MYELODYSPLASTIC NEOPLASMS (MDS)

MDS FOUNDATION FAMILY FORUM

Cecilia Arana Yi, MD, MSHS, FACP
Senior Associate Consultant
Director of Leukemia Services Mayo Clinic Arizona
Assistant Professor Mayo Clinic Alix School of Medicine
Quote of the Day

“Difficult roads can lead to beautiful destinations”

Kia Wynn
Survivor
OUTLINE

• Introduction to MDS
• Diagnosis and risk stratification
• Treatment of lower risk MDS and higher risk MDS
• Survivorship
• Future Directions/Challenges
DEFINITION-MDS

• Group of blood cancers in which the bone marrow does not produce healthy blood cells.

• Clonal disease: Mutations drive and shape MDS

• Risk for transformation to acute leukemia
MDS INCIDENCE PER AGE

Risk factors:
- Male gender
- Obesity
- Smoking
- Prior RT/CT
- De novo
- Secondary or t-MDS

Incidence of MDS per 100,000 persons

Median age: 70 years

Redrawn from Ma X. Am J Med 2012; Zeidan Blood Reviews 2019
MDS CASE: ANEMIA

- Mr. H is 70 yo male with worsening anemia and thrombocytopenia over the past year.
- He feels tired, dizzy, and noted bruises in arms
WHAT HAPPENS IN MDS?
FROM CLONAL HEMATOPOIESIS TO MDS

A. Clonal Hematopoiesis

- HSCs = disease-initiating cells in lower-risk MDS
- Progenitors = disease-initiating cells in high-risk MDS
- Mature myeloid cells

B. Low-risk MDS

- Normal Maturation
- Cytopenias

C. High-risk MDS/sAML

- LSCs
- Non-LSC blasts
- Cytopenias and transformation to sAML

MDS arises from the step-wise accumulation of mutations in HSCs:

- Acquired early mutations, e.g. DMNT3a
- Acquired additional mutations, e.g. U2AF1
- Acquired additional mutations, e.g. FLT3 or NRAS

Zhan D, Park C. Front Aging 2021
DIAGNOSTIC APPROACH
MDS DIAGNOSTIC APPROACH

• H & P: Family or personal history of cancer

• Persistent/Progressive cytopenia

• Not explained by other causes: Chronic blood loss, autoimmunity, infections
MDS WORK UP

- Laboratory studies: CBC diff, LDH, peripheral smear, reticulocyte counts
- Iron studies, B12, folate
- Thyroid function
- HIV, Hepatitis serology, ANA
- Bone marrow biopsy:
  - Morphology, chromosome analysis, FISH, molecular studies
- Genetic studies for inherited MDS
RISK STRATIFICATION
IPSS-R GUIDED TREATMENT: LOW VS. HIGH RISK

PROS
• Predictive and prognostic

CONS
• Does not consider other factors: transfusion dependence, molecular status, comorbidities
• Not predictive of outcomes in IR-MDS

− Blast
− Cytopenia
− Cytogenetics

↓ Time to AML

↓ OS

OS

\[ Y, \text{del}(11q) \]

MDS-RS + SF3B1mut

↓ OS

Clinical variables
Ferritin >1000ng/ml
EPO>300Ul/l

Patient-related variables
Elderly
ECOG >1
Comorbidities

Gene mutation
TP53,
SRSF2,
ASXL1,
SETBP1

Cytogenic abnormalities
Chr7, Chr3
and
Complex Karyotype (≥3)

IPSS: Intermediate-2/High-risk
IPSS-R: >3.5 score
WPSS: High/Very High Risk
MDASS: Intermediate-2/High Risk

Redrawn from Benton et al AJH 2018, Chen-Liang TH J Clin Med 2021
**IPSS-M:**

- Variables: Blood counts, blasts, CG, gene mutations

Redrawn from https://mds-risk-model.com
Bernard. NEJM 2022
MDS CASE

• Bone marrow biopsy: MDS-ring sideroblasts
• Cytogenetics: Normal
• Molecular studies: SF3B1
• IPSS-M Category: Very Low Risk
• Treatment?

