Introduction to the Review Series on Myelodysplasia

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The myelodysplastic syndromes (MDS) are a heterogenous group of clonal myeloid neoplasms originating in hematopoietic stem cells. They are characterized by ineffective hematopoiesis resulting in dysplasia in hematopoietic cells, and are associated with peripheral blood cytopenias, especially anemia, and a propensity to leukemic transformation.[1-4] The incidence of MDS increases with age and, in the general population, is approximately 5 cases per 100,000 people per year. The median age of onset is above the age of 70 years.[1-5] Patients with MDS are classified using one of several scoring systems.[6-9] Most patients are assigned to the lower-risk or higher-risk groups.

The recent revolution in malignant hematology has not skipped the field of MDS. Basic and clinical research over the last couple of decades has shed light on various aspects of these disorders. New genetic, digital and other tools have allowed a better understanding of the biology, leading to novel diagnostic and, most importantly, therapeutic approaches. In this issue of *Haematologica*, a series of major reviews summarizes the known information as well as the new developments.[10-14]

About three decades ago, it was hoped to find "the single MDS mutation". However, life is more complex. Nevertheless, a lot has been gained since. We learnt to detect dozens of somatic and germline myeloid mutations.[15,16] Almost every MDS patient has at least one mutation, many of which, although not specific, can be recognized as typical.[4] The gene functions and interactions are becoming clear. Some mutation-based (*SF3B1*, *TP53*) disease entities have recently been defined.[7-9] Finally, mutations have been introduced into the classifications and some of them serve as therapeutic targets. These exciting genetic developments are elegantly reported by Mario Cazzola and Luca Malcovati.[10]

We are becoming increasingly aware of the complexity of the pathogenesis of MDS. We know today that genetic mutations are common with normal/healthy aging,[17] resulting in clonal hematopoiesis, which could potentially lead to myeloid neoplasms, including MDS.[18] Clonal hematopoiesis in MDS has long been associated with systemic inflammatory conditions and disordered inflammatory signalling, and the term "inflammaging" has been coined to describe this phenomenon.[19] The inter-relationships between clonal hematopoiesis, aging and inflammation in the pathogenesis of MDS are reviewed by Matthew Villaume and Michael Savona.[11]

Since MDS has been recognized as a separate entity,[20] its diagnosis has been based on suspected clinical and laboratory features, exclusion of other entities, but mainly bone marrow morphology and blast count.[21-23] Flow cytometry and genetics have served as additional tools. The current "standard" diagnostic approach when MDS is suspected is fully reviewed by Howard Oster, Arjan van de Loosdrecht and Moshe Mittelman. Novel information is provided suggesting that modern tools such as genetic and digital techniques, and using peripheral blood instead of bone marrow, might shift the paradigm towards more accurate and less invasive approaches.[13]

The management of MDS is based on traditional regimens together with newly developed strategies.[21-23] For patients with lower-risk MDS and anemia, red blood cell transfusions with iron chelation and erythropoiesis-stimulating agents have been with us for three decades. Lenalidomide is effective in MDS-del(5q),[24] but also in non-del(5q).[25] Novel agents have recently been approved, such as luspatercept,[26] and imetelstat.[27] Others, such as roxadustat,[28] Ker 050 and AG-946 are still under investigation, raising hopes for the future. Thrombomimetics can address thrombocytopenia,[29] although their development has been suspended due to safety concerns, hopefully temporarily.[30] This is all reviewed by Almuth Maria Anni Merz and Uwe Platzbecker.[13]

Patients with higher-risk MDS can be treated with standard therapy for acute myeloid leukemia, as well as supportive treatment.[21-23] For more than a decade, hypomethylating agents have formed the basis of frontline treatment.[31] Attempts to surpass the barrier of response rate of about 50%, lasting for about 2 years, are still ongoing and are reviewed by Nicolaus Kröger, who summarizes the state of the art on hematopoietic cell transplantation in MDS which, to date, is still the only curable strategy.[14]

The entire review series on MDS provides the readers of *Haematologica* a comprehensive educational summary of

the current knowledge in the field, as well as information on novel, cutting-edge and future directions for interested specialists.

Disclosures

No conflicts of interest to disclose.

