MDS Foundation

The Myelodysplastic Syndromes Foundation, Inc.

Myelodysplastic Syndromes 2023: What's New?

ASH 2023 Friday Satellite Symposium December 8

Summary

The Symposium brought together an international faculty of experts who presented, debated, and discussed recent advances in diagnosis, classification, and management of patients with myelodysplastic syndromes (MDS). This is a summary of the presentations, which highlighted recent data, application of new tools, evidence on current practice, and future directions for optimizing MDS care.

MDS Challenges in 2023

Moshe Mittelman from the Tel-Aviv Sourasky Medical Center, Tel-Aviv University, Israel, outlined some current challenges and unmet needs in MDS.

Professor Mittleman emphasized the need to diagnose patients earlier and identify patients with pre-MDS states at risk for progression. An MDS diagnosis still relies on morphological evidence of dysplasia upon visual examination of bone marrow aspirate and biopsy. However, morphological changes can be subject to inter-observer variance (around 15–25%). A need therefore exists for new diagnostic tools which are more accurate and that are less invasive for patients.

Given the highly heterogeneous nature of MDS, characterized by numerous subtypes, the implementation of classification systems is imperative. However, several different systems for classification exist, in addition to the overlap with acute myeloid leukemia (AML). This can complicate diagnosis and management decisions, so harmonization of these classification systems would be beneficial.

Many challenges remain in the treatment of MDS. For anemia in lower-risk (LR)-MDS, red blood cell transfusions and erythropoietin stimulating agents (ESAs) have been used for decades; more effective and newer strategies are needed. For example, luspatercept could be considered in situations in which ESAs are currently used, use of lenalidomide could be expanded to a broader range of patients, and novel agents may be emerging. Similarly for thrombocytopenia, there is still a lack of effective treatments, with safety concerns halting development of two agents - eltrombopag and romiplostim. For high-risk (HR)-MDS, hypomethylating agents (HMAs) remain the standard first line. However, as only 50% of patients respond to treatment with a response duration of around 2 years, new treatment strategies are needed to overcome these limits. Future treatment directions could include novel agents, reconsidering roles of chemotherapy and stem cell transplant (SCT), and strategies such as chimeric antigen receptor (CAR)-T cell therapy and immunotherapy.

Other challenges in MDS include a need for better understanding of pathophysiology and the inflammatory microenvironment in which MDS arises; recent work is starting to elucidate roles of co-mutations and gene interactions and gene function. There is a need to improve iron chelation and strive for quality-of-life improvements for patients. Financial aspects of treatment are a problem that also needs to be addressed. Finally, the harmonization of guidelines is imperative and necessitates collaborative oversight from the MDS Foundation.

"Many challenges remain in the treatment of MDS."

A Classification of Myelodysplastic Syndromes that Aids Clinical Decision-Making

Mario Cazzola from the Fondazione IRCCS Policlinico San Matteo and University of Pavia, Italy discussed the implications of next-generation sequencing (NGS) on the diagnosis, classification, and prognosis of MDS, using MDS with ring sideroblasts as the main example of how genomic classification can provide further resolution on established morphological classification.

Morphology has some predictive value and has been used as an important diagnostic marker to date. MDS with ring sideroblasts was described over 20 years ago as a distinct entity, with this morphology being a prognostic indicator of a benign condition with a relatively indolent course. However, NGS has revealed various genomic subgroups of MDS with ring sideroblasts, each with distinct clinical outcomes.[1] Most patients (~80%) with ring sideroblasts have an *SF3B1* mutation which is associated with a benign disorder and a low risk of leukemic transformation. However, a minority of

patients also have other mutations such as *SRSF2* which is associated with a poor prognosis, and *TP53* multi-hit mutations which are associated with very poor outcomes. Building upon these results, another study proposed a molecular taxonomy of MDS, after identifying 18 distinct molecular MDS subgroups each associated with distinct clinical presentations and patient outcomes.[2]

In conclusion, genomic profiling allows the identification of MDS molecular subgroups associated with distinct clinical phenotypes and outcomes and developing a classification of MDS based on genomic classes may significantly benefit clinical decision-making.

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PRE-MDS STATES
How to Manage in the Clinic?

Michael R. Savona from the Vanderbilt University School of Medicine, Nashville, Tennessee, USA delivered a detailed presentation about clonal hematopoiesis (CH) as well as describing his group's work on a biorepository and registry for CH.

