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MYELOPROLIFERATIVE NEOPLASM (MPN)

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What is a myeloproliferative neoplasm (MPN) ?

Myeloproliferative neoplasms (MPNs) — formerly known as myeloproliferative disorders — are chronic blood cancers. They develop when a blood stem cell acquires a genetic abnormality that disrupts the regulation of blood cell production. The cause of this genetic change is not known. As a result, one or several types of blood cells proliferate excessively, from their precursors to fully mature circulating cells. These conditions are considered cancers because of this uncontrolled overproduction of blood cells, although they generally do not carry the same severity as most cancers.

We will present here the three main **Philadelphia chromosome–negative myeloproliferative neoplasms** (therefore chronic myeloid leukemia is not discussed): **polycythemia vera**, **essential thrombocythemia**, and **primary myelofibrosis**.

In **polycythemia vera**, the excessive proliferation mainly affects the red blood cell lineage. In **essential thrombocythemia**, platelet production is increased. In **primary myelofibrosis**, the proliferation may involve all three blood cell lineages (red blood cells, platelets, and white blood cells) and is accompanied by **bone marrow fibrosis** (a type of scar-like tissue that gradually replaces normal bone marrow cells).

What is the link between MPNs and liver vascular diseases?

The main short- and medium-term risk associated with MPNs is **thrombosis**, whether arterial or venous.

MPNs are the most common risk factors for **splanchnic vein thrombosis**. They are found in **30 to 50%** of patients with **Budd–Chiari syndrome (BCS)** or **portal vein thrombosis**, and in **5 to 20%** of cases of **porto-sinusoidal vascular disease**. Liver vascular disease is often the event that leads to the diagnosis of a previously unrecognized MPN.

What symptoms can one have when suffering from an MPN?

These diseases can be completely asymptomatic, and the diagnosis may therefore be considered after the incidental discovery of an abnormality on a complete blood count.

When present, symptoms are varied and not necessarily specific: fatigue, headaches, visual disturbances (phosphenes), hearing symptoms (tinnitus), itching (especially during or after a shower), erythromelalgia (burning sensations and redness of the hands or feet), abdominal discomfort, splenomegaly, pain in the spleen area, unexplained weight loss, excessive sweating (especially at night), or bone pain.

Symptoms may also be related to complications of myeloproliferative neoplasms, particularly thrombosis. Examples include leg pain suggestive of deep vein thrombosis, or digestive symptoms indicating splanchnic vein thrombosis…

How is an MPN diagnosed?

The diagnosis of a myeloproliferative neoplasm (MPN) is based on a combination of diagnostic criteria, mainly: abnormalities on the complete blood count, the presence of a mutation in the *JAK2* gene (or, less frequently, *CALR* or *MPL*), and characteristic findings on a bone marrow biopsy.

In the specific context of splanchnic vein thrombosis, abnormalities in the complete blood count are often masked by portal hypertension (making hematocrit and/or platelet counts appear "falsely" normal). In addition, the anticoagulation required to treat the thrombosis complicates the scheduling of a bone marrow biopsy, often delaying or temporarily preventing the procedure. In such situations, a diagnosis of an MPN may be established, but the specific subtype cannot always be determined immediately.

- **Diagnosis of Polycythemia Vera (PV)**

The diagnosis is based on a combination of elevated hematocrit/hemoglobin levels, the presence of a *JAK2* mutation, characteristic bone marrow features (hyperproliferation of all three cell lineages, predominantly erythroid), and a low or low-normal erythropoietin level.

In the presence of portal hypertension, hematocrit may be considered suspiciously elevated when it exceeds 42%. When hematocrit interpretation is difficult due to portal hypertension, an isotopic red cell mass measurement can be performed. This test separately measures red blood cell volume and plasma volume, allowing calculation of an individualized "target" hematocrit.

- **Diagnosis of Essential Thrombocythemia (ET)**

The diagnosis is based on the combination of thrombocytosis, the presence of a *JAK2*, *CALR*, or *MPL* mutation (found in 60–70% of ET cases), and characteristic bone marrow findings (predominant proliferation of the megakaryocytic lineage with atypical megakaryocytes).

In the context of portal hypertension, platelet counts may be considered abnormally elevated when they exceed 200–250 $\times 10^9$/L.

- **Diagnosis of Primary Myelofibrosis (PMF)**

The diagnosis is based on abnormalities on the complete blood count (particularly circulating myeloid precursors and/or blasts), splenomegaly, the presence of a *JAK2*, *CALR*, or *MPL* mutation (identified in 60–70% of PMF cases), and especially characteristic bone marrow findings (megakaryocytic proliferation with atypia, clustering of precursor cells, and reticulin or collagen fibrosis).

Interpreting splenomegaly can be challenging in patients with portal hypertension, as portal hypertension alone may significantly increase spleen size.

What are the treatments for MPNs?

