blood® commentary

MYELOID NEOPLASIA

Comment on Malcovati et al, page 157

SF3B1: the lord of the rings in MDS

Laura Palomo and Francesc Solé | Josep Carreras Leukaemia Research Institute

In this issue of *Blood*, Malcovati et al (for the International Working Group for the Prognosis of Myelodysplastic Syndromes [IWG-PM]) propose a new subtype of myelodysplastic syndrome (MDS) characterized by somatic mutations in *SF3B1*.[1]

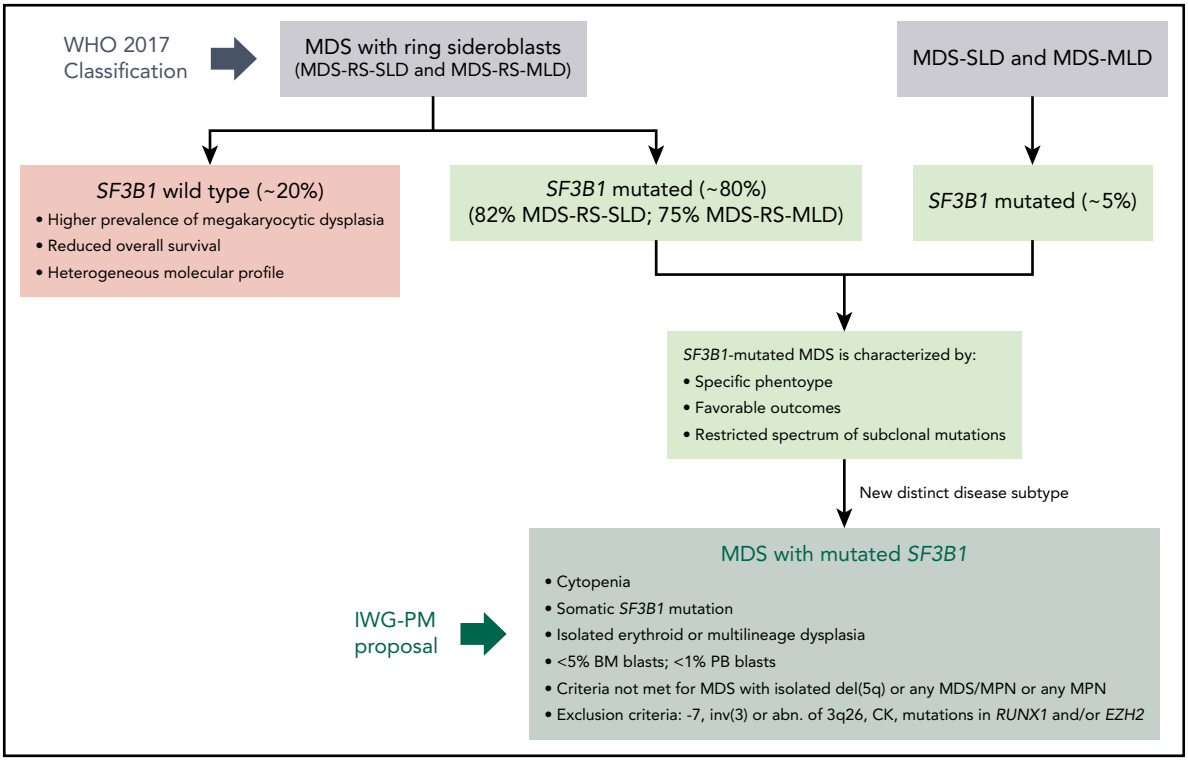
MDSs are a group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, myelodysplasia, peripheral cytopenias, and potential for clonal evolution. Recurrent gene mutations are present in ≥90% of MDS cases.[2] These mutations affect pathophysiological features of MDS and play a role in their clinical heterogeneity. Mutations also contribute to more precise classification and risk stratification of the patients.[3] However, the genetic basis of MDS is complex. The spectrum of mutations is heterogeneous, the driver genes are not specific for MDS, and some of these mutations can be present in individuals with clonal hematopoiesis of indeterminate potential (CHIP).[4] Therefore, the diagnosis of MDS remains heavily reliant on morphology. Although there is no doubt that morphology will continue to represent a fundamental step in the diagnostic process, closer integrartion of morphology and molecular profiles are needed in many hematological malignancies.

