Treatment Options in Myelodysplastic Neoplasms

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Disclosures

- Nothing to disclose

Learning Objectives

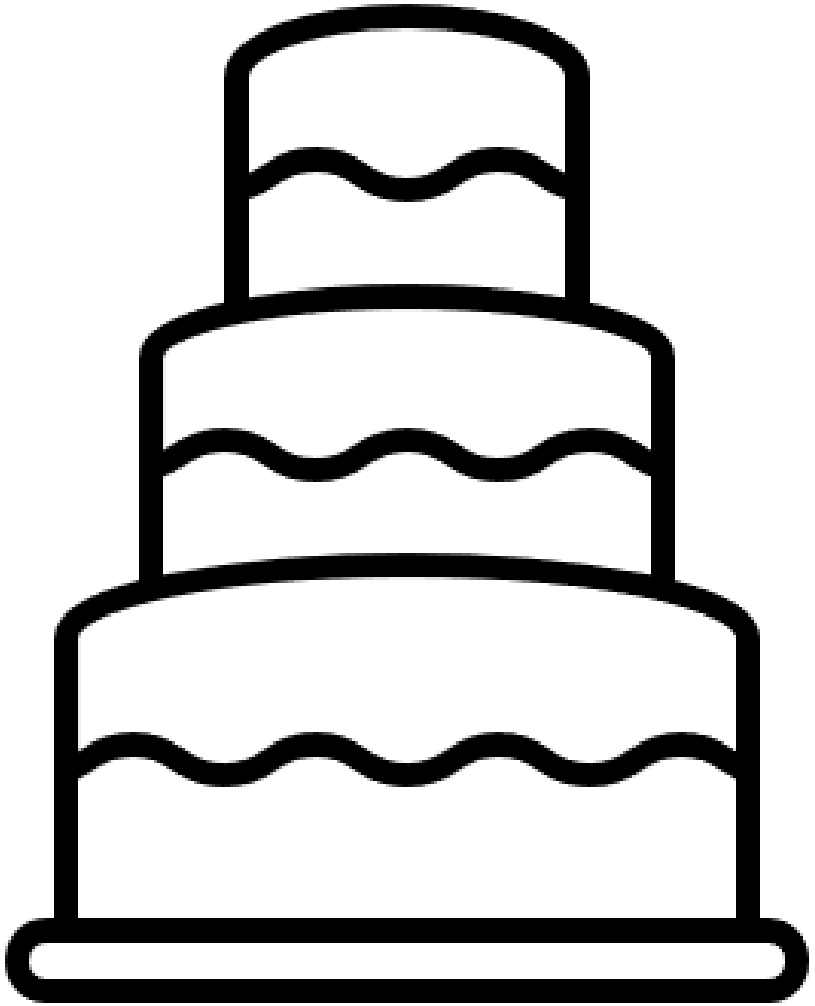
- To review recent updates to MDS classification and prognostic scoring systems
- To discuss emerging treatment strategies that include currently available therapies
- To discuss novel treatments currently in development for patients with MDS

MDS Classification and Prognostic Scoring Systems

WHO Classification 2022

- International, multidisciplinary experts who develop holistic guidelines on patient management from diagnosis through disease monitoring.
  - Myelodysplastic Syndromes (MDS) is now officially Myelodysplastic Neoplasms (MDS)
  - Types of MDS are now categorized based either on how the bone marrow looks (**morphology**) or whether there are specific mutations present (**genetic**)

The Bone Marrow Biopsy = Three Layer Cake



Layer 1 – What do we see? How healthy do the cells look? Do we see **dysplasia**? Are there blasts present?

Layer 2 – Are there any chromosome changes? Chromosomes are the "containers" for your genes.

Layer 3 – Are there any mutations in the DNA of your MDS blood cells?