Treatment Objectives

The main goal of treatment is to reduce the risk of thrombotic complications or recurrences. Management is based on three main components:

- **Antiplatelet therapy** for patients without a history of thrombosis or with a history of arterial thrombosis, or **anticoagulation** in the case of prior venous thrombosis, particularly portal vein thrombosis or Budd–Chiari syndrome.
- **Normalization of complete blood count parameters** through cytoreductive therapy in high-risk patients (age over 60 or history of thrombosis). Expert recommendations in the context of splanchnic vein thrombosis suggest the following targets: hematocrit <42% or below the personalized "target" hematocrit determined by red cell mass measurement, and platelet count <200–250 $\times 10^9$/L.
- **Management of other cardiovascular risk factors.**

At present, none of the available treatments has demonstrated a proven ability to prevent hematologic progression of MPNs, such as evolution to secondary myelofibrosis, myelodysplastic syndromes, or leukemia.

Cytoreductive treatments for polycythemia vera

Phlebotomy is the emergency treatment, allowing a rapid reduction of hematocrit. Each phlebotomy typically removes 300–400 mL of blood. It may be repeated two or three times a week initially.

Cytoreductive drug therapy is indicated in patients over 60 years of age or with a history of thrombosis. First-line treatments recommended by expert societies include **hydroxyurea** (Hydrea®, approved indication) or **pegylated interferon alfa-2a** (Pegasys®, off-label). Second-line options include either of these two agents or **ruxolitinib** (Jakavi®, approved indication).

- Hydroxyurea : An oral treatment. Besides myelosuppression (risk of anemia, thrombocytopenia, or leukopenia), main side effects include skin-related toxicity (dry skin and mucous membranes, leg ulcers, and an increased long-term risk of cutaneous carcinomas).
- Peginterferon alfa-2a : Administered as weekly subcutaneous injections. Besides myelosuppression, its main side effects include fatigue, liver test abnormalities, mood disturbances, and the induction of autoimmune or inflammatory conditions (most commonly hypothyroidism). It is the treatment of choice for younger patients because it is compatible with pregnancy planning, lacks cumulative skin toxicity, and some studies suggest it may positively influence the natural hematologic course of the disease.
- Ruxolitinib : An oral treatment. It is generally well tolerated and highly effective for symptom control in polycythemia vera (reduces fatigue, markedly improves pruritus, and decreases spleen size). Main side effects include weight gain, gastrointestinal symptoms, headaches, hypertension, infectious risk (particularly herpesvirus reactivation), and an increased long-term risk of cutaneous carcinomas. It is not recommended in patients with platelet counts <50 $\times 10^9$/L.

Cytoreductive treatments for essential thrombocythemia

For high-risk patients, first-line cytoreductive therapy includes **hydroxyurea** or **peginterferon alfa-2a**, according to expert recommendations. Second-line options include either of these agents or **anagrelide**.

- Anagrelide : An oral treatment. Main side effects include headaches, dizziness, gastrointestinal symptoms, tachycardia, and palpitations. A pre-treatment cardiologic evaluation and regular cardiac monitoring are required**.**

Cytoreductive and other specific treatments for myelofibrosis

Myelofibrosis is a heterogeneous disease, both in prognosis and clinical presentation. Treatment goals depend on these factors.

In patients with high-risk disease, the feasibility of **allogeneic hematopoietic stem cell transplantation** is a central consideration. In the setting of splanchnic vein thrombosis, hepatology assessment is essential to determine transplant eligibility.

For non-transplant candidates and for patients with low-risk disease, treatment is adapted to symptoms. **JAK2 inhibitors** are effective for general symptoms (night sweats, weight loss) and for symptomatic splenomegaly. Options include **ruxolitinib** (most widely used first-line), **fedratinib**, and **momelotinib**.

- Fedratinib : An oral treatment. It requires monitoring of vitamin B1 levels, with supplementation when needed to avoid neurological complications. Besides myelosuppression, its main side effects include gastrointestinal symptoms (improved when taken with a high-fat meal), headaches, and liver or kidney test abnormalities. It is not recommended in patients with platelet counts <50 $\times 10^9$/L.
- Momelotinib : An oral treatment. In some responding patients, it significantly improves anemia. Besides myelosuppression, main side effects include gastrointestinal symptoms, dizziness, headaches, and infectious risk (notably herpesvirus reactivation). It is not recommended in patients with platelet counts <25 $\times 10^9$/L.

What are the future treatments for MPNs?

Numerous clinical trials are ongoing in MPNs. **Rusfertide**, a treatment that modulates iron absorption and availability, is currently being studied in polycythemia vera. **Bomedemstat**, which targets megakaryocyte proliferation, is being evaluated in essential thrombocythemia and myelofibrosis. Combination therapies are also under investigation to potentially modify the natural history of MPNs, particularly in myelofibrosis. Finally, monoclonal antibodies targeting mutated **CALR** protein are in development.

Bone marrow and blood cell production