Prevention, diagnosis and management of myeloproliferative neoplasms: an introduction to a review series

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Introduction

The classical myeloproliferative neoplasms (MPN), including polycythemia vera, essential thrombocythemia and myelofibrosis, lead to substantial morbidity and reduce patients' survival, predominantly due to the effects of high blood counts (thrombosis, splenomegaly, inflammatory symptoms) or through progression to advanced disease (bone marrow failure or acute myeloid leukemia [AML]). Recent research has identified fascinating new insights regarding the origin of these blood cancers, commencing with disease predisposition, to the acquisition of mutations in blood stem cells and clonal progression leading to advanced disease. These biological insights have already helped to inform treatment approaches focused on eradicating stem cell populations with the eventual goal of preventing leukemic transformation and long-term mortality. The review series on MPN published in this issue of *Haematologica*, authored by experts in their respective fields, is not designed to be a definitive review of all aspects of MPN biology and treatment. Rather, we have selected a few key topics of particular interest to the field that have been informed by recent advances in basic or clinical research (Figure 1): (i) the evolution of MPN from normal blood stem cells: (ii) clinical and laboratory approaches to target and eradicate early disease-initiating stem cells; (iii) the pathogenesis and management of patients with molecularly defined high-risk MPN, and (iv) strategies to prevent or treat the devastating clinical consequence of AML arising from antecedent MPN, also known as blast-phase MPN.

As a collection, the insights from these papers inform and enlighten each other; for example, how do acquired gene mutations in high-risk genes impact the response of stem cell populations to therapy, and how can pre-MPN clonal hematopoiesis offer a target to prevent the progression to overt disease? We hope researchers and clinicians find these papers informative, thought-provoking and inspiring to help address some of the ongoing challenges in our field.

When a patient first receives the diagnosis of blood cancer, the question invariably turns to "why me"? Emerging research detailed in the first review paper, by Hormoz, Sankaran and Mullally, illuminates some of the mechanisms by which MPN arise from normal blood stem cells,[1] findings that have relevance to all the topics addressed in this issue. The first advance relates to an increased understanding of clonal hematopoiesis, sometimes called age-related clonal hematopoiesis because it becomes more common with age.[2] However, this term is too simplistic because the onset of clonal hematopoiesis is different for each patient and appears to depend on the specific genetic mutation that is found within the clonal hematopoietic cell. The relevance of this finding to MPN was explored through a fascinating set of lineage tracing studies evaluating the clonal evolution of MPN cells, and using computational methods to determine that some of these clonal mutations arose in early life, even during the embryonic period in some cases.[3,4] Through selective pressure of cell proliferation, inflammation, response to chemotherapy and even aging, these rare clones can expand and eventually lead to a diagnosis with one of the clinical phenotypes of MPN. Interestingly, there are many more patients with clonal hematopoiesis than with MPN, suggesting that extrinsic factors play a large role in the development of disease, and offering the tantalising prospect of early intervention to prevent disease evolution. Understanding the interactions between genes, specific mutations within each gene, extrinsic selective pressure and genetic cooperativity is a critical and likely impactful area of ongoing research. We should remain mindful that there are still no effective strategies to prevent the development of symptomatic myeloma from monoclonal gammopathy of undetermined significance, an analogous, although distinct form of lymphoid clonal proliferation.[5]