Classification of MDS

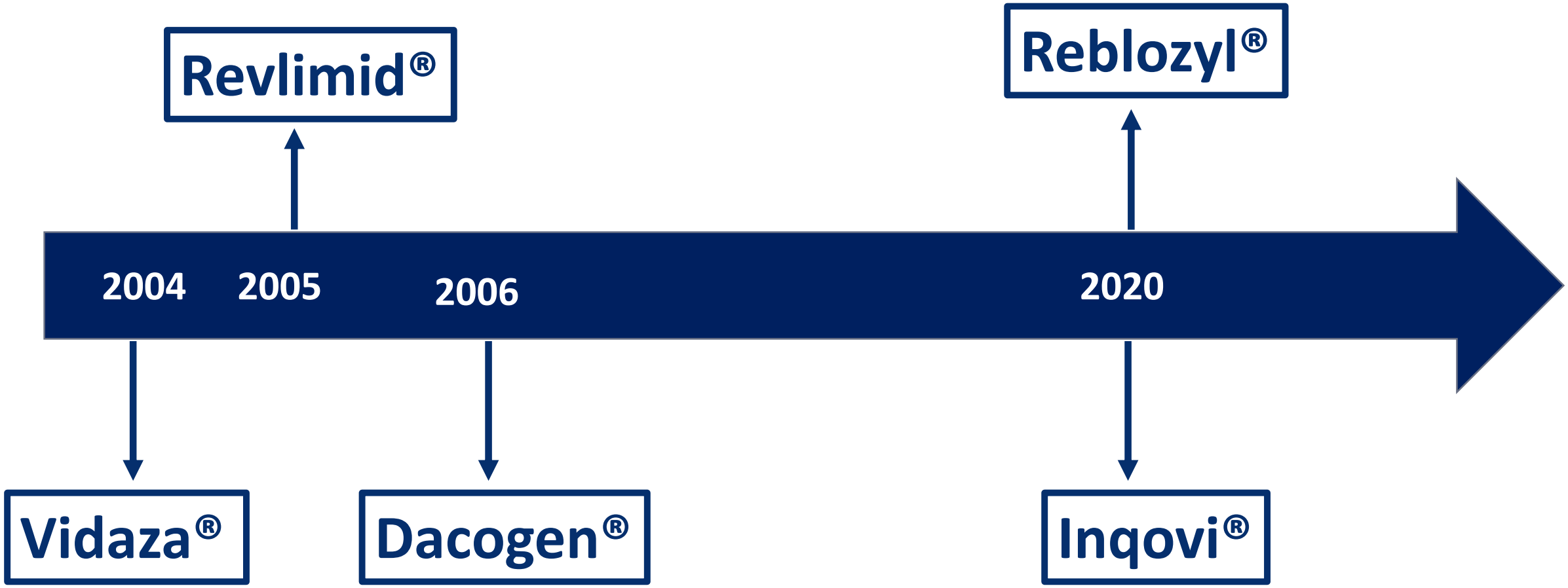
- **MDS with defining genetic abnormalities**
  - MDS with low blasts and isolated 5q deletion (MDS-5q)
  - MDS with low blasts and *SF3B1* mutation (MDS-*SF3B1*)
  - MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)
- **MDS, morphologically defined**
  - MDS with low blasts (MDS-LB)
  - MDS, hypoplastic (MDS-h)
  - MDS with increased blasts (MDS-IB)

MDS Prognostic Scoring Systems

- In general help to determine both the overall prognosis for a patient and treatment recommendations
  - IPSS (1st)
  - IPSS-R (2nd)
  - **IPSS-M** (3rd)
    - Incorporates mutation results (3rd layer)
    - Better than the IPSS-R at determining overall survival as well as the time to the development of leukemia

Emerging Treatment Strategies with Currently Approved Therapies

MDS FDA Drug Approvals



Reblozyl® (luspatercept) → Anemia

- Currently recommended for patients with low risk MDS and ringed sideroblasts in the bone marrow (**1st layer**) who are no longer responding to erythropoietin injections
- Recent data now shows that **there is additional benefit for a broader category of patients** with low risk MDS, decreasing the need for transfusion[1]

