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RECENT ADVANCEMENT IN TREATMENT OF MYELODYSPLASIA

Priya Rai, Pradeep Mehra, Ragini Kumari, Radhika Vishwkarma and Pushpendra K. Khangar*

Adina Institute of Pharmaceutical Sciences, NH86A, Lahdara, Sagar, MP, 470001.

***Corresponding Author: Pushpendra K. Khangar**

Adina Institute of Pharmaceutical Sciences, NH86A, Lahdara, Sagar, MP, 470001.

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ABSTRACT

Myelodysplastic syndromes (MDS/ Myelodysplasia) are a group of clonal hematologic disorder, which combine ineffective hematopoiesis and evolution to acute myeloid leukemia. Significant progress has been made in the understanding of the disease pathogenesis, diagnostics and classification. Promising new agents and innovative therapeutic strategies are currently used. In this article we will review these achievements and their impact on the treatment of MDS. Once thought to be rare disorders, the myelodysplastic syndromes (MDS) are now recognized as among the most common hematological neoplasms, probably affecting >30 000 patients per year in the United States. US regulatory approval of azacitidine, decitabine, and lenalidomide between 2004 and 2006 seemed to herald a new era in the development of disease-modifying therapies for MDS, but there have been no further drug approvals for MDS indications in the United States in the last 8 years. The available drugs are not curative, and few of the compounds that are currently in development are likely to be approved in the near future. As a result, MDS diagnoses continue to place a heavy burden on both patients and health care systems. Incomplete understanding of disease pathology, the inherent biological complexity of MDS, and the presence of comorbid conditions and poor performance status in the typical older patient with MDS has been major impediments to development of effective novel therapies. Here we discuss new insights from genomic discoveries that are illuminating MDS pathogenesis, increasing diagnostic accuracy, and refining prognostic assessment, and which will one day contribute to more effective treatments and improved patient outcomes. The pathogenesis of MDS involves abnormalities of the MDS clone itself such as abnormal apoptosis, signalling or epigenetic regulation and abnormalities of the microenvironment such as immune deregulation or increased angiogenesis, which represent potential therapeutic targets. There is currently no standard treatment for MDS and allogeneic stem cell transplantation remains the only curative strategy. However, besides conventional chemotherapy and growth factors, new agents including hypomethylating agents, antiangiogenic drugs, immune modulatory agents have proved effective. KEYWORDS: Myelodysplastic syndromes, Anemia, Luspatercept-Aamt.

INTRODUCTION

The myelodysplastic syndromes (MDS) represent the most common class of acquired bone marrow failure syndromes in adults. Although MDSs are increasingly well understood from a biological standpoint, including discovery of >40 MDS-associated recurrently mutated genes in the last 7 years, improved pathological insight has not yet translated into highly effective or curative therapies for most patients suffering from these disorders. Collectively, the term MDS describes a diverse group of clonal disorders of hematopoietic stem or progenitor cells characterized by ineffective hematopoiesis, abnormal "dysplastic" cell morphology, and potential for clonal evolution. Increasing failure of cellular differentiation is associated with evolution to secondary acute myeloid leukemia (AML), currently arbitrarily defined by the World Health Organization (WHO) as ≥20% myeloid blasts in the blood or marrow, or the presence of one of several AML-defining karyotypic abnormalities [eg, t(15;17), t(8;21), inv(16), or t(16;16)] regardless of blast proportion. AML is ultimately diagnosed in up to 30% of MDS cases. In this review, we describe recent advances in our collective understanding of the genetic basis of MDS in the context of existing knowledge and survey how these findings may contribute to improvements in diagnosis and prognostic assignment of patients, serve as predictors or biomarkers of response to treatment, and aid development of future therapies. MDS cell biology and immunobiology, animal models, the contribution of the marrow microenvironment to MDS development and persistence, and familial predisposition to MDS are also areas of active development but are beyond the scope of this review.

