# Highlights in myelodysplastic syndromes

M.C. Vekemans, MD[1]

**Myelodysplastic syndromes (MDS) represent a heterogeneous group of clonal hematopoietic malignancies characterized by peripheral blood cytopenias, due to ineffective erythropoiesis and a risk for progression to acute myeloid leukemia (AML). Progress in this field aims to decrease the transfusion burden, delay progression to AML, improve the quality-of-life of patients and extend survival.**
*(Belg J Hematol 2016;7(1):20-4)*

## Therapeutic options in MDS

Azacytidine (AZA), decitabine (DEC) and lenalidomide (LEN) are the only 3 agents approved by the FDA for the treatment of MDS. They are currently used in monotherapy with modest results. Recent clinical trials have demonstrated mixed results, with no new regimens or targeted therapies having shown either great promise or clear progress.

## Low-risk MDS

The major challenge in low-risk (LR) MDS is to deal with cytopenia, particularly anemia. In MDS, anemia is related to ineffective erythropoiesis, a process driven by excessive Smad 2/3 signaling. **Luspatercept**, a fusion protein (modified activin receptor 2b - human IgG1 Fc domain), acts as a ligand trap for TGF-ß ligands, inhibiting Smad 2/3 activation, promoting the late stage of erythroid differentiation and correcting ineffective erythropoiesis (*Figure 1*). Based on preliminary data of a 24-month extension trial in transfusion-dependent LR-MDS patients, Luspatercept given at 1-1.25 mg/kg every 3 weeks, led to a sustained hematological improvement (HI) for hemoglobin levels, decreased transfusion requirement or transfusion independence (TI) in the majority of patients, with a favorable safety profile. High response rates were also observed in patients refractory to erythropoietin stimulating agents (ESA) or with high serum EPO levels (up to 500 U/l).[1]
Another important challenge in LR-MDS remains severe thrombocytopenia which occurs in approximately 10% of patients. Treatment is usually limited to platelet (PLT) transfusions in case of bleeding. **Romiplostim**, a thrombopoietin-receptor (TPO-R) agonist, has been shown to reduce clinically significant bleeding events and decrease PLT transfusions when compared to placebo in a randomized trial, but there were some concerns about the increase of peripheral blast cell counts that led to study closure.[2] Further follow-up failed to identify any difference in terms of overall survival (OS) and AML-free survival between both groups.[3] **Eltrombopag**, an oral TPO-R agonist, also significantly improved PLT counts when compared to placebo, with durable PLT responses, better quality-of-life (Qol), manageable toxicity, and no association with AML evolution nor bone marrow (BM) fibrosis.[4]

Most non-del 5q LR-MDS patients are usually first treated with ESA, with about 50% (generally transient) responses. In a large retrospective cohort of non-del 5q LR-MDS patients failing ESA, only one-third received a second line therapy other than red blood cell (RBC) transfusion, mainly LEN or hypomethylating agents (HMA). No treatment was able to improve the OS compared to best supportive care (BSC).[5]
LEN has proven to be very effective for del 5q MDS patients and is currently evaluated for registration in non-del 5q patients. So far, there is no standard option after LEN failure. A large retrospective study analyzed

[1]Department of Hematology, Cliniques universitaires Saint-Luc, UCL, Brussels, Belgium
*Please send all correspondence to:* Marie-Christiane Vekemans, MD, Department of Haematology, Cliniques universitaires Saint-Luc, UCL, Avenue Hippocrate, 10, B-1200 Brussels, Belgium, Phone: +3227641872, E-mail: marie-christiane.vekemans@uclouvain.be
**Conflict of interest:** The author has nothing to disclose and indicated no potential conflict of interest.

