MDS/MPN: What it is and How it Should be Treated?

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MDS Foundation Patient & Family Forum: August 10, 2019
Features of Myelodysplastic Syndrome (MDS) and Myeloproliferative Neoplasm (MPN)

**MDS**
- Ineffective blood making
- Low Blood Counts (anemia most common)
- Abnormal blood cell morphology (dysplasia)

**MPN**
- “Super”-effective blood making
- Increased Blood Counts
- Constitutional Symptoms
- Increased spleen size
2016 WHO Classification Scheme for Myeloid Neoplasms

Acute
- Acute Myeloid Leukemia
  - Myelodysplastic Syndrome
    - MDS/MPN Overlap
      - Myeloproliferative Neoplasms
        - Chronic Myelomonocytic Leukemia (CMML)
        - Atypical Chronic Myeloid Leukemia (aCML)
        - Juvenile Myelomonocytic Leukemia (JMML)
        - MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
        - MDS/MPN unclassifiable (MDS/MPN-U)

Chronic
- Chronic Myeloid Leukemia
  - Polycythemia Vera
  - Essential Thrombocythemia
  - Primary Myelofibrosis
  - Chronic Neutrophilic Leukemia
  - Chronic Eosinophilic Leukemia, NOS
  - Mastocytosis
  - MPN unclassifiable
Hematopathologists’ Challenge

“Dysplasia with fibrosis”

MDS/MPN

“Fibrotic with Dysplasia”

MDS

MPN
What is MDS/MPN?

• Clonal myeloid neoplasm characterized by presence of both MDS and MPN features.
• MDS with presence of fibrosis does not justify placement in this category.
• Incidence is unknown
• Best Defined Entities Include:
  – Chronic Myelomonocytic Leukemia (CMML)
  – Atypical Chronic Myeloid Leukemia (aCML)
  – Juvenile Myelomonocytic Leukemia (JMML)
  – MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
  – MDS/MPN unclassifiable (MDS/MPN-U)
Goals of Therapy in MDS/MPN

- Cure
- Reduction of symptoms / splenomegaly
- Improvement of blood counts
- Cytogenetic / molecular remission
- Avoidance of disease progression / AML
- Few evidence based recommendations for management other than CMML
CMML

The aspirate smears show a myeloid predominance with increased monocytes (16%) and 2% blasts. There are subtle dysplastic features in the neutrophils.
Clinical Symptoms of CMML

- Fever, fatigue, night sweats, weight loss
- Infections
- Bleeding caused by low platelets
- Large spleen and liver

- Normal or low WBC presents more like MDS
- Elevated WBC presents more like MPN
Incidence and Diagnosis

- Incidence 0.3 per 100,000
- Median age 65-75 years
- Male predominance 3:1
- Typical presentation is monocytosis in the blood.
  - At least 1,000 per mm3 and at least 10% of the WBC on differential
- No BCR/ABL or PDGFR rearrangement.
- Fewer than 20% blasts in the blood or bone marrow
- Dysplasia in ≥ 1 cell line
Prognostic Factors in CMML

• Blood and marrow blast count
  – CMML- 0-blood < 2%; marrow < 5%
  – CMML-1- blood 2-4%; marrow 5-9%
  – CMML-2-blood 5-9%; marrow 10-19%

• WBC Count
  – MDS CMML ≤ 13,000
  – MF CMML > 13,000

• Low Hemoglobin (< 10 or transfusion dependent)

• Age

• Platelets < 100

• Genetic risk group based on cytogenetics and mutations.

Mayo, GFMScore, CPSS, Molecular Mayo
## CMML Prognostic Model: Bone Marrow Blast % and WBC Count

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<th>Subtype</th>
<th>Overall Survival (Months)</th>
<th>Overall Survival (Months)</th>
<th>Overall Survival (Months)</th>
<th>P-value</th>
<th>AML Progression at 2 years</th>
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<td>CMML/MDS n=204</td>
<td>CMML/MPN n=182</td>
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<td><strong>CMML-0</strong></td>
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<td>&lt;5% blasts</td>
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<td>15</td>
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<tr>
<td>n= 204</td>
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<td><strong>CMML-2</strong></td>
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<tr>
<td>10-19% blasts</td>
<td>13</td>
<td>17</td>
<td>10</td>
<td>.09</td>
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<td>n=81</td>
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*WBC ≤ vs >13,000 (CMML/MDS vs CMML/MPN)*

Schuler et al, Leuk Res 2015
CMML Prognostic Scoring System

![Graph showing overall survival over time for different risk groups.](image)

<table>
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<tr>
<th>No. at risk</th>
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<th>Int</th>
<th>High</th>
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<th>Absence</th>
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<td>Age (&gt;65)</td>
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<td>Anemia</td>
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<td>Thrombocytopenia (&lt;100)</td>
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<td>2</td>
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<tr>
<td>ASXL1 mutation</td>
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</table>