Epidemiology and diagnosis

Although MDS are common, the exact number of new cases in the United States each year has proven difficult to estimate accurately. This is in part because cancer registries such as the Surveillance, Epidemiology, and

End Results registry of the National Cancer Institute have only begun to classify MDS as neoplastic and capture data on MDS cases since 2001. Additionally, many elderly patients with mild unexplained cytopenias who may have MDS are incompletely evaluated, including avoidance of bone marrow aspiration, without which the diagnosis of MDS currently cannot be made with certainty. Estimates of disease incidence derived from insurance claims data may more accurately approximate epidemiological truth. Yet many patients with indolent or low-grade MDS never have an MDS-labeled claim filed, whereas other patients who do not truly have MDS are sometimes coded as such to justify use of a specific therapy, such as an erythropoiesis stimulating agent (ESA).[1] Taking these limitations into consideration, current estimates are that between 30 000 and 40 000 new cases of MDS occur in the United States each year, with perhaps twice as many cases in Europe; given the median survival of patients with MDS, the prevalence is likely to be 60 000 to 120 000 cases in the United States. Less is known about the incidence and prevalence of MDS in other global regions. In China and South Asia, patients with MDS are diagnosed at a younger age, some subtypes of MDS such as refractory anemia with ring side oblasts are seen less frequently, and complex karyotypes and monosomy 7 may be more common than in the West; the reasons for these differences are unclear, but may relate to genetic background or environmental exposures. MDS epidemiology is also distinct in Japan and in Eastern Europe, including an increased MDS risk in survivors of the 1945 Hiroshima and Nagasaki atomic bomb explosions persisting into the 21st century.[2]

The diagnosis of MDS is typically made by excluding other non-MDS causes of cytopenias in the presence of some combination of dysplastic cell morphology, increased marrow blasts, and a karyotypic abnormality. Common "MDS mimics" include cytopenias or morphologic abnormalities as a result of a medication (eg, methotrexate); deficiencies of cobalamin, folate, or copper; excessive alcohol use; HIV infection; immune-mediated cytopenias, including aplastic anemia and large granular lymphocyte leukemia; congenital syndromes such as Fanconi anemia and X-linked sideroblastic anemia; and other neoplasms such as myeloproliferative neoplasms. Bone marrow aspirate and biopsy allows assessment of both cell morphology and histological architecture, and, when coupled with conventional karyotyping (abnormal in approximately one-half of de novo MDS cases and >80% of cases arising secondary to exposure to a DNA-damaging agent), can in some cases confirm disease clonality. Morphologic dysplasia is not required for an MDS diagnosis in the presence of cytopenias if either excess blasts in the 5% to 19% range or evidence of clonally restricted hematopoiesis are present.[1,2]

Cases in which cytopenias are present, but the karyotype is normal, dysplastic changes are mild or absent, and there is no increase in blasts or other features convincing for an MDS diagnosis, present diagnostic difficulty. Such patients are sometimes referred to as having idiopathic cytopenias of undetermined significance (ICUS), which in contrast to monoclonal gammopathy of undetermined significance is by definition not known to be clonal. ICUS is also not a unique or well-defined clinical entity and includes a heterogeneous group of patients, only some of whom have an MDS or AML progression risk.In addition to ICUS, some elderly people have clonally restricted hematopoiesis without cytopenias, sometimes detectable as somatic mosaicism for large chromosomal abnormalities, and the rate at which these patients progress to MDS or other hematologic neoplasms appears to be increased compared with patients without clonal hematopoiesis. The recent finding of 450 somatic mutations in the healthy blood compartment of a 115-year-old woman is a striking illustration that not all detectable coding mutations are clinically consequential.[3]