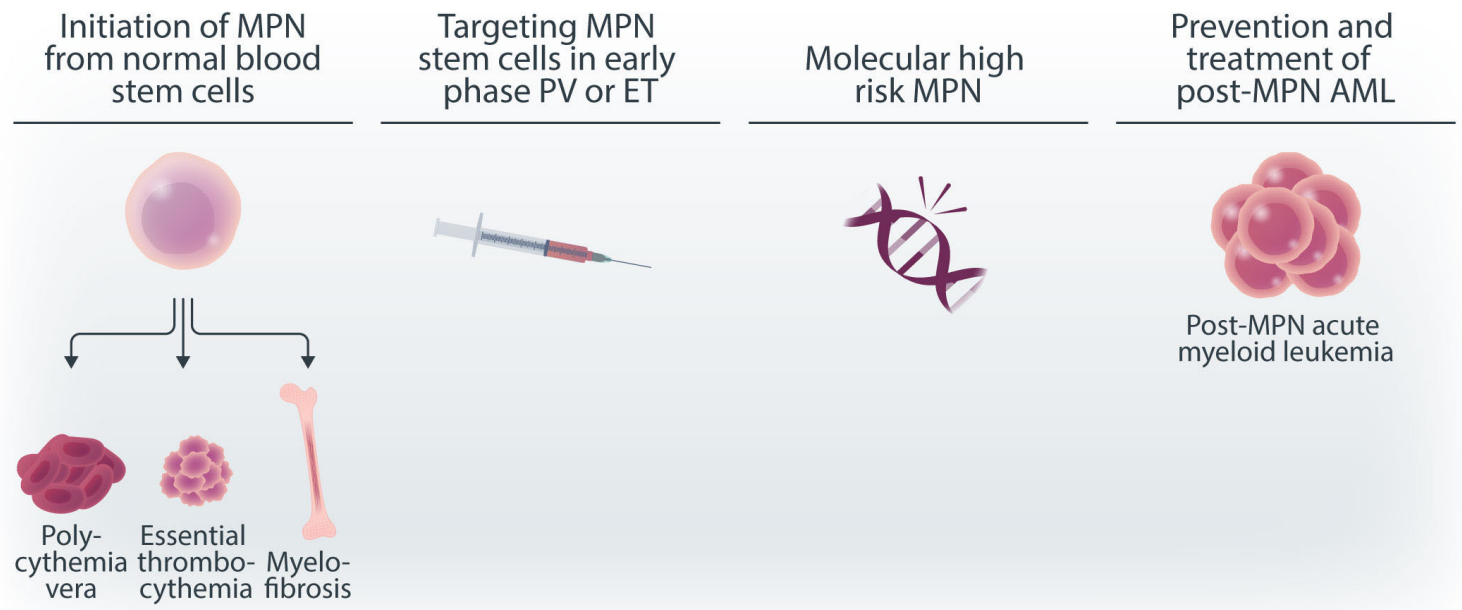

Figure 1. Current challenges in the field of myeloproliferative neoplasms. The series of review articles1,6,12,16 in this issue of Haematologica describes some current challenges within the field of myeloproliferative neoplasms (MPN). Specifically, these reviews examine the formation of MPN from normal blood stem cells, targeting stem cells using interferon, molecular definitions of high-risk MPN and the prevention and management of post-MPN acute myeloid leukemia. PV:polycythemia vera; ET: essential thrombocythemia; AML: acute myeloid leukemia.

Perhaps the most promising approach to eradicating MPN is found in the unique molecular responses seen with long-acting interferon-α therapy. The second review in the series expands on our knowledge of MPN stem cell biology to understand the mechanisms by which interferon-α can target and deplete long-term MPN disease-initiating stem cells.[6] This effect on stem cell populations is a major part of the clinical and molecular responses seen[7] and distinguishes interferon therapy from other strategies such as hydroxycarbamide or JAK inhibitors.[8] MPN are fundamentally driven by activating mutations in JAK-STAT tyrosine kinase signaling pathways that occur in long-term hematopoietic stem cells.[9,10] Importantly, additional mutations in epigenetic pathways, splicing factors or the TP53 pathway, affect both disease evolution and response to treatments, including interferon.[11] The review by Pasquier *et al.* provides a beautiful overview of this genetic complexity in the stages of MPN and links the acquisition and selection of mutations by the inflammatory MPN microenvironment. Again, questions are raised that challenge the field for future research, including whether clonal hematopoiesis is an invariable precursor of MPN and, if so, whether interferon represents the most logical and potentially effective approach to trial in these patients. The corollary of this question relates to understanding why the overt progression to MPN is found in only a small minority of patients with clonal hematopoiesis, and perhaps, if we answer this question, it might unlock the key to preventing disease initiation. Finally, does treatment of MPN with interferon-α prevent the progression of MPN to more advanced disease such as myelofibrosis or post-MPN AML, and how do the genetic complexities influence this progression?

High-molecular risk MPN is an emerging concept that raises a number of important clinical considerations, and the third review paper provides a comprehensive review of this.[12] Traditionally, high risk in polycythemia vera or essential thrombocythemia has been classified clinically, based on the propensity of patients to suffer thrombotic complications such as stroke or venous thromboembolism. Clinical factors, such as age and MPN subtype, also remain key predictors for risk of transformation. However, the availability of next-generation sequencing has allowed genetic assessment to become standard of care for patients with MPN, such as the incorporation of high-risk molecular lesions (*ASXL1*, *TP53*, *IDH1/2* and *EZH2*) in the MIPSS 70+ prognostic scoring system for patients with myelofibrosis.[13] Therefore, patients who appear clinically at low risk can be identified as more likely to undergo AML transformation at an earlier stage. Continued improvements in prognostication accuracy are important as it appears likely that intervention at the pre-leukemic stage will be necessary to reduce the long-term risk of AML. Some preliminary evidence comes from the DAHLIAH[11] and MAGIC-PV studies,[14] which have examined molecular responses after long-term treatment with pegylated interferon, or ruxolitinib, respectively. Here, it was observed that molecularly high-risk individuals may also have selection for these high-risk clones during treatment, identifying molecularly high risk as an independent risk factor for treatment failure. Conversely, those patients who had deep molecular responses did not develop advanced disease such as post-polycythemia vera myelofibrosis. The implication of this finding is that treatments that lead to deep molecular responses need to be identified,[15] because they could help to prevent the devastating late outcomes of secondary myelofibrosis and even post-MPN AML.

