearrangement
- Myeloid and lymphoid neoplasms with *FGFR*1 abnormalities

For both current practice and research and development of scientific works, is necessary to use diagnosis criteria developed by WHO in 2008[4,5] (Table 2).

Table 2. 2008 WHO diagnosis criteria of MPN

Polycythemia Vera (diagnosis requires both major criteria and one minor criterion or the first major criterion plus two minor criteria)
MAJOR CRITERIA:
1. Hb > 18.5 g/dl in men and > 16.5 g/dl in women or increased red cell mass > 25% compared to the normal;
2. Existing *JAK2*V617F mutation or similar mutation (exon mutation)
MINOR CRITERIA:
1. Bone marrow biopsy showing trilineage marrow proliferation (panmyelosis);
2. Under normal serum erythropoietin level;
3. Growth of endogenous erythroid colony formation in vitro

Essential thrombocythemia (diagnosis requires all four criteria)
1. Persistent thrombocytosis > 450 x 10^9/l;
2. Bone marrow biopsy reveals proliferation of large, mature megakaryocytes and the absence or slight granulocyte or erythroid proliferation;
3. Absence of WHO criteria for CML, PV, PMF, MDS or other myeloid malignancies
4. The presence of mutation *JAK2*V617F or other clonal markers or in the absence of these markers, no cases of reactive thrombocytosis

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Primary myelofibrosis (diagnosis requires all three major and two minor criteria)
MAJOR CRITERIA:
1. Atypical megakaryocytic proliferation accompanied by reticulin fibrosis and / or collagen or reticulin fibrosis without changes mgk must be accompanied by increased celularităţii marrow, granulocyte proliferation and often decreased erythropoiesis (eg prefibrotic stage of PMF);
2. Absence of WHO criteria for CML, PV, MDS or other myeloid malignancies;
3. The presence of *JAK 2*V617F or other clonal marker (eg. *MPL*W515K/L) or absence of reactive bone

marrow fibrosis
MINOR CRITERIA:
1. Leukoerythroblastosis;
2. Increased serum LDH level;
3. Anemia;
4. palpable splenomegaly

MANAGEMENT OF PV AND ET

Goals of therapy in patients with PV and ET are avoiding and recurrence of thrombotic and hemorrhagic complications and their treatment, minimizing the risk of progression to myelofibrosis and leukemic transformation, symptom control and treatment of special situations such as pregnancy and surgery. For choosing optimal therapies is necessary to evaluate the risk factors (the main is the thrombotic risk), which are common to PV and ET[6,7,8,9,10,11] (figure 1).

Figure 1. Low risk of thrombosis and hemorrhages (ET and PV)

- Age <60 years
- Absence of previous thrombosis
- Lack of cardiovascular risk factors and family history of clinically significant thrombophilia

For low risk patients with a platelet count <1500 x 10^9/l and complete lack of symptoms is recommended close monitoring (watch and wait strategy). If they are present microcirculatory disturbances is recommended 50 - 100mg/day Aspirin (ASP).[12] If hemoglobin and hematocrit are increased is performed phlebotomy for maintaining Ht <45% in men and <43% in women.[15]

Low risk patients should receive cytoreductive when passing in a high risk group.[6]

Criteria for intermediate risk of thrombosis and bleeding in TE and PV are illustrated in the figure 2

Figure 2. Intermediate risk of thrombosis and hemorrhages (ET and PV)

- Age 40 to 60 years.
- Absence of thrombosis in history
- Cardiovascular risk factors: hypertension, diabetes, smoking, hypercholesterolemia
- Tr 1000 - 1500 x 10^9/l

Thrombotic risk: association with vascular risk factors or thrombophilia
Bleeding risk: association of minor bleeding and long evolution.

The recommended treatment of patients with intermediate risk should be individualized. Low dose ASP12 is indicated for the most patients. For those with cardiovascular risk factors and thrombophilia, cytoreductive therapy is added. Patients with extreme thrombocytosis (> 1500 x 10^9 /l) may develop acquired von Willebrand disease,[13,14] which can cause bleeding. In this situation is required cytoreductive therapy. Also, if Hb and Ht are elevated, phlebotomy is associated.[15]

High risk factors are illustrated in figure 3.