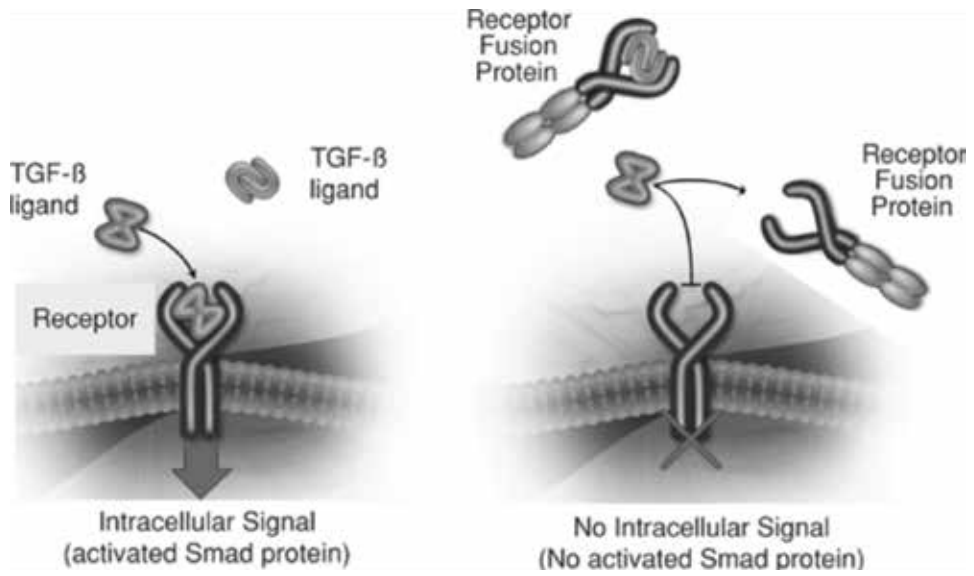


**Figure 1.** Luspatercept, a fusion protein that acts as a ligand trap, inactivating Smad 2/3 pathway, promoting the late stages of erythroid differentiation, thereby correcting ineffective erythropoiesis.

the outcome of MDS patients in this setting. Survival without treatment remains relatively poor in both del 5q and non-del 5q MDS, with a limited impact of conventional approaches. HMA is suggested to represent a valid option for del 5q patients.[6]

## High-risk MDS

AZA is the standard of care for HR-MDS patients. However, almost all patients ultimately fail AZA-therapy with the majority of them progressing within 2 years. When refractory to AZA, the median OS of patients does not exceed 4 to 6 months. Several studies have evaluated the efficacy and safety of combining AZA with other drugs, either LEN, administered concurrently or sequentially, or histone deacetylase inhibitors (HDACi) such as panobinostat or vorinostat.[7-9] However, all these combinations failed to improve the results observed with AZA alone in terms of overall responses (ORR) or OS, and were associated with more grade 3-4 hematological adverse events (AE). **Pracinostat**, a potent oral HDACi that had previously demonstrated an 89% complete response (CR) or CR with incomplete blood count recovery (CRi) rates, failed to improve the clinical effectiveness of AZA in a phase 2 study, primarily due to AE that led to early study discontinuation.[10] **Birinopant** is an antagonist of a family of proteins called 'inhibitors of apoptosis' that are responsible for caspase activation, NF-kb inhibition and increased apoptosis (*Figure 2*). In a phase 1b trial, in combination with AZA, it showed interesting clinical activity in both AZA naïve or refractory patients, with 45% of them achieving a decrease ≥50% in BM blast count or a reduction ≤5% blasts in BM.[11] **Rigosertib** is a small molecule that targets the Ras-binding domain of RAF, inhibiting the PI3-kinase survival and Polo-like kinase mitotic signaling pathways (*Figure 3*). Compared to BSC in patients with primary HMA failure, it previously showed better OS in the ONTIME phase 3 trial.[12] In combination with AZA, oral rigosertib demonstrated an ORR of 77% with 65% marrow CR, both in de novo MDS or after failure of prior HMA therapy. Safety profile was similar to single agent AZA, without cumulative toxicity after repetitive cycles.[13]

## Transplantation

AlloSCT remains the sole potential curative option in MDS. Outcome is dependent on disease- and patient-related factors. There are no prospective trials comparing transplant with non-transplant approaches, and numerous questions remain unanswered. Among them, the role of cytoreduction before alloSCT remains a debatable issue. AZA has been compared to conventional chemotherapy (ICT) in 2 retrospective studies without showing any differences in terms of OS, relapse or non-relapse mortality (NRM). The rationale to use AZA before alloSCT is that it could reduce tumor burden without