CH is an over-representation of mature blood cells derived from a single, genetically identical clone. It is an age-associated phenomenon, with 15% of patients over the age of 65 years estimated to have one of two CH conditions: CH of indeterminate potential (CHIP) and clonal cytopenia of undetermined significance (CCUS). CH increases the potential to progress to hematological malignancies and is therefore considered a premalignant state. Dr. Savona highlighted a risk score, called the clonal hematopoiesis risk score (CHRS), which can estimate a patient's risk of progression from CHIP or CCUS to a myeloid malignancy.[1] Available online, the CHRS can aid clinical decision making by identifying those patients who are at highest risk of progression and who may benefit from intensive surveillance and early therapeutic intervention.

Dr. Savona introduced the CHIVE (Clonal Hematopoiesis and Inflammation in the VasculaturE) project: a registry and repository aimed at understanding the

natural history and the genotype-phenotype relationships of CH. Patients with CH, and those at risk for CH, provide sequential blood and bone marrow (when available) samples at normally scheduled visits and are monitored over time for changes. Using guidance from the patterns established from retrospective data, CHIVE investigators monitor patients as 'low risk' or 'high risk' every 12 or 6 months, respectively. Preliminary analysis of around 200 patients found trends towards male sex, older age, and a higher BMI in CH+ patients. Increased risks of chronic kidney disease (CKD) and cardiovascular (CV) endpoints were also seen in CH+ vs CH- patients. Six patients progressed from CH to MDS/AML in 1.5 years follow up, five of whom had either multiple mutations, high-risk mutations or high variant allele frequency (VAF).

The researchers hope to validate and expand risk models through longitudinal follow up of a large, diverse cohort. It is hoped that this project will help to shape care for patients with CH and ultimately lead to guidance for clinical trials.

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DEBATE I
ESA- Still the 1st Line for LR-MDS?

'No' Perspective

Matteo G Della Porta, from the Humanitas Research Hospital, Milan, Italy began by highlighting that severe transfusion-dependent anemia not only negatively affects quality of life, but also reduces the life expectancy of patients with LR-MDS. Therefore, one of the main goals of treatment is to manage anemia and its associated complications. ESAs have historically served as a cornerstone therapy for transfusion-dependent anemia, particularly for patients with low serum erythropoietin (sEPO; <500 U/L) and a red blood cell transfusion requirement of less than 2 red blood cell units per month. In patients with sEPO higher than 500 U/L, the expected response rate to ESAs is less than 10%. Overall, approximately two-thirds of patients either do not respond to ESAs, or relapse within 1 year of treatment, with the majority of these patients then only receiving red blood cell transfusions.
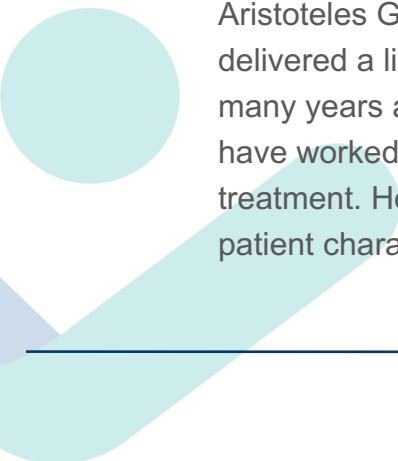
Therefore, there is an urgent need for more effective treatment options for patients with transfusion-dependent anemia after ESA failure.

One such option is luspatercept, approved in 2020 by the US Food and Drug Administration (FDA) for the treatment of anemia in patients with low- to intermediate-risk MDS, who are refractory to or unlikely to respond to an ESA. Luspatercept is a first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models.

Interim results from the ongoing Phase 3, open-label, randomized controlled COMMANDS trial showed the potential of luspatercept as a first-line therapy over epoetin alfa in ESA-naïve patients with transfusion-dependent LR-MDS.[1] The primary endpoint - red blood cell transfusion independence for at least 12 weeks with a concurrent increase in mean hemoglobin of at least 1.5 g/dL (Weeks 1–24) – was reached in 86/147 (59%) patients who received luspatercept versus 48/154 (31%) patients treated with epoetin alfa therapy (p<0.0001). Achievement of the primary endpoint favored luspatercept in patient subgroups stratified according to endogenous sEPO levels (≤200 U/L vs >200–500 U/L), the severity of transfusion dependency (<4 U/8 weeks vs ≥4 U/8 weeks), and *SF3B1* mutational status (mutated vs WT), but did not favor luspatercept in patients without ring sideroblasts. The median duration of red blood cell transfusion independence lasting at least 12 weeks was longer with luspatercept than with epoetin alfa (127 vs 77 weeks). In terms of safety, luspatercept demonstrated a manageable and predictable safety profile, consistent with previous clinical experience and convenient (Q3W) administration.