Figure 3. Increased risk of thrombosis and hemorrhages (ET and PV)

- Age> 60 years
- History of thrombosis
- Risk of severe bleeding: Platelets> 1500 x 10^9/l and a history of major bleeding or minor bleeding when platelets > 1000 x 10^9/l, especially in patients evolving > 15 years

For high risk patients is mandatory cytoreductive therapy. Are used cytostatic and non cytostatic drugs. It should be noted that in parallel with cytoreductive therapy the cardiovascular risk factors should be treated appropriately. The most effective and used chemotherapy agent is Hydroxyurea (HU), an antimetabolite (ribonucleotide reductase inhibitor). Induction dose is 15-20 mg / kg / day. When remission is achieved (normalization of blood counts, remission of splenomegaly) is continued with the lowest effective dose to maintain normal values of blood counts.[15, 16,17] Some studies have raised the leukemogenic effect of HU,[18,19] especially because is a long term treatment, so it is particularly appropriate for elderly patients. The side effects of HU are gastrointestinal damages and mucocutaneous toxicity (hyperpigmentation of the skin, painful leg ulcer, ulcerative stomatitis), effects that may require replacement with other drugs, namely Busulphan, Pipobroman, Purinethl and Lanvis.

Non cytostatic therapy for PV and TE is represented by Interferon (IFN) and Anagrelide (ANA). Interferon alpha-2 may induce up to 80% hematologic response,[15,20,21] trials proving also molecular response (reduction to extinction of *JAK*2V617F gene).[22]

Not mutagenic, is indicated for the treatment young people and pregnant women.[15]

Induction dose is 3 MU / day until remission is achieved followed by maintenance therapy with the lowest dose to maintain response. Side effects, acute and chronic (flu syndrome, myalgia, fatigue, depression, neurological disorders, autoimmune diseases, etc.), are numerous and reduce compliance. Pegylated interferon may be better tolerated, because weekly administration. It begins with 0.5mcg/kg / week, doubling the amount if not get response after 12 weeks, then continue with the lowest maintenance dose.

Anagrelide is another non cytostatic cytoreductive drug. It is an oral imidazoquinazoline with anti-cyclic

AMP phosphodiesterase activity affecting maturation of megakaryocyte[and causing reduced production of platelets. Thus, ANA is the only drug with selective mechanism of action and is effective for the treatment of all MPN thrombocytosis.[6,25,27] The main indication is ET.[6,25.27, 23.25]

Anagrelide is also effective in cases resistant or intolerant to HU or IFN,[6,24] which may be associated for the platelet-lowering effect of ANA and the effect on leukocytosis, erythrocytosis or splenomegaliei of the other drugs. Is indicated in all risk groups, but in the elderly is recommended prior cardiological assessment because early treatment with ANA can give palpitations, tachycardia and hypotension. Other side effects are headache, diarrhea, fluid retention, dizziness, insomnia. They are rare and attenuate to extinction during treatment. Induction dose of 0.5 mg / day and progressively increased to a maximum of 5 mg/day. For maintenance is used the lowest dosel necessary to maintain normal blood counts.

CEMPO (European Central Myeloproliferative Organiasation) recommends five risk factors (age> 65 years, thrombotic history, presence of *JAK2* V617F, acquired or inherited thrombophilia and cardiovascular risk factors), which divides patients into two risk groups: standard and increased. Depending on that, the patients receive appropriate treatment.[28]

TREATMENT OF PRIMARY MYELOFIBROSIS

The main goal of therapy in PMF is prolongation of survival and even cure by allogeneic peripheral blood stem cell (alloSCT) in selected cases. If it is not possible to extend life, the main goal is palliative treatment of symptoms and quality of life.[6,29]
It is made in accordance with the five standard risk factors (shown in figure 4), which are evaluated according to International Prognostic Score System (IPSS) [30] for newly diagnosed patients. During disease progression, risk IPSS score is determined by dynamica IPSS adding cytogenetic evaluation and transfusion status.[31]

Figure 4: Risk factors for PMF according to IPSS

- Age> 65 years
- Hb <10 g / dl
- L> 25000/μL
- Constitutional symtoms
- Blasts > 1

Each symptom is numbered 1 point, marking the final amount four risk groups, with a specific survival (Figure 5).