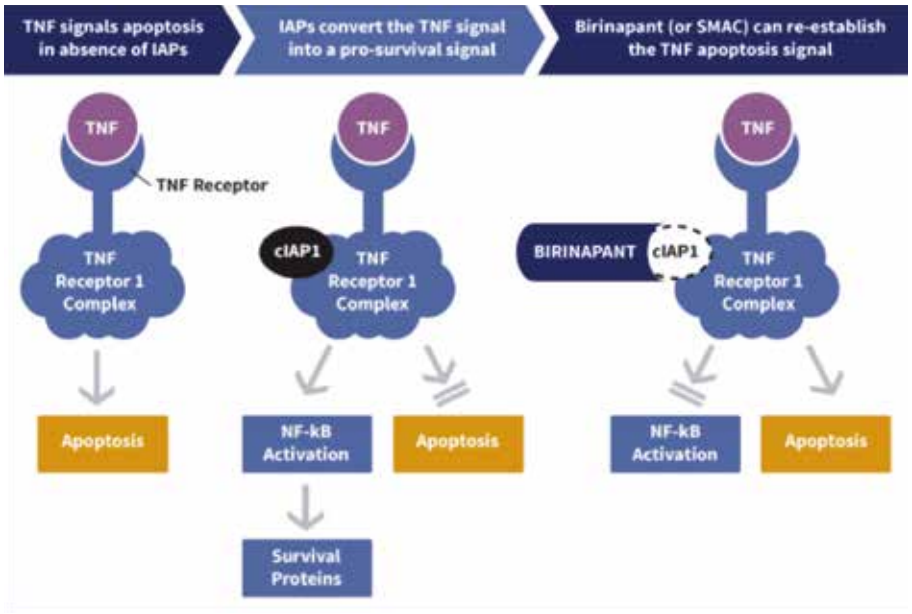


**Figure 2.** Birinopant, an antagonist of a class of molecules called 'inhibitors of apoptosis', that induces caspase activation and NF-Kb inhibition, increasing apoptosis.

impacting the physical condition of the patient. The Groupe Français de Greffe de Moelle analyzed 128 consecutive MDS patients who received a reduced intensity (RIC) or nonmyeloablative (NMA) conditioning before alloSCT. Fourty patients received AZA while 88 were transplanted upfront. With a median follow-up of 60 months, the absence of cytoreduction before alloSCT did not alter the outcome of patients.[14]

The conditioning regimen to be applied before transplant is also a matter of debate. RIC has a lower toxicity profile and lower treatment related mortality (TRM), but is associated with higher relapse rates with similar OS when compared to myeloablative conditioning (MAC) in patients with myeloid malignancies. In 2014, the EBMT was the first to compare MAC to RIC in a phase 3 randomized trial in MDS and secondary AML with <20% blasts at the time of transplant. The study was prematurely closed due to slow recruitment, but RIC gave at least equivalent results as MAC, and it was suggested that RIC might be better in cytogenetic LR-MDS.[15]

The Bone and Marrow Transplant Clinical Trials Network (BMT CTN) reported a phase 3 randomized trial comparing outcome by conditioning in patients with MDS/AML, with 18-month post-randomization OS as primary endpoint. Accrual was stopped early due to a presumed benefit of MAC. RIC resulted in higher relapse rates and a lower TRM compared to MAC, with a statistically significant advantage in relapse-free survival (RFS) for MAC, supporting MAC as the standard of care for patients able to receive it.[16]

## Molecular Biology of MDS

Recent large-scale analyses using next-generation sequencing (NGS) have dramatically improved the understanding of the molecular pathogenesis and the biological and clinical implications of gene mutations associated with MDS. More than 200 recurrently mutated genes have been identified. Most of them are rare, but the most frequently mutated genes are *TET2, SF3B1* and *ASLX1*, seen in >20% of MDS patients. In addition to this, *SRSF2, DNMT3A* and *RUNX1* are also observed in >10% of patients.[17,18] Mutations affect RNA splicing machinery, DNA methylation, histone modifications, transcription factors, signal transduction proteins and components of the cohesion complex. They arise stepwise: mutations in RNA splicing and DNA methylation occur early and are considered as 'founding mutations', whereas others that occur later are regarded as 'subclonal mutations'. Mutations carry prognostic information independent of the International Prognostic Scoring System (IPSS) and the revised IPSS (IPSS-R). Attempts are made to integrate molecular information into a clinical scoring system such as the IPSS-Rm.[19]