In the revised 2017 World Health Organization (WHO) Classification, MDS with isolated del(5q) remains the only MDS subtype defined by a genetic abnormality, although *SF3B1* mutation has been included as a diagnostic criterion in MDS with ring sideroblasts (MDS-RS).[5] More specifically, a diagnosis of MDS-RS (with single- or multilineage dysplasia) can be made if RS comprise ≥15% of nucleated erythroid cells or if ≥5% RS plus an *SF3B1* mutation are present. Mutations in the splicing factor *SF3B1* occur in 25% of all MDS cases but affect >80% of MDS-RS.[6,7] In addition, they are independent predictors of favorable outcomes in MDS.[8] This is a clear example of a genotype-phenotype relationship and supports the inclusion of *SF3B1* mutation as a diagnostic criterion in MDS-RS. Patients with MDS-RS are characterized by ineffective erythropoiesis, erythroid dysplasia, low blast percentage, and generally favorable outcomes. However, the inclusion of *SF3B1* mutations in the WHO classification raised new questions: Is the phenotype and outcome of these patients really associated with the presence of RS or with the presence of *SF3B1* mutations? How have the 15% and 5% cutoffs been defined? Do these cutoffs discriminate patients with unique features? For example, in patients with RS, *SF3B1* mutations identify 2 groups of patients with clearly different outcomes, but the presence of >15% RS does not have an impact on *SF3B1*-mutated MDS.[9]

In this report, Malcovati et al, writing for the IWG-PM, provide evidence supporting the recognition of *SF3B1*-mutant MDS as a distinct diagnostic entity and further validate this proposal by interrogating the IWG-PM data set.[1] This data set includes 3479 patients with known *SF3B1* mutation status and represents the largest MDS data set with genetic data reported to date. Thus, prior reports of the correlation of *SF3B1* mutations with clinical phenotype in MDS are strengthened by the validation in this large data set.

As reviewed by the authors, several lines of evidence support recognition of somatic *SF3B1* mutations, and not the presence of RS, as a disease-defining feature (see figure). First, *SF3B1* mutations often represent a founding genetic lesion, with several lines of evidence consistent with this mutation being a driver event. Second, *SF3B1* is a major determinant of disease phenotype. Specifically, (1) *SF3B1*-mutant MDS has ineffective erythropoiesis with erythroid dysplasia and RS; (2) in *SF3B1*-mutant MDS with multilineage dysplasia, very mild dysplasia in granulocytic or megakaryocytic lineages is present, which lacks clinical significance; (3) the presence of excess of blasts significantly affects survival; (4) there is a female prevalence; and (5) there is no difference in survival in *SF3B1*-mutant MDS depending on the RS percentage or the number of dysplastic lineages. Third, *SF3B1* mutations have an independent prognostic value on survival and risk of progression to acute myeloid leukemia. *SF3B1* mutations predict a favorable outcome in very low and low Revised International Prognostic Scoring System categories and in sideroblastic categories, but they have no impact in MDS with excess blasts. In addition, the authors explore the prognostic value of co-occurring cytogenetic abnormalities and somatic mutations in *SF3B1*-mutant MDS. Fourth, *SF3B1* mutations may predict response to specific agents, such as luspatercept.

Considering all the above, Malcovati et al propose the following classification criteria for MDS with mutated *SF3B1* (see figure): (1) cytopenia defined by standard hematologic values; (2) somatic *SF3B1* mutation; (3) isolated erythroid or multilineage dysplasia; (4) bone marrow blasts <5% and peripheral blood blasts <1%; and (5) WHO criteria for MDS with isolated



Definition of a distinct MDS disease subtype characterized by somatic mutations in *SF3B1*. MDS patients with somatic *SF3B1* mutations share a common phenotype, with favorable outcomes and a restricted spectrum of subclonal mutations, independently of their WHO 2017 category. Malcovati et al propose a new MDS subtype characterized by *SF3B1* mutations, following the classification criteria depicted in the figure. Abn, abnormalities; BM, bone marrow; CK, complex karyotype (≥3 chromosomal alterations); MLD, multilineage dysplasia; MPN, myeloproliferative neoplasms; PB, peripheral blood; SLD, single-lineage dysplasia.

del(5q), myelodysplastic/myeloproliferative neoplasm with RS and thrombocytosis or other myelodysplastic/myeloproliferative neoplasms, and primary myelofibrosis or other myeloproliferative neoplasms are not met. The following genetic lesions represent exclusion criteria: monosomy 7, inv(3) or abnormalities of chromosome 3q26, complex karyotype (≥3 chromosomal alterations), and co-occurring mutations in *RUNX1* and/or *EZH2*.

