

Chapter 10

Diagnostic Approach to Myeloid Neoplasms Myeloid Neoplasms With Hyperproliferative Activity: MPN, Myeloid–Lymphoid Neoplasms With Eosinophilia

ABSTRACT

Myeloproliferative neoplasms comprise BCR-ABL1 positive CML, Classic MPNs BCR-ABL1 negative, and a group of nonclassical MPNs. They share the common feature of hyperproliferation of one or more hemopoietic lineages, initially effective and gradually becoming ineffective with progression into fibrotic or leukemic phases. The fusion oncogene BCR-ABL1 is the genetic hallmark of CML. The pathogenesis of classic BCR-ABL1 negative MPNs is dynamic, with a complex interaction of tumor subclones with the bone marrow microenvironment and feedback drivers. The primary driver mutations of MPNs are the cytokine signaling pathway genes JAK2 and MPL and the loss-of-function CALR mutations, mainly through the JAK-STAT pathway. Nonclassical Philadelphia-negative MPNs: Chronic Neutrophilic Leukemia (CNL), Chronic Eosinophilic Leukemia (CEL), CEL-NOS, Juvenile MyeloMonocytic Leukemia (JMML), and MPN-unclassifiable (MPN-U), each has characteristic molecular pathogenesis.

INTRODUCTION

Hyperproliferative myeloid neoplasms comprise a spectrum of overlapping entities sharing features of marrow hypercellularity and one or more lineage hyperproliferation, initially effective hemopoiesis, and a tendency to progress with fibrosis, leukemic transformation, and rarely other forms of myeloid neoplasia. They include the following subtypes:

- A. Chronic Myeloid Leukemia (CML) with Philadelphia chromosome and BCR-ABL1 fusion transcript
- B. The Classical Philadelphia-negative MPNs: PV (Polycythemia Vera), ET (Essential Thrombocythemia), and PMF (Primary Myelofibrosis), with mutually exclusive somatic driver mutations of JAK2 (Janus kinase), CALR (calreticulin), and MPL (myeloproliferative leukemia virus oncogene) genes

- C. Non-classical Philadelphia-negative MPNs: Chronic Neutrophilic Leukemia (CNL) with CSF3R mutations, Chronic Eosinophilic Leukemia (CEL), CEL-NOS lacking specific cytogenetic profiles, Juvenile MyeloMonocytic Leukemia (JMML), and MPN, unclassifiable (MPN-U)

Each subtype's specific clinical-laboratory features depend on the differentiation lineage, molecular landscape, and disease stage. After a variable period of effective hemopoiesis, bone marrow failure, end-organ damage, and blast transformation ultimately commence. (*Veitia & Innan, 2022*)

The main objectives of this chapter are to emphasize the molecular landscape and pathogenesis, characteristic clinicopathologic features, standard workup, and diagnostic methods, as well as risk factors, therapeutic strategies, and follow-up of each subtype.,

Chronic Myeloid Leukemia (CML), Philadelphia Chromosome, and BCR-ABL1 Fusion Transcript Positive

CML is an uncontrolled clonal proliferation of myeloid cells driven by the BCR-ABL1 oncoprotein. Classically, the disease progresses through 3 Clinical Phases a Chronic Phase (CP) which lasts about 3 to 5 years, an Accelerated Phase (AP) of variable duration, and a Highly aggressive Blast Phase (BCP). Recently, the great therapeutic advancement achieved with tyrosine kinase inhibitors (TKI) has limited the clinical relevance of the AP and enhanced the importance of monitoring progression risk during the CP and early detection of TKI resistance.

Molecular Pathogenesis

- **BCR-ABL1 Fusion Oncogene** generates a 210 KD chimeric oncoprotein with tyrosine kinase activity deriving a clonal expansion of hematopoietic stem cells (HSC). (*Mojtahedi et al., 2021*). The BCR-ABL **fusion** is the initial oncogenic event in CML, but it alone is insufficient to generate CML-LSCs. Copy number variations, additional mutations, and genomic instability are necessary for full transformation.
- **CML-Leukemic Stem Cell (CML-LSC):** is Critical in the pathogenesis of treatment resistance, relapse, and progression through molecular pathways promoting their survival and resistance to apoptosis. Activation of various signaling pathways drives the progression of LSC-derived disease. (*Mojtahedi et al., 2021*).

The CML-LSC Shares Features with HSC, including Self-renewal, Differentiation, Quiescence, and Cell surface phenotype. In addition, it expresses Unique Markers like CD25, CD26, and interleukin-1 receptor accessory protein.

Maintenance and Immune Evasion: maintaining CML-LSCs by the sustained BCR-ABL kinase activity, and protecting its long-term persistence in a quiescent state, by the bone marrow Niche and signaling molecules (serving as a reservoir for residual disease) contribute to therapy resistance and recurrence risk.

CML-LSCs have recently evolved as potential Novel therapeutic Targets.

- **Molecular pathogenesis of CML progression:** During CML progression to the blast phase (BP), additional genetic abnormalities arise, including Co-expression of P210BCR-ABL1 and

53 more pages are available in the full version of this document, which may be purchased using the "Add to Cart" button on the publisher's webpage:

www.igi-global.com/chapter/diagnostic-approach-to-myeloid-neoplasms-myeloid-neoplasms-with-hyperproliferative-activity/350012

Related Content

Cancer Stem Cells and Advanced Novel Technologies in Oncotherapy

Shalini Sakthivel, Manjita Srivastava, Muneesh Kumar Barman, Nerethika Ravichandiran, Salonee Martins, Meenakshi Singh, Kailash Chand, Subash C. Sonkarand Prudhvilal Bhukya (2021). *Handbook of Research on Advancements in Cancer Therapeutics* (pp. 486-513).

www.irma-international.org/chapter/cancer-stem-cells-and-advanced-novel-technologies-in-oncotherapy/267054

The Dark Side of Medical Tourism?: End of Life Choice, Human Trafficking, and Organ Transplants

Malcolm Cooperand Mayumi Hieda (2017). *Oncology: Breakthroughs in Research and Practice* (pp. 203-215).

www.irma-international.org/chapter/the-dark-side-of-medical-tourism/158919

Improved Automatic Anatomic Location Identification Approach and CBR-Based Treatment Management System for Pediatric Foreign Body Aspiration

Vasumathy M.and Mythili Thirugnanam (2022). *Research Anthology on Pediatric and Adolescent Medicine* (pp. 119-133).

www.irma-international.org/chapter/improved-automatic-anatomic-location-identification-approach-and-cbr-based-treatment-management-system-for-pediatric-foreign-body-aspiration/298206

Intellectual Disability (ID): An Overview from History, Terminology, and Classification to Recent Trends

Rejani Thudalikunnil Gopalan (2020). *Developmental Challenges and Societal Issues for Individuals With Intellectual Disabilities* (pp. 1-12).

www.irma-international.org/chapter/intellectual-disability-id/236978

Self-Perceived Health Status

Maria Otília Zangão (2020). *Handbook of Research on Health Systems and Organizations for an Aging Society* (pp. 1-11).

www.irma-international.org/chapter/self-perceived-health-status/238266