However, gene mutation analysis is not yet performed routinely and incorporation into diagnostic and clinical

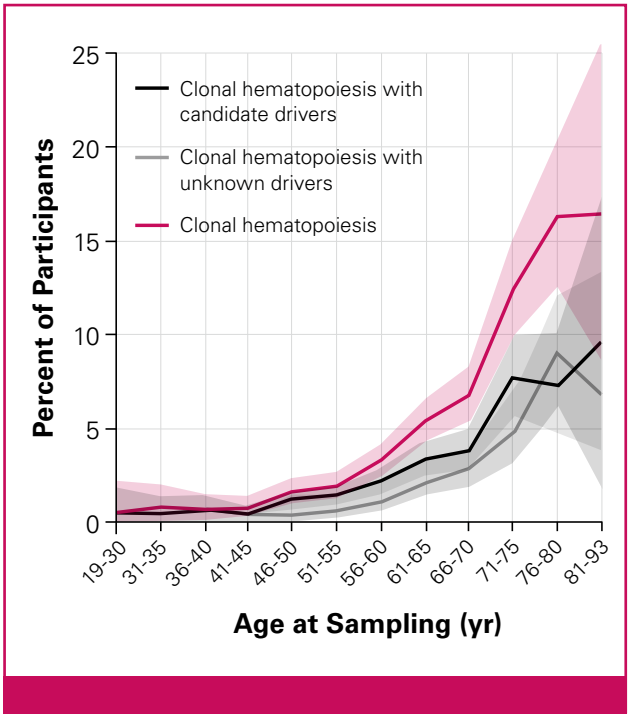


**Figure 3.** Clonal hematopoiesis of indeterminate potential (CHIP). Analyses of somatic mutations in 17,182 healthy individuals show a low incidence under the age of 40, and a rise in frequency with age. The presence of a somatic mutation is associated with an increased risk of hematological cancer.[21]

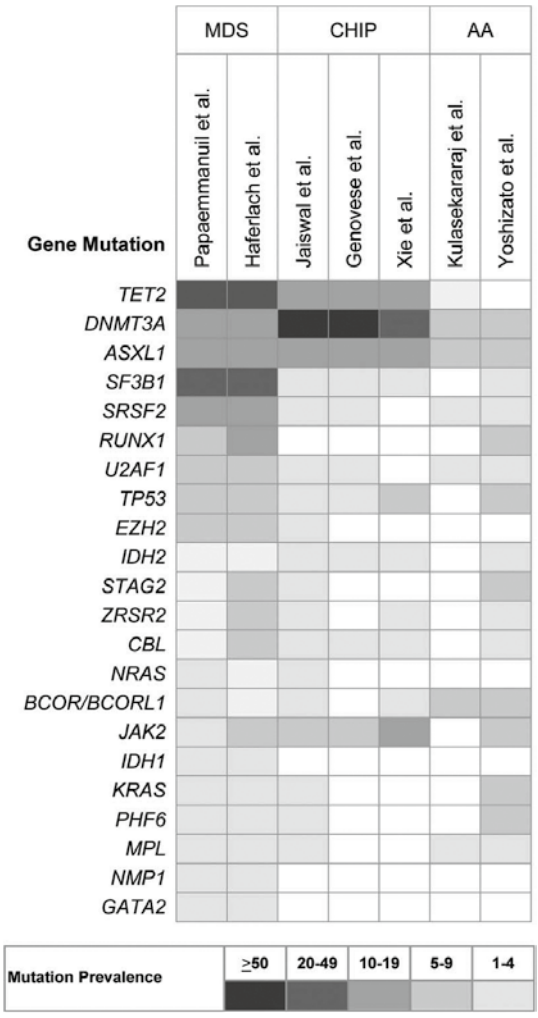


**Figure 4.** Frequency of recurrent somatic mutations in MDS, clonal hematopoiesis of indeterminate potential (CHIP) and aplastic anemia (AA).[20]