1. Platzbecker U, et al. Abstract 459. ASH Annual Meeting. 2022

Revlimid® (Lenalidomide) → Anemia

- Currently recommended for patients with low risk MDS with or without a deletion of chromosome 5 **once there is a need for RBC transfusion**
- A recent study randomized patients with low risk MDS to either placebo or Revlimid 5mg daily **prior to the patient needing RBC transfusions[2]**
  - **Could starting Revlimid sooner delay the time to needing regular transfusions?**

2. Cadenas et al. Abstract 460. ASH Annual Meeting. 2022

Revlimid® (Lenalidomide) → Anemia

- **54 patients enrolled in the trial**
  - No difference in survival between the 2 groups
  - Patients who received Revlimid remained free from needing transfusions for 66.3 months while those who received the placebo needed to start on transfusions in 11.6 months
  - 70% of the patients who received Revlimid improved their anemia
  - There wasn't a higher risk for transformation to AML in those who received Revlimid
  - There wasn't a higher risk for acquiring new mutations in those who received Revlimid

Venetoclax

Venclexta® (Venetoclax)

- Approved for the treatment of acute myeloid leukemia in combination with Vidaza, Dacogen or low dose cytarabine
- Complete remission was achieved in 66.4% of patients with newly diagnosed AML who had never been treated compared to only 28.3% in patients who received Vidaza alone.[3]
- Venetoclax + Vidaza is a new standard of care for patients with newly diagnosed AML who aren't eligible for more intensive chemotherapy

3. Dinardo et al. NEJM.2020;383:617-629.

Venclexta® (Venetoclax)

- Given the similarities between AML and MDS (both can have low blood counts and both can have an increased number of blast cells in the bone marrow) venetoclax is being studied in MDS
- In patients who have been treated with vidaza and then venetoclax is added, the overall response rates have been variable
- In 57 patients with untreated MDS, a small trial has shown an overall response rate of 77% with a complete remission rate of 42%[5]

5. Garcia et al. Abstract 656. ASH Annual Meeting 2020.

Venclexta® (Venetoclax)

- The **VERONA** trial is a randomized double-blind phase 3 trial for patients with high risk MDS who will receive Vidaza alone OR combined with Venetoclax
- The study opened in September 2020 and is estimated to be complete in February 2025

Ivosidenib and Enasidenib

Tibsovo® (Ivosidenib)

- FDA approved for patients with AML and an *IDH1* mutation (3rd layer)
- *IDH1* mutations are **not** a common mutation in MDS (3%)
- In 16 patients with previously treated MDS and an *IDH1* mutation, the overall response rate was 81%[4]
  - 44% achieved a complete remission
  - 69% had improvement in blood counts

5. Sallman et al. Abstract 7053. ASCO Annual meeting 2022

Idhifa® (Enasidenib)

- FDA approved for patients with AML and an *IDH2* mutation (3rd layer)
- *IDH2* mutations are **not** a common mutation in MDS (5%)
- In 27 patients with newly diagnosed MDS who received enasidenib and Vidaza, the overall response rate was 74% and complete remission rate of 26%[6]
- In 23 patients with MDS who had been treated with other agents, enasidenib alone led to an overall response rate of 35% and complete remission rate of 22%[6]

6. Dinardo C, et al. Blood Advances. August 2022.

Novel Therapies in Development

Clinical Trials at Moffitt Cancer Center

- **Low Risk MDS**
  - MCC 19635 LB-100 for low or intermediate risk MDS
    - LB-100 is a protein phosphatase 2A inhibitor
  - MCC 20552 Canakinumab + Aranesp for low risk MDS after ESA failure
    - Canakinumab inhibits interleukin-1 beta
  - MCC 21142 Open-label Platform Study of Select Drug Combinations in lower risk MDS
  - MCC 21405 Luspatercept for anemia in lower risk MDS
- **High Risk MDS**
  - MCC 19658 Phase I of SX-682 in patients with MDS and disease progression
    - Inhibits CXCR1 and CXCR2 receptors
  - MCC 20838 AG120 in patients with and *IDH1* mutation