Improvements to the diagnosis and classification of MDS

Advances in molecular understanding of MDS are poised to become part of routine clinical care of patients. A precedent for this can be seen in the myeloproliferative neoplasms, where detection of *BCR-ABL* rearrangements are critical for chronic myeloid leukemia (CML) diagnosis and treatment monitoring, and discovery of *JAK2* mutations quickly led to incorporation of mutation testing into diagnostic criteria for polycythemia vera (PV), essential thrombocythemia, and primary myelofibrosis. The greater molecular heterogeneity of MDS compared with CML or PV makes clinical translation of mutation analysis a more challenging prospect, but a challenge that is being addressed. For example, establishing a diagnosis of MDS currently relies on a morphologist's qualitative assessment of dysplasia and quantification of blast forms that may be highly distorted Even experienced pathologists frequently have interobserver variability. Furthermore, hematopoietic cell dysplasia is not specific for MDS, and karyotypic abnormalities that can confirm an MDS diagnosis are not present in most cases. All of these factors can contribute to uncertainty or error in diagnosis. Targeted gene sequencing and SNP array analysis can identify somatic events in the majority of MDS patients, including many with normal karyotypes or more indolent disease, and can conclusively establish the presence of clonal hematopoiesis. Recently, it has been shown that ≥1 mutation typical for MDS can be found in nearly one-half of patients with suspected MDS who do not meet morphologic diagnostic criteria. Whether ICUS patients with somatic mutations will have a disease course comparable to that of more overt MDS cases is not yet known, but identification of clonal hematopoiesis can help rule out competing benign causes of cytopenias and suggests that close follow up for disease progression is warranted.

Not all somatic mutations will be of equal value diagnostically.[3,4] Acquired mutations of certain genes, like *TET2* and *DNMT3A*, can be found in patients with diagnoses other than MDS, including lymphoid disorders. Mutations of these genes can also be identified in some healthy persons without cytopenias. Mutations of genes strongly associated with clinical phenotypes will have the greatest diagnostic utility and may help better classify MDS subtypes. For example, splicing factor mutations are enriched in patients with dysplasia compared with nondysplastic myeloid disorders. In particular, *SF3B1* mutations are strongly associated with ring sideroblasts, and patients with *SF3B1* mutations harbor fewer mutations in genes associated with a poor prognosis and generally have a more indolent disease course.[4]

Mutations of *TP53*, although not associated with a specific morphology or clinical phenotype, are associated with adverse disease features including excess blasts, thrombocytopenia, and complex karyotypes (ie, ≥3 chromosomal abnormalities) and fewer cooperating lesions in recurrently mutated genes. In contrast, patients with complex karyotypes without *TP53* mutations appear to have an overall survival comparable to that of patients without multiple karyotype abnormalities. In the del(5q) setting, *TP53* mutations or p53 protein expression in marrow cells predict less frequent cytogenetic responses to lenalidomide and higher AML progression rate. In this case, the presence or absence of a molecular lesion may help classify patients and refine prognosis predicted by karyotyping.[5]

The different types of myelodysplastic syndromes are diagnosed based on certain changes in the blood cells and bone marrow.

- **Refractory anemia**: There are too few red blood cells in the blood and the patient has anemia. The number of white blood cells and platelets is normal.
- **Refractory anemia with ring sideroblasts**: There are too few red blood cells in the blood and the patient has anemia. The red blood cells have too much iron inside the cell. The number of white blood cells and platelets is normal.
- **Refractory anemia with excess blasts**: There are too few red blood cells in the blood and the patient has anemia. Five percent to 19% of the cells in the bone marrow are blasts.[6] There also may be changes to the white blood cells and platelets. Refractory anemia with excess blasts may progress to acute myeloid leukemia (AML).
- **Refractory cytopenia with multilineage dysplasia**: There are too few of at least two types of blood cells (red blood cells, platelets, or white blood cells). Less than 5% of the cells in the bone marrow are blasts and less than 1% of the cells in the blood are blasts. If red blood cells are affected, they may have extra iron. Refractory cytopenia may progress to acute myeloid leukemia (AML).[7]
- **Refractory cytopenia with unilineage dysplasia**: There are too few of one type of blood cell (red blood cells, platelets, or white blood cells). There are changes in 10% or more of two other types of blood cells. Less than 5% of the cells in the bone marrow are blasts and less than 1% of the cells in the blood are blasts.
- **Unclassifiable myelodysplastic syndrome**: The numbers of blasts in the bone marrow and blood are normal, and the disease is not one of the other myelodysplastic syndromes.
- **Myelodysplastic syndrome associated with an isolated del (5q) chromosome abnormality**: There are too few red blood cells in the blood and the patient has anemia. Less than 5% of the cells in the bone marrow and blood are blasts. There is a specific change in the chromosome.

