

CHRONIC MYELOPROLIFERATIVE NEOPLASMS: A COMPREHENSIVE REVIEW

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Abstract

Chronic myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell disorders characterized by the overproduction of one or more types of blood cells. These disorders are typically slow-progressing but may evolve into acute leukemia or bone marrow failure over time. This review provides an in-depth discussion of the main types of Ph-negative MPNs: polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). It covers their clinical features, genetic mutations, diagnostic criteria, treatment approaches, and prognosis.

Keywords: myeloproliferative neoplasms, polycythemia vera, essential thrombocythemia, primary myelofibrosis, JAK2, CALR, MPL, hematologic malignancy

1. Introduction

Myeloproliferative neoplasms (MPNs) are a group of hematologic malignancies that arise from a multipotent hematopoietic stem cell and are characterized by the excessive proliferation of one or more myeloid cell lines. The World Health Organization (WHO) classifies MPNs into BCR-ABL1-positive (chronic myeloid leukemia) and BCR-ABL1-negative subtypes. The latter group includes polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), which are often referred to as “classic” Ph-negative MPNs.

These conditions are driven by somatic mutations, particularly in the **JAK2**, **CALR**, and **MPL** genes, which result in dysregulated JAK-STAT signaling and uncontrolled cell proliferation.

2. Pathogenesis and Molecular Genetics

2.1 Common Mutations

- **JAK2 V617F**: Found in approximately 95% of PV cases and 50–60% of ET and PMF cases.
- **CALR (Calreticulin)**: Mutated in ~20–25% of ET and PMF patients who are JAK2-negative.
- **MPL (Thrombopoietin receptor)**: Found in ~3–5% of ET and PMF cases.
- These mutations lead to **constitutive activation** of the JAK-STAT pathway, resulting in increased cell proliferation, resistance to apoptosis, and clonal expansion.

2.2 Disease Evolution

MPNs may remain stable for years but can progress to:

- **Myelofibrosis**: Extensive bone marrow fibrosis.
- **Acute myeloid leukemia (AML)**: Blastic transformation in 5–20% of cases, often with poor prognosis.

3. Types of Chronic Myeloproliferative Neoplasms

3.1 Polycythemia Vera (PV)

Clinical Features:

- Increased red blood cell mass (absolute erythrocytosis)
- Hyperviscosity symptoms: headache, dizziness, visual disturbances
- Aquagenic pruritus
- Splenomegaly
- Thrombotic and hemorrhagic events

Diagnosis (WHO 2022 Criteria):

- Hemoglobin >16.5 g/dL (men), >16.0 g/dL (women)
- Hypercellular bone marrow with trilineage growth
- Presence of JAK2 V617F or exon 12 mutation
- Subnormal serum erythropoietin levels

Treatment:

- Phlebotomy
- Low-dose aspirin
- Cytoreductive therapy: hydroxyurea, interferon-alpha
- JAK inhibitors (e.g., ruxolitinib) for advanced cases

3.2 Essential Thrombocythemia (ET)

Clinical Features:

- Persistently elevated platelet count ($>450 \times 10^9/L$)
- Thrombosis and bleeding
- Microvascular symptoms: burning pain in hands/feet, erythromelalgia
- Often asymptomatic and diagnosed incidentally

Diagnosis:

- Sustained thrombocytosis
- Bone marrow biopsy showing increased megakaryocytes
- Exclusion of other myeloid neoplasms
- Presence of JAK2, CALR, or MPL mutations

Treatment:

- Low-risk: aspirin alone
- High-risk: hydroxyurea, interferon-alpha
- Consider anticoagulation if prior thrombotic events

3.3 Primary Myelofibrosis (PMF)**Clinical Features:**

- Bone marrow fibrosis
- Anemia, splenomegaly, constitutional symptoms (fever, night sweats, weight loss)
- Leukoerythroblastic blood smear (tear-drop cells)
- Extramedullary hematopoiesis (in spleen, liver)

Diagnosis:

- Bone marrow fibrosis grade ≥ 2
- Mutational analysis (JAK2, CALR, MPL)
- Elevated LDH, anemia, leukoerythroblastosis

Treatment:

- JAK inhibitors (ruxolitinib, fedratinib)
- Allogeneic stem cell transplantation (only curative option)
- Supportive care: transfusions, anemia management

4. Differential Diagnosis

Condition	Differentiating Features
Reactive thrombocytosis	Associated with inflammation, iron deficiency
Chronic myeloid leukemia (CML)	BCR-ABL1 fusion gene (Philadelphia chromosome)
Myelodysplastic syndromes	Dysplasia in bone marrow, cytopenias
Secondary polycythemia	High erythropoietin due to hypoxia, tumors

5. Prognosis and Risk Stratification**5.1 Risk Factors:**

- Age >60 years
- History of thrombosis

- Leukocytosis
- Type of mutation (e.g., CALR mutations associated with better prognosis in ET/PMF)

5.2 Prognostic Scoring Systems:

- **IPSS** and **DIPSS** for PMF
- **ELN risk stratification** for PV and ET

Survival varies:

- PV and ET: Median survival >15 years (with management)
- PMF: Median survival ~5–7 years (worse with high-risk mutations)

6. Future Directions and Emerging Therapies

- Development of second-generation JAK inhibitors
- Combination therapies with anti-fibrotic agents
- Targeted gene therapy and novel molecular targets (e.g., telomerase inhibitors)
- Use of next-generation sequencing (NGS) for personalized treatment strategies

7. Conclusion

Chronic myeloproliferative neoplasms are complex hematologic malignancies with varied clinical presentations and outcomes. Accurate diagnosis through clinical, morphologic, and molecular assessments is essential. While current therapies manage symptoms and reduce complications, future treatment advancements may offer curative options. Early detection and individualized care remain critical to improving patient outcomes.

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