Tefferi A, AJH 2021
TREATMENT
TREATMENT PRINCIPLES

- Risk Oriented Treatment → IPSS-R, IPSS-M
- Chemotherapy only? → Growth factors, immunotherapy, clinical trials
- Goals: Survival, quality of life → Outcomes, transfusion independence, PRO
- Transplant cures MDS → Transplant modalities, supportive care
LOW-RISK MDS
Watchful waiting

Treatment of anemia/thrombocytopenia: PRBC, ESA, luspatercept, platelets

ESA: EPO or DAR for LR-MDS without 5q, EPO <500

Multiple cytopenia/Hypoplastic MDS: ATGAM, HMA
LOW RISK MDS

Epo <200mU/mL, <2 U RBC/month

- ESA
  - Non-del (5q)
    - LEN/ESA
    - AZA

Del (5q) Iso or +1

- Lenalidomide
  - MDS-RS
    - Luspatercept

Epo >200mU/mL, ≥2 U RBC/month

- Age
  - >60
    - SF3B1
      - MDS>24m
    - Non-del(5q) pathway
  - Age ≤ 60
    - No SGM or SF3B1
      - HLA-DR15+, +8
    - IST

Redrawn from Volpe et al, Clin Lymphoma, Myeloma and Leukemia 2021
NOVEL THERAPEUTIC AGENTS IN LR-MDS

Redrawn from Santini V. Hemato 2022
LUSPATERCEPT IN MDS (MEDALIST)

- Phase 2 (PACE-MDS)
- Phase 3 (MEDALIST)

Redrawn from Fenaux, NEJM 2020
IMETELSTAT

- Telomerase inhibitor
- >50% reduction hTERT expression and decrease of SF3B1 mutational burden
- Response duration >1 year
- Phase III randomized trial results pending
INFLAMMATION IN MDS

- Inflammation shapes MDS

- Agents:
  1. Canakinumab: mAb IL-1β
  2. R289 IRAK1/4 inhibitor

- Studies in LR MDS, alone and in combination
SEQUENTIAL LR-MDS TREATMENT?

- ESA
- IMETELSTAT
- LUSPATERCEPT: RA-RS
- LENALIDOMIDE in 5q-

Canakinumab, IRAK1/4 combinations
MDS CASE TREATMENT TIMELINE

12/2021
Dx: MDS
Hb: 7.8 g/dl

06/2022
EPO
Hb: 8.5 g/dl

06/2022-Present
Luspatercept
Hb: 9 g/dl

transfusion

Hb: 7.5 g/dl
HIGH RISK MDS
MANAGEMENT OF HIGH RISK MDS

- **HSCT candidate**
  - **Blasts > 10%**
    - yes: HMA or induction chemo to decrease blasts < 5%
    - no: Proceed with HSCT
  - no: HMA
    - HMA failure: Clinical trial
      - Targeted therapy
        - Venetoclax
      - Chemotherapy

Redrawn from Volpe V. Clin Lymphoma and Leukemia 2022
THERAPEUTIC OPTIONS IN HR-MDS

- HMA
- Targeted Therapies
- Immunotherapy

Redrawn from Platzbecker U. Blood 2019
HMA IN MDS

• Phase III AZA-MDS-001 mOS:24m
• Phase III DAC ORR 17% m DOR 10.3m
• Real-World data: 10-17m only?