Luspatercept is the first and only therapy to demonstrate superiority in a head-to-head study against ESAs and is posed to bring a paradigm shift in the treatment of transfusion-dependent anemia in LR-MDS.

'Yes' Perspective

Aristoteles Giagounidis from the Marien Hospital, Düsseldorf, Germany delivered a lively rebuttal noting that ESAs have been used successfully for many years according to the "if it's not broken, don't fix it" principle. If ESAs have worked well for a patient in the past, there is no need to change treatment. He also presented results of the COMMANDS trial, focusing on patient characteristics within the trial.[1]

COMMANDS inclusion criteria stipulated patients must be transfusion dependent with an endogenous EPO level of <500 U/L; however, it has been shown that ESAs are most effective in patients with non-transfusion dependent anemia and an EPO level of <200 U/L.[2] Around 20% of the COMMANDS trial population had sEPO levels of 200–500 IU/L, a range in which ESAs have suboptimal efficacy. When analyzing the trial data, removing patients with endogenous EPO levels in this range and those who were transfusion dependent would increase the response rates for epoetin alfa treatment. In addition, when looking at subgroups in the trail, ring sideroblast-negative patients had a higher response rate to epoetin alfa than luspatercept (46.3% vs 41.0%, respectively). In terms of side-effect profiles, luspatercept had a higher incidence of fatigue, diarrhea, nausea, peripheral edema, dyspnea and hypertension compared with epoetin alfa.

Professor Giagounidis argued that the COMMANDs trial was not reflective of clinical practice, in that most patients with LR-MDS will be diagnosed before they become transfusion dependent and so the treating physician will most often be confronted with a patient suffering from anemia, but not necessarily from transfusion dependent anemia. As long-term exposure to RBC transfusions is associated with adverse outcomes, it is more appropriate to treat patients preemptively with ESAs, before they become transfusion dependent.

Professor Giagounidis concluded ESAs should remain as standard-of-care for patients with LR-MDS who are not transfusion dependent, have an EPO level of <200 U/L or are ring sideroblast–negative.

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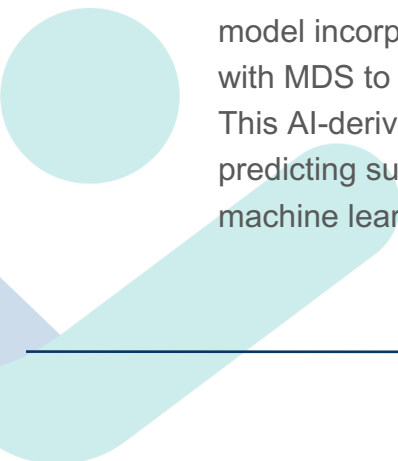2. Fenaux P, et al. *Leukemia.* 2018;32(12):2648–2658.

Artificial Intelligence in MDS Practice

Aziz Nazha, from the Thomas Jefferson University, Philadelphia, PA, USA, and the AI Innovations Institute, Incyte, gave an overview of the current applications of Artificial Intelligence (AI) in the diagnosis and management of MDS. The amount of healthcare data available currently is vast, with the amount of genomic data doubling every 7 months. There is also huge computational power that has drastically reduced in cost in recent years that

could be used to analyze this data with AI. Examples of current AI applications in healthcare include AI-assisted drug design, and FDA-cleared algorithms.

AI-powered models have the potential to improve the accuracy and efficiency of diagnosing MDS, predict disease progression and transformation to AML, and optimize treatment selection.[1–5] One study demonstrated that a machine learning model could identify MDS from other myeloid malignancies with 95% accuracy by analyzing genomic and blood count data from patients.[2] Such diagnostic applications of AI have enormous potential to revolutionize clinical practice.

"Generative AI models can be prone to generating incorrect or inaccurate data which could be especially dangerous in a healthcare setting."

Personalized prediction models for MDS were also mentioned. One such model incorporated both clinical information and genomic data from patients with MDS to predict survival outcomes and risk of disease transformation. This AI-derived model outperformed the IPSS-M calculator in terms of predicting survival and transformation.[3] Other research has leveraged machine learning to analyze genomic biomarkers to predict resistance to

hypomethylating agents (HMAs)[4] and also to assess response to HMAs by analyzing early changes in patients' blood counts.[5]

Turning to generative AI (e.g., ChatGPT), Dr Nazha warned that current generative AI models can be prone to generating incorrect or inaccurate data which could be especially dangerous in a healthcare setting. There is also a substantial carbon footprint and monetary cost associated with the computational power needed to process data. Generative AI does show promise in aiding with writing tasks such as manuscripts or grant proposals. However, more validation work is still needed before clinicians can rely on AI to aid clinical decision making in complex diseases like MDS.