References

1. Mittelman M. The myelodysplastic syndromes--1990. Isr J Med Sci. 1990;26(8):468-478.
2. Tefferi A, Vardiman JW. Myelodysplastic syndromes. N Engl J Med. 2009;361(19):1872-1885.
3. Malcovati L, Hellstrom-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood. 2013;122(17):2943-2964.
4. Cazzola M. Myelodysplastic Syndromes. N Engl J Med. 2020;383(14):1358-1374.
5. de Swart L, Smith A, Johnston TW, et al. Validation of the Revised International Prognostic Scoring System (IPSS-R) in patients with lower-risk myelodysplastic syndromes: a report from the prospective European LeukaemiaNet MDS (EUMDS) registry. Br J Haematol. 2015;170(3):372-383.
6. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System for myelodysplastic syndromes. Blood. 2012;120(12):2454-2465.
7. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228.
8. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703-1719.
9. Bernard E, Tuechler H, Greenberg PL, et al. Molecular International Prognostic Scoring System for myelodysplastic syndromes. NEJM Evid. 2022;1(7):EVIDoa2200008.
10. Cazzola M, Malcovati L. Genome sequencing in the management of myelodysplastic syndromes and related disorders. Haematologica 2025;110(2):319-329.
11. Villaume MT, Savona MR. Pathogenesis and inflammaging in myelodysplastic syndromes. Haematologica 2025;110(2):283-299.
12. Oster H, van de Loosdrecht AA, Mittelman M. Diagnosis of myelodysplastic syndromes: the classic and the novel. Haematologica 2025;110(2):300-311.
13. Merz AMA, Platzbecker U. Treatment of lower-risk myelodysplastic syndromes. Haematologica 2025;110(2):330-338.
14. Kröger N. Treatment of high-risk myelodysplastic syndromes. Haematologica 2025;110(2):339-349.
15. Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med. 2011;364(26):2496-2506.
16. Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia. 2014;28(2):241-247.
17. 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.
18. Steensma DP, Bejar R, Jaiswal S, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood. 2015;126(1):9-16.
19. Weeks LD, Marinac CR, Redd R, et al. Age-related diseases of inflammation in myelodysplastic syndrome and chronic myelomonocytic leukemia. Blood. 2022;139(8):1246-1250.
20. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol. 1982;51(2):189-199.
21. Garcia-Manero G, Chien KS, Montalban-Bravo G. Myelodysplastic syndromes: 2021 update on diagnosis, risk stratification and management. Am J Hematol. 2020;95(11):1399-1420.
22. Sekeres MA, Taylor J. Diagnosis and treatment of myelodysplastic syndromes: a review. JAMA. 2022;328(9):872-880.
23. Hellström-Lindberg E, Tobiasson M, Greenberg P. Myelodysplastic syndromes: moving towards personalized management. Haematologica. 2020;105(7):1765-1779.
24. Fenaux P, Giagounidis A, Selleslag D, et al. MDS-004 Lenalidomide del5q Study Group: a randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with low-/intermediate-1-risk myelodysplastic syndromes with del 5q. Blood. 2011;118(14):3765-3776.
25. Santini V, Almeida A, Giagounidis A, et al. Randomized phase III study of lenalidomide versus placebo in RBC transfusion-dependent patients with lower-risk non-del(5q) myelodysplastic syndromes and ineligible for or refractory to erythropoiesis-stimulating agents. J Clin Oncol. 2016;34(25):2988-2996.
26. Platzbecker U, Della Porta MG, Santini V, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. Lancet. 2023;402(10399):373-385.
27. Platzbecker U, Santini V, Fenaux P, et al. Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2024;403(10423):249-260.
28. Mittelman M, Henry DH, Glaspy JA, et al. Roxadustat versus placebo for patients with lower-risk myelodysplastic syndrome: MATTERHORN phase 3, double-blind, randomized controlled trial. Am J Hematol. 2024;99(9):1778-1789.
29. Oliva EN, Alati C, Santini V, et al. Eltrombopag versus placebo for low-risk myelodysplastic syndromes with thrombocytopenia (EQoL-MDS): phase 1 results of a single-blind, randomised, controlled, phase 2 superiority trial. Lancet Haematol. 2017;4(3):e127-e136.
30. Mittelman M. Good news for patients with myelodysplastic syndromes and thrombocytopenia. Lancet Haematol. 2018;5(3):e100-e101.
31. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009;10(3):223-232.