**ORAL DECITABINE IN MDS**

- Phase II Study in I-HR-MDS
- Equivalent to IV DAC

---

**Product-Limit Survival Estimates**

*With Number of Subjects at Risk*

- Sequence A
  - Days: 0, 200, 400, 600, 800
  - Subjects: 41, 39, 80, 33, 17
- Sequence B
  - Days: 0, 200, 400, 600, 800
  - Subjects: 33, 31, 64, 40, 7
- Total
  - Days: 0, 200, 400, 600, 800
  - Subjects: 74, 70, 144, 73, 24

---

**DNA demethylation: ≤1% difference**

**Efficacy: clinical response**

- Complete response: 21%
- Clinical response: 60% (n=48)

**Safety: most common grade ≥3 AEs (regardless of causality)**

- Neutropenia: 46%
- Thrombocytopenia: 38%
- Febrile neutropenia: 29%

---

Redrawn from Garcia Manero et al., Blood 2020
HMA AND VENETOCLAX

- BCL2 overexpressed in leukemia stem cells
- ORR 77% (TN) and 40% (R/R)
- High rate of marrow remission (59%), HI (41%), and HSCT (62%)

mOS = 19.5m
RFS = 15.4m

IMMUNOTHERAPY/CELL THERAPY
MAGROLIMAB

- Macrophage immune-checkpoint inhibitor, allows immune system evasion by cancer cells
- Phase 1b N=95, MDS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All (N=95*)</th>
<th>TP53-wt MDS (N=61)</th>
<th>TP53-mut MDS (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate, %</td>
<td>75</td>
<td>79</td>
<td>68</td>
</tr>
<tr>
<td>CR, % (95% CI)</td>
<td>33 (23, 43)</td>
<td>31 (20, 44)</td>
<td>40 (21, 61)</td>
</tr>
<tr>
<td>Marrow CR, %</td>
<td>32</td>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>SD w/Hi, %</td>
<td>11</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>DCR, median (95% CI) mos</td>
<td>11.1 (7.6, 13.4)</td>
<td>12.9 (8.0, NR)</td>
<td>7.6 (3.1, 13.4)</td>
</tr>
<tr>
<td>Marrow CR with Hi/Any Hi, %</td>
<td>17/59</td>
<td>20/61</td>
<td>12/56</td>
</tr>
<tr>
<td>Converted to RBC transfusion independence, %</td>
<td>14</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>PFS, median (95% CI) mos</td>
<td>11.6 (9.0, 14.0)</td>
<td>11.8 (8.8, 16.6)</td>
<td>11.0 (6.3, 12.8)</td>
</tr>
<tr>
<td>OS, median (95% CI) mos</td>
<td>NR (16.3, NR)</td>
<td>NR (21.3, NR)</td>
<td>16.3 (10.8, NR)</td>
</tr>
</tbody>
</table>

Redrawn from Sallman D, JCO 2022
CAR T Cells: Mechanism of Action

- **T cell**
  - Viral DNA Insertion
  - Expression of CAR

- **Tumor cell**
  - CAR enables T cell to recognize tumor cell antigen
  - CAR T cells multiply and release cytokines
  - Tumor cell apoptosis
  - Antigen
CAR T CELL THERAPY

• Ideal antigen in MDS?

• Potential targets:
  • Natural Killer group 2D NKG2D
  • CD123

Redrawn from Kapoor S, Cancers 2021
HR-MDS TREATMENT SUMMARY

- HSCT eligibility at diagnosis
- Age <60, no HR mutations, IC
- HR mutations, transplant ineligible: HMA based chemo
- Cell Therapy in R/R

Clinical trials: Triplets, doublets?
HIGH RISK MDS TREATMENT ASPECTS

- Communication with Hematology/BMT team
- Survivorship care plan
- Complications post transplant: GVHD, infections
- IST side effects
- Transfusion aspects
- Palliative Care/End of Life
SURVIVORSHIP
MDS SURVIVORSHIP

• “An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life”

Redrawn from NCI, 2019; Garcia-Manero G, AJH 2021
STANDARDS OF SURVIVORSHIP CARE

- Cancer recurrence
- Long term effects
- Prevention and detection of late effects of cancer
- Management of cancer related symptoms
- Coordination of care

- Survivorship Care Plan
- Survivorship Clinics
- Physician led
- Nurse led
- Group vs Individual counseling
CONCLUSIONS

• Heterogenous group of disorders with variable prognosis

• Molecular studies are key in prognosis and treatment options

• Novel treatments improve outcomes.

• Goals: Improving quality of live and survival.
QUESTIONS & DISCUSSION