The final review in the series focuses on post-MPN AML, or blast-phase MPN as it is frequently known.[16] The devastat-

ing outcomes of patients with blast-phase MPN, regardless of therapy choice, are summarized comprehensively in the review and make for sobering reading. In the absence of established effective interventions, new therapeutic approaches through clinical trials are recommended. Progression to AML is associated with clonal evolution, either through linear or branched evolution, and is predominantly driven by the acquisition of disease-defining secondary mutations. Early identification of these lesions may well offer clinical opportunity to pursue preventative strategies to monitor, and pre-emptively intervene or target patients exhibiting signs of early clonal evolution. Here, these concepts of high molecular risk and post-MPN AML overlap. It will, therefore, become even more important to define the disease-modifying factors (inflammation, genetic instability, selection by chemotherapeutic agents) in order to identify the correct group of patients in whom intervention could be effective. In support of this approach, the clinical outcomes appear to be superior in patients with accelerated-phase MPN, rather than overt blast-phase MPN.

As we reflect on the work contained within these reviews, there are a number of commonalities and themes that should help to focus the field for the future. Our current prognostic systems are very useful at the population level, but do not predict the outcomes for individual patients. Future work should help to develop and refine algorithms to predict which patients are likely to progress, based on our understanding of disease state, clinical factors, genetic complexity and extrinsic selective pressures. A collaborative approach to clinical trials, including molecular endpoints and data-sharing, will help to accelerate strategies that offer long-term survival and avoidance of secondary myelofibrosis and AML. It appears likely that combination treatments will be required to target and eliminate high-risk disease-initiating clones, and therefore it is important that promising agents are not discarded prematurely. This review series provides fertile ground to stimulate further discussion and research that can move us closer to finding a cure for patients with MPN.

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Contributions

YY and SWL co-wrote this Introduction.

References

1. Hormoz S, Sankaran VG, Mullally A. Evolution of myeloproliferative neoplasms from normal blood stem cells. Haematologica. 2025;110(4):840-849.
2. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371(26):2488-2498.
3. Van Egeren D, Escabi J, Nguyen M, et al. Reconstructing the lineage histories and differentiation trajectories of individual cancer cells in myeloproliferative neoplasms. Cell Stem Cell. 2021;28(3):514-523.e519.
4. Sousos N, Ní Leathlobhair M, Simoglou Karali C, et al. In utero origin of myelofibrosis presenting in adult monozygotic twins. Nat Med. 2022;28(6):1207-1211.
5. Rögnvaldsson S, Love TJ, Thorsteinsdottir S, et al. Iceland screens, treats, or prevents multiple myeloma (iStopMM): a population-based screening study for monoclonal gammopathy of undetermined significance and randomized controlled trial of follow-up strategies. Blood Cancer J. 2021;11(5):94.
6. Pasquier F, Pegliasco J, Martin JE, Marti S, Plo I. New approaches to standard of care in early-phase myeloproliferative neoplasms: can interferon-α alter the natural history of the disease? Haematologica. 2025;110(4):850-862.
7. Gisslinger H, Klade C, Georgiev P, et al. Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. Lancet Haematol. 2020;7(3):e196-e208.
8. Austin RJ, Straube J, Bruedigam C, et al. Distinct effects of ruxolitinib and interferon-alpha on murine JAK2V617F myeloproliferative neoplasm hematopoietic stem cell populations. Leukemia. 2020;34(4):1075-1089.
9. Grinfeld J, Nangalia J, Baxter EJ, et al. Classification and personalized prognosis in myeloproliferative neoplasms. N Engl J Med. 2018;379(15):1416-1430.
10. Mullally A, Lane SW, Ball B, et al. Physiological Jak2V617F expression causes a lethal myeloproliferative neoplasm with differential effects on hematopoietic stem and progenitor cells. Cancer Cell. 2010;17(6):584-596.
11. Knudsen TA, Skov V, Stevenson K, et al. Genomic profiling of a randomized trial of interferon-α vs hydroxyurea in MPN reveals mutation-specific responses. Blood Adv. 2022;6(7):2107-2119.
12. Ling V, Heidel FH, Bywater MJ. Pathogenesis and management of high molecular risk myeloproliferative neoplasms. Haematologica. 2025;110(4):863-876.
13. Tefferi A, Guglielmelli P, Lasho TL, et al. MIPSS70+ version 2.0: Mutation and karyotype-enhanced International Prognostic Scoring System for primary myelofibrosis. J Clin Oncol. 2018;36(17):1769-1770.
14. Harrison CN, Nangalia J, Boucher R, et al. Ruxolitinib versus best available therapy for polycythemia vera intolerant or resistant to hydroxycarbamide in a randomized trial. J Clin Oncol. 2023;41(19):3534-3544.
15. Ross DM, Lane SW, Harrison CN. Identifying disease-modifying potential in myelofibrosis clinical trials. Blood. 2024;144(16):1679-1688.
16. Patel AA, Rampal RK. Prevention and treatment of transformation of myeloproliferative neoplasms to acute myeloid leukemia. Haematologica. 2025;110(4):829-839.