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Can we do Better than HMA Alone in HR-MDS?

Treatment options for patients with HR-MDS include HMAs, AML-like therapy, and SCT. Guillermo Garcia-Manero from the University of Texas MD Anderson Cancer Center, Houston, TX, USA explained that currently, no other treatment has shown superiority over single agent azacitidine in a randomized trial, and SCT is still restricted to fit patients with a suitable donor.

Azacitidine remains the gold standard for treatment of HR-MDS since the landmark study in 2010 demonstrated azacitidine increased overall survival (OS) compared with conventional care (median OS [mOS] of 24.5 months vs 15.0 months, respectively).[1] Since then, our understanding of the genetic landscape of MDS has evolved. This has led to refinements in prognostic scoring systems, from the IPSS, to the IPSS-R, to now the IPSS-M that combines genomic profiling with hematologic and cytogenetic parameters. But this now poses a shift in risk stratification of patients; a patient who would have previously been classified as lower risk may now be classified as high-risk based on genomic testing. This in turn leads to re-evaluation in assessment of treatment approaches. How do we integrate traditional low-risk

disease classification with the new understanding of the high-risk paradigm, and how should this be reflected in treatment regimens?

Oral HMAs represent a transformative advancement for patients, as they will no longer be required to receive frequent injections. Professor Garcia-Manero discussed the development of oral HMAs highlighting an oral azacitidine compound (CC-486)[2] and a combination of decitabine and cedazuridine (ASTX727) which was approved by the FDA in 2020 for the treatment of MDS.[3] The Phase 3 study of decitabine/cedazuridine – ASCERTAIN – demonstrated pharmacokinetic equivalence to parenteral decitabine, encouraging activity with a complete response (CR) rate of 22%, and a consistent safety profile. Interestingly, a retrospective analysis of ASCERTAIN also revealed that 44/125 patients had *TP53* mutations.[4] As expected, leukemia-free survival and OS were longer in patients with *TP53-wt* (31.7 and 33.7 months, respectively) compared with *TP53-mut* (22.1 and 25.5 months, respectively). What was surprising though was the prolonged leukemia-free survival and OS in these patients with *TP53-mut* compared with historical results where expected OS is less than 1 year.

Professor Garcia-Manero highlighted the investigational agent guadecitabine which failed to meet the primary endpoint of OS in a Phase 3 clinical trial (ASTRAL-3). However, when looking at OS by *TP-53* mutational status, mOS was 32.5 months in patients with *TP53-wt* (11.1 months in *TP53-mut*) which is longer than with current HMAs. This underscores the need for futures trial designs to take molecular heterogeneity into consideration and incorporate the IPSS-M so that patients can be treated according to the molecular features of their MDS.

Turning to doublet approaches for the treatment of HR-MDS, Professor Garcia-Manero discussed the promising trials exploring HMAs in combination with BCL2 inhibitor venetoclax. These included the studies performed by his group at the MD Anderson Cancer Center (MDACC) such as the Phase 1 study of IV/SC azacitidine combined with venetoclax[5] and the Phase 1/2 study of oral decitabine/cedazuridine in combination with venetoclax.[6] Nevertheless, results from the Phase 3 VERONA trial are eagerly anticipated.[7] If the trial is positive, the combination of venetoclax with azacitidine is expected to replace single-agent azacitidine.

Finally, Professor Garcia-Manero described how SCT is taking a more prominent role in the treatment of HR-MDS and outlined the MDACC

treatment approach to front-line treatment of HR-MDS, as seen in the table below.

Age	Risk	Treatment	SCT
Younger	Standard	HMA / AML-like / clinical trial	Yes
Younger	Favorable (i.e., *NPM1*)	HMA / AML-like / clinical trial	Yes
Younger	Adverse (i.e., *TP53*)	HMA / clinical trial	Individualize
Older	Standard	HMA / clinical trial	Individualize
Older	Favorable (i.e., *NPM1*)	HMA / AML-like / clinical trial	Individualize
Older	Adverse (i.e., *TP53*)	HMA / clinical trial	Individualize
Targetable lesion (*IDH1, IDH2, Flt-3, ASXL1*)		HMA / targeted therapy / venetoclax / clinical trial	Individualize

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DEBATE II
Should Cytoreduction Precede Transplant?