The presence of an *SF3B1* mutation on its own is not sufficient to diagnose MDS, since *SF3B1* mutations have been reported in other hematological and nonhematological cancers[7] and in individuals with CHIP.[4] In patients with unexplained cytopenia, *SF3B1* mutations are highly predictive of developing MDS-RS,[10] although prospective studies are needed to validate these observations and establish the predictive value of *SF3B1*-mutated clones in this context.

Patients with RS but no *SF3B1* mutation constitute a heterogeneous group of patients with less favorable outcomes. If *SF3B1*-mutant MDS is recognized as a distinct entity, additional studies will be needed to define how to best reclassify these patients. The presence of specific genetic lesions might be useful to assess their prognosis.

Our understanding of hematological malignancies is inevitably associated with the progress of molecular genetics. Therefore, the inclusion of molecular data has the potential to significantly improve diagnostic and prognostic assessment. The *SF3B1* paradigm is a clear example of that, as captured in this Special Report by Malcovati et al. However, although the evidence supports the distinction of *SF3B1*-mutant MDS as a disease subtype, morphology remains essential to classify these patients. Thus, an integrated diagnosis, including genetic data as well as morphological, biological, and clinical parameters, is necessary.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

REFERENCES

1. Malcovati L, Stevenson K, Papaemmanuil E, et al. *SF3B1*-mutant MDS as a distinct disease subtype: a proposal from the International Working Group for the Prognosis of MDS. *Blood*. 2020;136(2):157-170.
2. Papaemmanuil E, Gerstung M, Malcovati L, et al; Chronic Myeloid Disorders Working Group of the International Cancer Genome Consortium. Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood*. 2013;122(22):3616-3627, quiz 3699.
3. Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. *Leukemia*. 2014;28(2):241-247.
4. 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.
5. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.
6. Yoshida K, Sanada M, Shiraishi Y, et al. Frequent pathway mutations of splicing machinery in myelodysplasia. *Nature*. 2011;478(7367):64-69.
7. Papaemmanuil E, Cazzola M, Boultwood J, et al; Chronic Myeloid Disorders Working Group of the International Cancer Genome Consortium. Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. *N Engl J Med*. 2011;365(15):1384-1395.

8. Malcovati L, Papaemmanuil E, Bowen DT, et al; Chronic Myeloid Disorders Working Group of the International Cancer Genome Consortium and of the Associazione Italiana per la Ricerca sul Cancro Gruppo Italiano Malattie Mieloproliferative. Clinical significance of SF3B1 mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms. *Blood*. 2011;118(24):6239-6246.

9. Malcovati L, Karimi M, Papaemmanuil E, et al. SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts. *Blood*. 2015;126(2):233-241.

10. Cargo CA, Rowbotham N, Evans PA, et al. Targeted sequencing identifies patients with preclinical MDS at high risk of disease progression. *Blood*. 2015;126(21):2362-2365.

DOI 10.1182/blood.2020005719

CLINICAL TRIALS AND OBSERVATIONS

Comment on Rocca et al, page 171

Aspirin in ET: will twice a day keep thrombosis away?