Recent current treatment approaches

Decitabine Plus Cedazuridine

Decitabine is a hypomethylating agent that has been approved for the treatment of MDS. However, this drug is delivered intravenously or parenterally, as it is rapidly degraded by the enzyme cytidine deaminase present in the gut and liver.[8] As a result, patients taking decitabine may require clinic visits for 5-7 days per month for dosing, which is an important consideration in the era of COVID-19.

In this trial, we varied the dose of the inhibitor, cedazuridine, in combination with decitabine in an effort to match the pharmacokinetic profile for IV administered decitabine," Garcia-Manero explained.[9]

Dose-escalation of cedazuridine was done until the inhibition of cytidine deaminase was maximized. Once that dosage had been optimized, then dose-escalation of oral decitabine was performed if the mean area under the curve (AUC) of oral drug was less than 90 percent of the value obtained for IV decitabine in that cohort and if no dose-limiting toxicities were observed. Here, a dose-limiting toxicity was defined a grade 3 or higher non-hematologic toxicity or a grade 4 hematologic toxicity lasting more than 2 weeks and being unrelated to the malignancy. In the Phase I portion of the study, the dosage chosen for the fixed-dose combination was 100 mg cedazuridine and 35 mg decitabine, as the optimal decitabine AUC for the combination appeared between the values obtained for the 100 mg cedazuridine/30 mg decitabine and 100 mg cedazuridine/40 mg decitabine cohorts.[10]

In the Phase II portion of this study, the oral single-dose combination of 100 mg cedazuridine/35 mg decitabine (hereafter referred to as ASTX727) was compared with IV-dosed 20 mg/m^2 decitabine (*Blood* 2020;136(6):674-683). Data revealed at the 2019 International Symposium on Myelodysplastic Syndromes showed that the AUC obtained for the orally dosed combination was approximately 98 percent that of the IV-dosed

decitabine. In addition to the positive pharmacokinetic data, durable responses were noted in the study participants. A complete response was noted in 21.3 percent of the orally dosed patients, while the overall response was 60 percent. The median duration of response was 13.3 months, while the median overall survival was 18.3 months.

Further evaluation of the fixed-dose combination was accomplished in the aforementioned Phase III ASCERTAIN study. Preliminary data for this study was delivered in an oral presentation at the 2019 ASH Annual Meeting (*Abstract 846*).[11] In this crossover study, patients were randomized in a 1:1 fashion to one of two distinct sequences: Sequence A—1 cycle of oral combination , then 1 cycle of IV decitabine (1 hour infusion for 5 days) followed by 3 or more cycles of oral ASTX727; Sequence B-in which the IV-dosed and orally dosed cycles are reversed, followed by 3 or more cycles of oral ASTX727.[12]

This study included 133 patients (Sequence A-66 and Sequence B-67) with intermediate- to high-risk MDS, chronic myelomonocytic leukemia, and acute myeloid leukemia. The study's primary endpoint was equivalence for decitabine 5-day AUC between the oral and IV dosing cycles.

The study met its primary endpoint with high confidence, as the 5-day decitabine AUC for oral dosing was approximately 99 percent of the IV dosing 5-day AUC," Garcia-Manero stated. "In addition, individual decitabine exposures from fixed orally dosed ASTX727 largely overlapped with IV decitabine, which was based on body surface area-based dosing.

A complete response was noted in 11.9 percent of patients, while the overall response was 64.4 percent. "The efficacy data are very preliminary as a result of the short median follow-up period of 5 months," he noted, "[therefore], 32 patients could not be evaluated for response."[13]

"Safety was similar between oral ASTX727 and IV decitabine in the first 2 randomized cycles, with most common adverse events being the expected thrombocytopenia, neutropenia, and anemia; none of the adverse event differences were significant," Garcia-Manero explained. "The near absence of grade 3 gastrointestinal adverse events was notable. These were less than 1 percent for IV or oral dosing in the first 2 cycles.

"ASTX727 is the only oral hypomethylating agent in development with systemic exposure that is equivalent to its IV form, providing a more patient-friendly oral dosing alternative to IV decitabine."