practice is not easy. Practically, splicing factor mutations are disease defining. Mutations in *SF3B1* define a distinct molecular and clinical entity in MDS, characterized by lower blast counts and higher presence of ringed sideroblasts. Molecular testing of *SF3B1* more accurately identifies patients in this group, compared to the blast or ringed sideroblast percentage. *SF3B1* is also an independent prognostic predictor of clinical outcome associated with favorable prognosis, with lower incidence of disease progression. Coexisting mutations in DNA methylation genes are associated with multi-lineage dysplasia but have no effect on clinical outcome.[20]

Recent studies have provided consistent evidence of age-related hematopoietic clones driven by mutations of genes that are currently mutated in myeloid neoplasms and associated with an increased risk of hematological cancer. This refers to the notion of 'clonal hematopoiesis of indeterminate potential' (CHIP), where a subset of mutated genes, mainly involved in epigenetic regulation, are likely initiating lesions driving the expansion of a premalignant clone (*Figures 3* and *4*). MDS-associated somatic mutations and clonal hematopoiesis are common in idiopathic cytopenias of undetermined significance (ICUS).[21]

## WHO classification

In 2016, a revision to the WHO classification of MDS originally published in 2008 is expected.[22] Although the basic diagnostic principles of the WHO classification remain unchanged, several modifications will be proposed. The new classification will retain a 10% threshold to define a lineage as dysplastic, continue to recommend counting of blasts on BM aspirates, provide more detailed definition of dysplasia and emphasize the importance of considering non-MDS causes of dysplasia. Karyotype will remain essential, since an abnormal karyotype supports clonality and specific karyotypic abnormalities are considered to be diagnostic in morphologically subtle cases. In contrast, detection of a gene mutation will not be considered as proof of clonality, since it also occurs in healthy

individuals. Flow cytometry will be considered useful but will not be required or recommended in the work-up of MDS. The new WHO classification will also incorporate new discoveries in MDS that impact existing disease categories. It will include the prognostic significance of gene mutations in MDS, revise the diagnostic criteria for ring sideroblasts entities based on the detection of *SF3B1* mutations (diagnosis retained if >15% ring sideroblasts or >5% ring sideroblasts with *SF3B1* mutation), enlarge criteria for MDS entities with isolated del 5q, allowing a second cytogenetic abnormality with the exception of monosomy 7, create a new entity 'myeloid neoplasms with genetic predisposition' (presence of *RUNX1, GATA2, …* mutations), reclassify most cases of the erythroid/myeloid type of erythro-leukemia, recognize the familial link in some cases of MDS. Finally the routine use of "refractory anemia or refractory cytopenia" will be abandoned.

## Conclusion

Treatment of MDS depends on an individualized approach based on a patient-specific risk stratification. Unfortunately, so far there are no new drug approvals. The better understanding of the molecular biology of MDS might become an important factor in improving the diagnostic accuracy and prognostic assessment, ultimately leading to more specific targeted therapies in the near future.

## References


1. Giagounidis A, et al. Luspatercept treatment leads to long term increases in hemoglobin and reductions in transfusion burden in patients with low or intermediate-1 risk myelodysplastic syndromes (MDS):preliminary results from the Phase 2 PACE-MDS extension study. Blood 2015;126(23): Abstract 92.

2. Giagounidis A, et al. Results of a randomized, double-blind study of romiplostim versus placebo in patients with low/intermediate-1–risk myelo-dysplastic syndrome and thrombocytopenia. Cancer 2014;120(12): 1838-46.

3. Kantarjian H, et al. Romiplostim in thrombocytopenic patients with low-risk or intermediate-1-risk myelodysplastic syndrome results in reduced bleeding without impacting leukemic progression: updated follow-up from a randomized, double-blind, placebo controlled study. Blood 2015;126(23): Abstract 2863.

