EDITORIAL

Understanding infectious complications in patients with lower-risk myelodysplastic syndromes: a step towards improving survival

Guillermo Garcia-Manero

Department of Leukemia, Section of MDS, University of Texas, MD Anderson Cancer Center, Houston, TX, USA

Correspondence: G. Garcia-Manero
ggarciam@mdanderson.org

Received: May 27, 2025.
Accepted: June 10, 2025.
Early view: June 26, 2025.

https://doi.org/10.3324/haematol.2025.287847

The myelodysplastic syndromes (MDS), now neoplasms, are a complex and heterogeneous group of myeloid malignancies characterized by peripheral blood cytopenias and increased risk of transformation to acute myelogenous leukemia (AML).[1] The most frequent cause of death in patients with MDS, particularly those with lower-risk disease, is an infection followed by a cardiovascular complication.[2] In this issue of *Haematologica*, Houtman *et al*. provide a detailed analysis of the characteristics associated with infectious complications in a large cohort of patients with lower-risk MDS.[3] To do so, the authors analyzed data from a large European database, the EUMDS Registry, which contains information on patients from 146 centers in 17 countries. Because of the chronology of different risk scoring systems, the authors used the International Prognostic Scoring System (IPSS)[4] to define lower risk (low and intermediate-1) and restricted time to infection to 1 year after the initial MDS diagnosis. The authors analyzed the data from 2,552 patients evenly distributed between low- and intermediate-1-risk groups. Of these patients, 193 (0.07%) had 220 infectious episodes. Of interest, 43% of those episodes occurred during the first 100 days after the initial diagnosis. Infection was associated with a 30% risk of death and constituted 25% of all causes of death in this group of patients. Subsequently, the authors analyzed factors associated with risk of infection and death. Of interest, anemia, thrombocytopenia, neutropenia, poor-risk cytogenetics and need for transfusions were associated with infection. In addition, for death, age was a significant characteristic but, interestingly, neutropenia was not.

What are the implications of these data? The goal of therapy in MDS should be an improvement in survival. Traditionally, patients with MDS have been divided into those with lower-risk disease and those with higher-risk disease. For a long time, the goals of therapy have been considered different for the patients with lower-risk disease *versus* those with higher-risk features. For those with lower risk, the recommendation has been to provide supportive care measures to mitigate the complications of the cytopenia: mainly transfusions when needed and erythroid growth factors. But perhaps there is something beyond just correcting a number in a complete blood cell count. In their article, Houtman *et al*. establish an association between the risk of infection and characteristics of the disease (cytopenia, transfusions, cytogenetics) but infection-related death was not clearly associated with neutropenia, suggesting a more complex relationship with disease features. Understanding this relationship could lead to interventions that could result in improvement in survival; after all, I am sure that patients and their families with lower-risk MDS would also like to live longer and better. The manuscript[3] has several limitations: it lacks details on the types of infections. Importantly, the study also lacks details of the therapy administered and molecular characteristics (i.e., IPSS-M[5]) of the disease. Notwithstanding these limitations, the data are of great interest, and trigger the question: is the cause of infection-associated death in lower-risk MDS just related to a neutrophil count threshold or is it the consequence of a more complex biology? I think the results suggest the latter. To further explore this issue, perhaps we can learn from recent studies in clonal hematopoiesis indicating a close interplay between clonal hematopoiesis of indeterminate potential/clonal cytopenia of undetermined significance and comorbidities.[6] The association between comorbidities and specific mutations is not stochastic but appears to be mutation-specific, at least in MDS.[7] In view of the fact that in MDS most stem cells are mutated and therefore almost no “normal” hematopoiesis exists[8] and the implication therefore that molecular remissions

may not be possible today, strategies to improve survival by dampening MDS-related complications may result in improved survival.

MDS is characterized by significant alterations in innate immune signaling.[9] Interventions targeting these pathways (Toll-like receptor inhibitors, IRAK inhibitors, cytokine inhibitors, inflammasome inhibitors) together with approaches to improve cytopenias (erythroid stimulation, neutrophil production, platelet biogenesis) may result in improvement in survival. Indeed, a recent analysis from the COMMANDS trial[10] indicates that luspatercept, an erythroid-maturing agent designed to reduced transfusions, is associated with an improvement in survival (Garcia-Manero, ASCO 2025). Luspatercept is a transforming growth factor-β modulator that affects innate immunity signaling and can result in bi- and tri-linear hematologic responses.[11] Of course, these interventions need to be understood in the full context of the molecular characteristics of the disease and the type of infectious complications.

The future implications of the study by Houtman *et al.*[3] are that combination approaches, as proposed above, could be associated with improvement in survival in lower-risk MDS. A final corollary will be that, in the future, clinical trials in lower-risk MDS should measure the impact of the intervention tested on the survival of the patients.

Disclosures

GG-M has acted as a consultant for and received research support from Taiho, Genentech, AbbVie, BMS, Curis, Chordia, Novartis, Rigel, Ascentage and Servier.

References

1. Garcia-Manero G. Myelodysplastic syndromes: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023;98(8):1307-1325.
2. Dayyani F, Conley AP, Strom SS, et al. Cause of death in patients with lower-risk myelodysplastic syndrome. Cancer. 2010;116(9):2174-2179.
3. Houtman B, Taylor A, van Marrewijk C, et al. Infections in lower-risk mydelodysplastic syndromes - prevalence and risk factors: a report from the European MDS registry. Haematologica. 2025;110(10):2367-2375.
4. Greenberg P, Cox C, LeBeau MM, et al. International Scoring System for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89(6):2079-2088.
5. Bernard E, Tuechler H, Greenberg PL, et al. Molecular International Prognostic Scoring System for myelodysplastic syndromes. NEJM Evid. 2022;1(7):EVIDoa2200008.
6. Jaiswal S, Ebert BL. Clonal hematopoiesis in human aging and disease. Science. 2019;366(6465):eaan4673.
7. Naqvi K, Sasaki K, Montalban-Bravo G, et al. Clonal hematopoiesis of indeterminate potential-associated mutations and risk of comorbidities in patients with myelodysplastic syndrome. Cancer. 2019;125(13):2233-2241.
8. Ganan-Gomez I, Yang H, Ma F, et al. Stem cell architecture drives myelodysplastic syndrome progression and predicts response to venetoclax-based therapy. Nat Med. 2022;28(3):557-567.
9. Ganan-Gomez I, Wei Y, Starczynowski DT, et al. Deregulation of innate immune and inflammatory signaling in myelodysplastic syndromes. Leukemia. 2015;29(7):1458-1469.
10. 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.
11. Garcia-Manero G, Mufti GJ, Fenaux P, et al. Neutrophil and platelet increases with luspatercept in lower-risk MDS: secondary endpoints from the MEDALIST trial. Blood. 2022;139(4):624-629.