Myelodysplastic Syndromes 2023: What's New?

ASH 2023 Friday Satellite Symposium, December 8
Patient summary

The Symposium brought together an international faculty of experts who presented, debated, and discussed recent advances in myelodysplastic syndromes (MDS). This summary describes the presentations, highlighting current challenges, new developments, as well as potential future approaches to improve the diagnosis and treatment of MDS.

Summaries of the presentations

MDS challenges in 2023

Moshe Mittelman from the Tel-Aviv Sourasky Medical Center, Tel-Aviv University, Israel, outlined some of the current challenges and unmet medical needs in MDS. The diagnosis of MDS still relies on bone marrow tests and a need exists for new diagnostic tools which are less invasive and more accurate. It is also important to try and diagnose patients earlier and identify those patients with pre-MDS states who are at risk for progression. Currently there are several different systems that can be used to classify MDS. This can complicate diagnosis and management decisions and so it may be beneficial if the current classification systems were combined into one system.

Many challenges remain in the treatment of MDS. For lower-risk (LR)-MDS, red blood cell transfusions and erythropoietin stimulating agents (ESAs) have been used to treat anemia for many decades; more effective and newer agents are needed. Similarly for thrombocytopenia, safe and effective treatments are needed. For higher-risk (HR)-MDS, hypomethylating agents (HMAs) remain the standard initial treatment. However, as only half of patients respond to treatment, with most patients losing response within 2 years, newer treatment strategies need to be investigated to improve outcomes for patients.

A classification of myelodysplastic syndromes that aids clinical decision making

Next-generation sequencing (NGS) is a powerful technology that can capture a large amount of genomic information about a cancer. Mario Cazzola from the Fondazione IRCCS Policlinico San Matteo and University of Pavia, Italy discussed the implications of NGS on the diagnosis, classification, and prognosis of MDS. Focusing on a type of MDS called MDS with ring sideroblasts, NGS has revealed different subgroups within this type of MDS, depending on which gene is mutated. This is relevant because some gene mutations (e.g. *SRSF2* and *TP53*) are associated with poor prognosis, whereas others (e.g. *SF3B1*) are associated with a better prognosis. Therefore, developing a classification of MDS based on the different genomic subtypes may significantly help clinical decision-making.

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), which is a common aging-associated condition that may evolve over time to MDS and other blood cancers. He also described the CHIVE (**C**lonal **H**ematopoiesis and **I**nflammation in the **V**asculatur**E**) project which is a registry and repository aimed at understanding the natural history of CH. Patients with CH, or those at risk for CH, provide blood and tissue samples at scheduled visits and are monitored over time for any changes. As well as increasing understanding of CH, it is hoped that this project will help to shape care for patients with CH and ultimately lead to guidance for clinical trials.

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 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. Two-thirds of patients either don't experience a response to ESAs or relapse, so there is an urgent need for a more effective treatment option. One such option is luspatercept which was 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 had failed to respond to an ESA. Luspatercept is an erythroid maturation agent and works differently than ESAs. Interim results from an ongoing clinical trial called COMMANDS showed that luspatercept was better than ESAs when used as first-line treatment for patients with transfusion-dependent LR-MDS. Treatment with luspatercept resulted in significant improvements in red blood cell transfusion independence and hemoglobin increase (the trial primary endpoint), and improvements in the duration of response compared with ESA.

Yes perspective

Aristoteles Giagounidis from the Marien Hospital, Düsseldorf, Germany delivered a lively rebuttal, also presenting the result of the COMMANDS trial, but focusing on the characteristics of the patients who were included in the trial. The inclusion criteria of the COMMANDS trial stipulated that patients had to be transfusion dependent and have an endogenous erythropoietin (EPO) level of <500 U/L. However, most patients with LR-MDS will be diagnosed before they become transfusion dependent. In addition, it is known that ESAs work best in patients with non-transfusion dependent anemia and an EPO level of <200 U/L. When looking at subgroups in the COMMANDS trial, ESAs were more effective at achieving the primary endpoint in one subgroup of patients: those who had ring sideroblast–negative status. Therefore, ESA should remain as standard-of-care for LR-MDS in patients who are not transfusion dependent, have an EPO level of <200 U/L and ring sideroblast–negative.

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. AI-powered models can improve the accuracy and efficiency of diagnosing MDS, are able to predict disease progression and transformation to acute myeloid leukemia (AML), and also optimize treatment selection. Looking to the future, generative AI (e.g. ChatGPT) has the potential to revolutionize MDS and cancer research.

Can we do better than HMA alone in HR-MDS?

Treatment options for patients with HR-MDS include HMAs, AML-like therapies and stem cell transplantation (SCT). Guillermo Garcia-Manero from the University of Texas MD Anderson Cancer Center, Houston, TX, USA explained that no other treatment has been shown to be superior to single agent azacitidine in a randomized clinical trial and SCT is still restricted to fit patients with a suitable donor.

New classifications and molecular data are helping to understand different subsets of patients. As a consequence, the definition of HR-MDS is evolving. For example, a patient who would have previously been classified as lower risk, may now be classified as high-risk based on molecular testing results. The implications on how this affects treatment decisions remains unclear.

HMAs, including decitabine or azacitidine, are recommended as standard-of-care treatment for patients with HR-MDS. Until a few years ago, the only option was to give HMAs by intravenous (IV) or subcutaneous (SC) infusion which caused a significant burden on patients. In 2020, an oral form of

HMA - a combination of decitabine and cedazuridine – was approved by the FDA for the treatment of MDS, therefore reducing the need for patients to visit the clinic so frequently. HMAs in combination with another treatment (also referred to as 'doublets') are currently being investigated in clinical trials. Notably, the Phase 3 VERONA trial is investigating the combination of azacitidine and venetoclax and the results are eagerly anticipated in 2024.

Debate II: Should cytoreduction precede transplant?

Yes…if…

Uwe Platzbecker from the University Hospital Leipzig, Leipzig, Germany highlighted that the value of treating patients with HMA or chemotherapy before allogeneic transplantation is not clear and has not been studied in randomized clinical trials. Retrospective analyses have shown that treatment with a HMA before transplant improves outcomes in patients who are in complete remission compared with patients who have active disease at the time of transplant. However, HMA and induction chemotherapy can also cause short-term toxicity and many patients with MDS tend to have a delayed recovery of their blood counts. This leaves the question of when and how to 'bridge' to transplant. New combination therapies, such as azacitidine and venetoclax, may pave the way for new, effective treatments before transplant.

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 and can sometimes be counterproductive. There are no data to show that cytoreduction before transplant improves patient outcomes. In addition, there is a risk that patients become ineligible for transplant while they are receiving cytoreductive treatment due to disease progression to AML or adverse effects such as infections.

Dr Gibson concluded his presentation by summarizing what he does in clinical practice:

- **Does not cytoreduce** in patients with <5% blasts or in patients who are borderline transplant candidates.
- **Nearly always cytoreduces** patients with rapidly increasing blast counts, or patients with 10–20% blast counts.
- **Sometimes cytoreduces** patients with 5–10% blast counts depending on the disease trajectory and clinical scenario.