YES…IF…

Uwe Platzbecker from the University Hospital Leipzig, Leipzig, Germany started by noting that the value of treating patients with HMA or chemotherapy before allogeneic transplantation has not been directly studied in randomized clinical trials and is instead supported by indirect evidence. Two recent clinical trials in the US[1] and Germany (VidazaAllo Study)[2] support that transplant is superior to current standard of care (mainly azacitidine) in patients with HR-MDS.

The aim behind lowering bone marrow blast count prior to transplantation is to reduce disease burden. According to current prognostic models, while

disease status and blast count at transplant are important, cytogenetics provide additional prognostic value for a given patient. Looking at the IPSS-R, SCT would not be considered for patients in the very low or low groups, while for the intermediate risk group, information about molecular abnormalities would be needed to define the patient pathway. However, for patients with high and very high IPSS-R/IPSS-M risk scores, transplantation is warranted because those patients only have a mOS of 1.6 and 0.8 years respectively with supportive care. In these cases, cytoreduction should be considered as bridging therapy. European Leukemia Net (ELN) guidelines also suggest considering cytoreductive therapy in cases where patients have ≥10% bone marrow blasts before proceeding to transplant.[3]

"The aim behind lowering bone marrow blast count prior to transplantation is to reduce disease burden."

Cytoreduction aims to reduce disease burden, however it can also accelerate disease biology and cause short-term toxicity. Cytoreduction with HMAs alone (azacitidine or decitabine) can give a CR/complete response with incomplete hematological recovery (CRi) rate of 20–30%, although no biomarkers exist that can predict the response. In the VidazaAllo trial of 4–6 cycles of azacitidine prior to SCT in patients with higher-risk MDS, nearly a third of the trial population did not make it to transplant after starting bridging treatment with azacitidine.[2]

Retrospective data shows patients receiving upfront SCT are generally younger with a less advanced disease stage.[4] Another retrospective study suggests no difference in outcomes between azacitidine and induction chemotherapy therapy prior to transplant.[5] However, a recent Phase 1 trial of azacitidine plus venetoclax prior to transplant in treatment-naive patients with

HR-MDS demonstrated a CR rate of 41% and a composite response rate (marrow CR with hematologic improvement) of 30.4%.[6]

To conclude, Dr. Platzbecker predicted that in future, it is likely that the question will not be *if* patients should receive therapy before transplant, but rather which patients should receive it and for how long. For the moment, fast track SCT is advisable for vulnerable patients and for those with high-risk features such as *TP53* mutations.

NOT ROUTINELY

Christopher Gibson from the Dana Farber Cancer Institute, Boston, MA, USA argued that routine cytoreduction before transplant is not supported by current evidence. Broadly speaking, there are no data to show that cytoreduction before transplant improves outcomes for high-risk transplant patients. There are no prospective randomized controlled trials (RCTs) that address this question. Retrospective studies have generally shown equivalent survival between patients who received HMAs or intensive induction chemotherapy before transplant compared with those who went straight to transplant. However, it was noted that these retrospective studies do not all look at equivalent groups, and it should be considered that patients who received cytoreduction may be at a higher risk upfront, and some studies have included both secondary AML and MDS. Furthermore, MDS is a heterogeneous disease, and in these retrospective studies, subgroups were not analyzed separately.

Dr. Gibson argued that 'effective' cytoreduction may not improve outcomes either. A molecular analysis of the CTN 1102 study evaluated the impact of MDS genetics on the benefit of SCT and demonstrated that SCT improved OS in patients with *TP53* mutations, irrespective of pre-transplant *TP53* allelic status.[7] In addition to arguing that cytoreduction is ineffective, Dr. Gibson highlighted the potential risks of delaying transplant, highlighting that patients may become ineligible for transplant while they are receiving cytoreductive therapy. As mentioned in the 'yes' argument, there was a high drop-out rate in the VidazaAllo trial before transplant, predominantly due to progressive disease and death from infectious complications.[2]

Dr Gibson caveated his 'no' argument by presenting the situations in his own practice in which he does cytoreduce. Disease trajectory makes a difference as to whether patients should be cytoreduced before transplant:

Does not Cytoreduce:

- MDS with <5% blasts
- Borderline transplant candidates (those with one shot at curative therapy, to avoid the possibility of them becoming ineligible and losing that chance)

Nearly always Cytoreduces:

- MDS with 10–20% blasts
- MDS with rapidly increasing blast counts (or other evidence of incipient transformation)

Sometimes Cytoreduces:

- MDS with 5–10% blasts – depends on trajectory and scenario
- 2–3 cycles maximum, if possible

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