4. Oliva E, et al. Eltrombopag for the treatment of thrombocytopenia of low and intermediate-1 IPSS risk myelodysplastic syndromes: interim results on efficacy, safety and quality of life of an International, multicenter prospective, randomized trial. Blood 2015;126(23): Abstract 91.

5. Park S, et al. Outcome of lower risk non del5q MDS after failure of erythropoiesis stimulating agents (ESA), and impact of post-ESA treatment on survival: a retrospective European study. Blood 2015;126(23): Abstract 1665.

6. Prebet T, et al. Outcome of patients treated for myelo-dysplastic syndromes after failure of lenalidomide therapy. Blood 2015;126(23): Abstract 95.

7. Finelli C, et al. Association of Azacytidine and lenalidomide (combined vs sequential treatment) in high-risk myelodysplastic syndromes. Final results of a randomized phase 2 multicenter trial. Blood 2015;126(23): Abstract 2871.

8. Garcia-Manero G, et al. Panobinostat plus azacytidine in adult patients with MDS, CMML, or AML: results of a phase 2b study. Blood 2015;126(23): Abstract 2861.

9. Sekeres M, et al. Additional analyses of a randomized phase 2 study of Azacytidine combined with Lenalidomide or with Vorinostat vs Azacytidine monotherapy in Higher-risk myelodysplastic syndromes and chronic myelomonocytic leukemia: North American Intergroup Study SWOG S1117. Blood 2015;126(23): Abstract 908.

10. Garcia-Manero G, et al. A randomized, placebo-controlled, phase 2 study of Pracinostat in combination with Azacytidine (AZA) in patients with previously untreated myelodypslatic syndrome. Blood 2015;126(23): Abstract 911.

11. Borthakur G, et al. A Phase 1b study of Birinopant in combination with 5-Azacytidine in patients with myelodysplastic syndrome who are naive, refractory or have relapsed to 5-Azacytidine. Blood 2015;126(23): Abstract 93.

12. Garcia Manero G, et al. Overall survival and subgroup analysis from a randomized phase 3 study of Rigosertib vs best supportive care in patients with higher-risk myelodysplastic syndrome after failure of hypo-methylating agents. Blood 2014;124(21): Abstract 163.

13. Navada SC, et al. A phase 2 study of the combination of oral rigosertib and azacytidine in patients with myelodysplastic syndromes. Blood 2015;126(23): Abstract 910.

14. Damaj G, et al. Upfront allogeneic stem cell transplantation after reduced-intensity conditioning/nonmyeloablative conditioning for patients with myelodysplastic syndrome: a study by the Société Française de Greffe de Moelle et de Thérapie Cellulaire. Biol Blood Mar Transpl 2014;20:1349-55.

15. Kröger N, et al. Reduced intensity vs standard conditioning followed by allogeneic stem cell transplantation for patients with MDS or secondary AML: a prospective, randomized phase 3 study of the Chronic Malignancies Working Party of the EBMT (RICMAC trial). Blood 2014;124(21): Abstract 320.

16. Scott BL, et al. Results of a phase 3 randomized, multicenter study of allogeneic stem cell transplantation afyter High versus reduced intensity conditioning in patients with myelodysplastic syndrome or acute myeloid leukemia: Blood and Marrow Transplant Clinical Trials Network 0901. Blood 2015;126(23): Abstract LBA-8.

17. Papaemmanuil E, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood 2013;122(22):3616-27.

18. Haferlach T, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia 2014;28(2):241-7.

19. Bejar R, et al. Somatic mutations in MDS patients are associated with clinical features and predict prognosis independent of the IPSS-R: analysis of combined datasets from the International Working Group for Prognosis in MDS-Molecular Committee. Blood 2015;126(23): Abstract 907.

20. Malcovati L, et al. SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts. Blood 2015;126: 233-41.

21. Jaiswal S, et al. Age-related clonal hematopoiesis associated with adverse outcomes. New Engl J Med 2014;371:2488-98.

22. Arber D, et al. Reclassifying myelodysplastic syndromes: what's where in the new WHO and why. Blood 2015;126(23): Abstract 77362A.