Luspatercept-Aamt

MDSs are bone marrow disorders which occur predominantly in the elderly and are characterized by impaired hematopoiesis and possible disease progression to acute myeloid leukemia.[14]

"Lower-risk MDS frequently presents with symptomatic anemia," Garcia-Manero explained, "and in the elderly, chronic anemia is associated with a number of issues, including cardiovascular complications, increased risks of falls and bone fracture, as well as shorter survival."

Many patients with MDS are aided by the use of an erythropoiesis-stimulating agent, such as erythropoietin. These agents are considered a first-line treatment for patients with anemia and low-risk MDS; mechanistically, these agents stimulate erythroid precursor cell proliferation and inhibit apoptosis. When patients no longer respond to these erythropoiesis-stimulating agents, they become dependent upon transfusions.[15]

One potential new therapy for these patients no longer responding to erythropoiesis-stimulating agents is the recombinant fusion protein luspatercept-aamt. Mechanistically, luspatercept binds to b superfamily ligands, thus reducing the SMAD2 and SMAD3 signaling which can inhibit red blood cell maturation.

Recently, results from the Phase III MEDALIST study (NCT02631070) were published (*N Engl J Med* 2020;382:140-151). In that study, the use of luspatercept was evaluated in patients with very low-risk, low-risk, or intermediate-risk MDS with ring sideroblasts who had received regular red cell transfusions. Participants were randomized in a 2:1 ratio to luspatercept or placebo. Dosing was subcutaneous every 3 weeks.[16]

"The primary study endpoint," Garcia-Manero explained, "was transfusion independence for 8 weeks or longer during weeks 1 through 24. The key secondary endpoint was transfusion independence for 12 weeks or longer, as assessed during both weeks 1-24 and 1-48."

A total of 229 patients were randomly assigned (153 to luspatercept and 76 to placebo). Transfusion independence was observed in 38 percent and 13 percent of the luspatercept and placebo participants, respectively.[17,18] This primary endpoint was statistically significant, with P<0.001. For the key secondary endpoint, luspatercept clearly outperformed placebo at both the weeks 1-24 (28% vs. 8%, p<0.001) and the weeks 1-48 (33% vs. 12%, p<0.001) timepoints.

Safety was generally good, with the most frequently observed luspatercept-associated adverse events being asthenia, diarrhea, dizziness, fatigue, and nausea. Consequently, the investigators concluded that luspatercept reduced the severity of anemia in patients with lower-risk MDS who had received red blood cell

transfusions and who had disease that had not responded to an erythropoiesis-stimulating agent. In their April 2020 statement, the FDA cited the results obtained in this study as rationale for their approval for luspatercept.

Magrolimab

Magrolimab, formerly referred to as Hu5F9-G4, is a monoclonal antibody that targets CD-47, a macrophage immune checkpoint, and the so-called "don't eat me signal" for malignancies.[18] In a Phase Ib trial (NCT03248479), magrolimab is being evaluated alone or in combination with the hypomethylating agent azacitidine in patients with acute myeloid leukemia or high-risk MDS. Azacitidine was added to the monoclonal antibody, as it is an approved therapy for MDS, and it is thought to show synergy with magrolimab by enhancing phagocytosis. Results for patients with MDS (*Abstract S187*) and acute myeloid leukemia (*Abstract S144*) were presented virtually at the 2020 European Hematology Association Annual Congress.

Results presented included data from 39 patients with high-risk MDS who were dosed with magrolimab plus azacitidine.[19] The antibody/hypomethylating agent combination was generally well-tolerated, displaying a safety profile similar to that of azacitidine monotherapy.

Common treatment-related adverse events or adverse events of interest included anemia (44%), infusion reaction (18%), fatigue (18%), neutropenia (8%) and thrombocytopenia (5%). Importantly, no treatment-related febrile neutropenia or discontinuations due to treatment-related adverse events were noted. On-target anemia was typically mild and transient; the priming dose sequence tended to attenuate this effect, with a number of patients requiring fewer red blood cell transfusions. In those patients who were transfusion-dependent, 58 percent achieved transfusion independence.[20]

A total of 30 of the 33 efficacy-evaluable patients (91%) had an objective response. Of these responses, the following level of responses was noted: complete response-42 percent; marrow complete response-24 percent (of these, half also had hematologic improvement); partial response-3 percent; hematologic improvement alone-21 percent; stable disease-9 percent. Importantly, the responses in these patients tended to deepen over time, with a 56 percent complete response rate at a 6-month or longer follow-up.