Evan M. Braunstein and Shruti Chaturvedi | Johns Hopkins University School of Medicine

In this issue of *Blood*, Rocca et al show that aspirin insensitivity or incomplete platelet inhibition with standard once-per-day low-dose aspirin in patients with essential thrombocythemia (ET) is overcome by twice-per-day dosing of low-dose aspirin without an increase in adverse effects. This presents an attractive strategy for improving vascular outcomes in ET.[1]

Thrombosis, particularly arterial thrombosis, is a leading cause of morbidity and mortality in ET. Patients with the JAK2 V617F mutation, older individuals, and those with other cardiovascular risk factors are at particularly high risk. Low-dose aspirin is the cornerstone of thromboprophylaxis in ET, and cytoreductive therapy is recommended for those with higher risk disease.[2] However, there are no randomized trials showing that aspirin reduced vascular events in ET, and benefit is indirectly inferred from observational data and a single randomized trial that showed reduced thrombotic events in patients with polycythemia vera who received aspirin.[3] The lifetime rate of thrombosis in ET is ~60%; however, the risk varies widely between low-risk and high-risk patients. As an example, annual risk of thrombosis is <2% in patients who are younger than age 60 years with no history of thrombosis[4] compared with an annual recurrence rate of 6% to 8% among patients, even those receiving antiplatelet therapy, who have already had a thrombotic event.[5] A recent systematic review that included 18 observational studies with more than 6000 individuals with ET concluded that the benefit of aspirin in ET is questionable. The authors estimated a very modest median risk reduction of 26%, which is lower than that seen in polycythemia vera[3] or patients without myeloproliferative neoplasms. In this landscape, there is a critical need to improve antithrombotic strategies for patients with ET, and novel approaches such as low-dose anticoagulation with apixaban (ClinicalTrials.gov identifier: NCT04243122) and different aspirin regimens are being evaluated.

Enhanced platelet activation is a characteristic feature of ET, and several groups have demonstrated elevated levels of thromboxane B_2 (TXB_2) generation and increased urinary excretion of thromboxane metabolites, which are stable and validated markers of platelet activation. Platelet production is frequently enhanced several-fold in myeloproliferative disorders, and this has been proposed as a major mechanism underlying aspirin resistance in ET (see figure). Aspirin exerts its antithrombotic and cardioprotective effects by irreversibly inhibiting platelet cyclooxygenase 1 (COX-1) and blocking TXA_2 biosynthesis.[6] Despite its short plasma half-life (~10-20 minutes), the biological effects of aspirin last several days because of the time required for megakaryocytes to provide a new pool of fresh aspirin-naive platelets.[6] In fact, only about 10% of the platelet pool is replaced every 24 hours in healthy individuals who take low-dose aspirin once per day with almost complete suppression of serum TXB_2 levels that take ~3 days to recover[6]; however, this is less effective in patients with ET.[7] Pascale et al[8] showed that the immature platelet fraction independently predicted serum TXB_2, which suggests that accelerated renewal of platelets led to a shorter duration of aspirin effect. In support of this hypothesis, they found that increasing dosing frequency to twice per day improved TXB_2 reduction significantly, whereas doubling the aspirin dose without increasing frequency of dosing did not have the same effect. The more critical question is whether improved suppression of thromboxane synthesis translates into clinical benefit. Indirect evidence comes from a study by Eikelboom et al[9] who demonstrated that aspirin-resistant thromboxane production was associated with a several-fold increased risk of myocardial infarction and cardiovascular death in a cohort of patients at high risk for cardiovascular disease. However, benefit needs to be demonstrated in robust clinical trials.

This initial report from the randomized, double-blind Aspirin Regimens in Essential Thrombocythemia (ARES) study is an important first step in this direction. The dose finding component of the study evaluated aspirin 100 mg given 1, 2 or 3 times per day for 2 weeks. Twice-per-day dosing significantly reduced serum TXB_2 levels (there was interindividual variability in these levels) and reduced TXA_2-dependent platelet activation in vivo without an increase in gastrointestinal adverse effects. Three-times-per-day dosing had a similar effect on platelet activation markers but led to increased gastrointestinal disturbances. Urinary prostacyclin metabolite, a surrogate marker for endothelial prostacyclin production and vascular safety, was not significantly reduced with either experimental regimen. A reduction in microvascular disturbances such as erythromelalgia was not noted. On the basis of these results, the long-term phase of the ARES study will evaluate aspirin 100 mg dosed once per day vs twice per day to answer the more pressing questions of whether shorter dosing intervals will have a meaningful impact on clinical end points, including thrombotic events and cardiovascular mortality. Cytoreduction is