Fig. 5: Risk factors and survival in PMF

No prognostic factors		Survival (months)
• INCREASED RISK	≥ 3	27
• INTERMEDIATE RISK -	12	48
• INTERMEDIATE RISK - 2	1	95
• LOW RISK	0	135

Treatment of anemia. Medication for the treatment of anemia include erythropoiesis-stimulating agents (Eritropoietins), corticosteroids, androgens and danazol and immunomodulators. Treatment is initiated at hemoglobin levels below 10 to 11 g / dl. Eritropoietins are administered at a dose of 30000U x 3/week and Darbepoetin alfa at a dose of 300 mcg / week. Response rate is 40-50%, half of pcienţi response lasting> 12 months, especially in cases where endogenous erythropoietin serum level is <125 U / L.[32.33] Prednisone is administered at a dose of 0.5 -1 mg / kg / zi.[6, 29] As can be useful anabolic Testosterone enanthate at a dose of 400-600 mg / week or Fluoximesteron 10 mg x 2/day.[34] Danazol, a semisynthetic androgen,is administered at a dose of 600 mg / day, slowly falling to the lowest effective maintenance dose.[35] As immunomodulatory are used Thalidomide 50 mg / day with prednisone 15-30 mg / day[36.37] or Lenalidomide 10 mg / day, particularly effective in cases with deletion (5) (Q31) .[38] New immunomodulatory agents such as oral Pomalidomide (a second- generation of thalidomide analogue), alone or combined with prednisone, resulted in anemia response rates of up to 36%.[39]

Splenomegaly, constitutional symtoms and hypercellularity phase are treated mainly with HU, [40,41,42] which also controls symptomatic thrombocytosis or/and leukocytosis. Interferon is preferred in young patients.[43] In cases refractory to HU treatment can be done with alternative drugs such as Cladribine[6.44] (5 mg/m2 x 5 days month, 4 to 6 cycles), oral Melphalan[6,45] (2.5 mg x 3/săpt) or busulfan[6] (2 to 6 mg / day, with careful monitoring of blood counts). In addition, splenomegaly may be treated with radiation therapy at a dose of 0.1 - 0.5 Gy in 5 to 10 sessions that can relieve symptoms but duration of response is short of 3 to 6 months and the procedure is associated with a mortality rate of> 10%.[46] Splenectomy is indicated in portal hypertension (bleeding from esophageal varices, ascites), marked splenomegaly refractory to chemotherapy, painful and severe cachexia associated transfusion-dependent anemia.[6] The procedure has a perioperative mortality of 5 to 10% and postoperative complications can reach 50% (local bleeding, abscess subfrenic, hepatomegaly quickly installed with extreme thrombocytosis thrombosis and leukocytosis with excess of blasts. Splenectomy candidate must have a

good performance status, platelet count below 400 x 10^9/L because of postoperative thrombocytosis and no signs of disseminated intravascular coagulation.[47] Extramedullary nonhepatosplenic hematopoiesis is most commonly located in the thoracic spine. Other sites are lymph nodes, lungs, pleura, small intestine, peritoneum, urogenital tract and heart. Is treated with radiotherapy at a dose of 0.1 - 0.5 Gy in 5 to 10 fractions.[6]

Allogeneic peripheral blood stem cell is indicated in patients at high and intermediate risk under 60 years.[48,49] It is the only potentially curative procedure but has a high mortality and morbidity. Treatment-related mortality at one year performed with standard-intensity conditioning alloSCT is 30% and overall survival is 50%. AlloSCT with reduced intensity conditioning has a median survival of 45% at 5 years with a similar incidence of treatment related mortality and relapse. Recent studies have shown that survival of patients eligible for transplant but did not receive TCSP Hello, namely those with high or intermediate risk, survival at 1 and 3 years ranged from 71-90% and 55-77%. Therefore candidates for transplant are those with an expected survival less than 5 years.

Treatment of blast-phase MNP. Blast-phase duration is 6 months and they are limited therapeutic options and outcomes. Palliative or experimental treatment is recommended. AlloSCT nay be considered, but results are extremely poor.[50]

For patients with JAK2 positive NMP, recent research studies ***JAK2 inhibitor treatment*** that improves constitutional signs, splenomegaly, pruritus and quality of life, especially in patients with PFM and PV and TE those with advanced disease refractory HU.[51]

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