The investigators concluded that the azacitidine/magrolimab combination was generally well-tolerated and produced durable responses in patients with MDS. Further evaluation of magrolimab is ongoing in the Phase III ENHANCE trial (NCT04313881), where the combination of azacitidine plus magrolimab was being compared with azacitidine plus placebo.[21]

Advances in MDS therapy

There have been no new drugs approved by the US Food and Drug Administration (FDA) for MDS therapy since 2006, and currently available therapies will fail the majority of patients within 2 to 3 years after treatment initiation even if there is initial favorable response. Therefore, new effective agents are greatly needed.[22] One of the challenges of developing such therapies, however, is that targetable constitutively activating kinase mutations are rare in MDS; for many of the new described mutations outlined above, such as those that effect pre-mRNA splicing or transcriptional regulation, it is not immediately obvious how to develop a targeted therapy. This is not just true for MDS: even for mutations that have been well described in various types of cancer for decades, such as mutations in *TP53*, Ras family members, or *MYC*, there are as of yet no FDA-approved targeted therapies, although several are in development.

In addition, the clonal heterogeneity and complexity of the clonal architecture of MDS presents a challenge, as it is often not known which mutations are early initiating events and which are later events of consequence only for a subclone.[23] Finally, in many patients with MDS, there may be a paucity of healthy hematopoietic stem cells to replace disease clones once the latter have been eliminated, so that successful cytoreduction of clonal MDS cells results in prolonged, severe cytopenias. Just as the human aging process is not yet reversible, cumulative damage to marrow hematopoietic elements across the span of an 8- or 9-decade human lifespan may not be repairable without innovations in stem cell therapy.

Future Directions for Research

Summarizing, Garcia-Manero noted, "2020 has been a very eventful year from a regulatory perspective for patients having MDS. One cannot overstate the importance of the approval for the orally dosed ASTX727 combination of cedazuridine plus decitabine. This is the first instance where an orally dosed hypomethylating agent was shown to be equivalent in pharmacokinetic studies to the IV-dosed agent.[24] This will greatly reduce the patient's burden of having to come to a clinic several times a month for dosing."

When asked to speculate on the future for this orally dosed hypomethylating agent combination, Garcia-Manero stated, "I believe a logical next step would be the evaluation of new drug combinations with ASTX727. One logical addition to ASTX727 in this patient population, based on disease biology, might be a BCL-2 inhibitor, such as venetoclax. Another logical addition to ASTX727 might be a monoclonal antibody, such as the CD47-targeting magrolimab," he concluded.[25]

CONCLUSION

This is a particularly exciting time for MDS biological research, but laboratory advances are only just beginning

to be translated into clinical improvements. In addition to the availability of molecular tests to help secure a diagnosis in difficult cases, a better prognostic tool inclusive of mutation status, the Revised IPSS Incorporating Molecular Data (IPSS-RM), is currently being developed. Perhaps more importantly, identification of novel targets for therapy that will help individualize treatment based on disease genotypes is a high priority. However, it seems likely that until a better method is found both to suppress abnormal clones and replace or expand normal hematopoietic elements in elderly patients who have undergone global stem cell attrition from both the effects of aging and disease, MDS will continue to frustrate patients and clinicians alike. MDS, which are hematologic malignancies characterized by ineffective clonal hematopoiesis and a risk for progression to AML, are challenging to treat. Allogeneic transplant is the only curative treatment, and other therapies help only a minority of patients. Progress in the treatment of MDS has been limited during the last decade; however, advances in molecular genomics that have increased our understanding of the pathogenesis of MDS, evolving diagnostic criteria for these malignancies, improved risk stratification tools, and new therapeutic targets have led to the emerging strategies previously described and give hope that outcomes for patients will improve soon.

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