Treatment for CMML

• Low risk patients
  – Monitoring or symptom management
  – ESAs for patients with cytopenias
  – Hydrea or etoposide for high WBC count or splenomegaly (60% response rate)

• High risk and young or fit patients
  – Multiagent chemotherapy for leukemic transformation
  – Hypomethylating agents (may not improve survival over supportive care)
  – Allogeneic Transplantation
Phase I/II Trials of Hypomethylating Therapy in Patients with CMML

- Overall response rate: 25-70% (usually ~30-40%)\(^1\)
- Complete remission rate: 10-58%
- Overall Survival (OS): 12-37 months
- Prognostic factors for OS in pts treated with Azacitidine
  - Worse OS: BM blasts >10% and WBC >13 x 10\(^9\)/L \(^2\)
  - Better OS: Absolute monocyte count <10 x 10\(^9\)/L and PB blasts <5% \(^3\)

\(^2\) Ades *et al*, *Leuk Res*, 2013
\(^3\) Fianchi, *et al*, *Leuk Lymphoma*, 2013
Transplantation for CMML

• No randomized trials
• Increasing use of reduced intensity conditioning
  – Other donor sources: haploidentical; double umbilical cord units
• CMML at Fred Hutch (n = 129)\(^1\)
  – 10-yr overall and relapse-free survival: 38% and 28%, respectively
  – poor-risk molecular and cytogenetics as well as minimal residual
disease at the time of transplant were associated with reduced
relapse-free survival.
• CMML at EBMT (n=513; 95 pts with sAML)\(^2\)
  – 4-year overall and relapse-free survival: 33% and 27%, respectively
  – In multivariate analysis, the only significant prognostic factor for
survival was the presence of a complete remission at time of
transplantation

\(^1\)Woo J, Haematologica 2019
\(^2\)Symeonidis et al, Br J Haematol, 2015
Clinical Trials

- Guadacitabine (just completed at our center)
- Oral decitabine with the cytidine deaminase inhibitor cedazuridine
- Lenalidomide + HMA (68% response rate)
- Ruxolitinib (35% response rate)
- Tipifarnib (Farnesyl Transferase Inhibitor)
- CD123 Antibody (targets CMML cells)
Atypical CML

“Dysgranulopoiesis”
Clinical Presentation and Diagnosis

• Adults with male predominance
• Organomegaly
• Elevated WBC, neutrophilia but *no basophilia (CML) or monocytosis (CMML)*
• Hallmark is severe “dysgranulopoiesis”
• Hypercellular BM with granulocytic proliferation and dysplasia.
• No PDGFR rearrangement
• BCR/ABL negative
Molecular Pathogenesis

• Chromosomal abnormalities in 20-88%
  – Aneuploidy in 33%-most common trisomy 8, del20q

• Somatic gene mutations
  – SETBP1 mutation in 18-33% (worse prognosis)
    • Coexists with ASXL1 in 48-65%
  – CSF3R mutations in 10-40%
  – KRAS and NRAS in 10-30%
  – ETNK1 mutations in 9%
Atypical CML: Disease Course

- Median age 70
- Male predominance
- 1-2 cases for every 100 cases of BCR/ABL positive CML
- Overall median survival: 14 to 30 months.\textsuperscript{2-4}
- Transformation to AML in 40% at a median time from diagnosis of 18 months\textsuperscript{1}
- Predictors of shorter survival:
  - Older age (>65 years)
  - Female gender
  - WBC count (>50x10\textsuperscript{9}/L)
  - Hb < 10
  - > 10% immature circulating cells.
  - SET BP1 mutation

\textsuperscript{1} Breccia \textit{et al, Haematologica}, 2006
\textsuperscript{2} Kurzrock \textit{et al, J Clin Oncol}, 2001
\textsuperscript{3} Martiat \textit{et al, Blood}, 1991
\textsuperscript{4} Hernandez \textit{et al, Ann Oncol}, 2000
SETBP1 Mutation in Atypical CML

WBC (p=0.008)  Hb (p=0.44)  Platelets (p=0.16)

SETBP1- = 77 months  SETBP1+ = 22 months

p=0.01, HR=2.27

Piazza R. et al, Nat Genetics 2013
Treatment Options

• Symptomatic control
  – Hydrea, INF-alpha: complete and partial responses with duration of months
  – Splenectomy not recommended
  – ESAs-poor response

• HMAs-CRs shown in limited numbers of patients

• Clinical trials
  – Ruxolitinib (JAK inhibitor) in patients with CSF3R and JAK2 mutations
  – Dasatinib (SRC kinase inhibitor) for patients with CSF3R mutations
  – Trametinib (MEK inhibitor) in patients with CSF3R mutations
Hematopoietic stem cell transplant in Atypical CML

• 21 patients with aCML¹
  – 17 alive at 5 years post transplant with median survival 46.8 months

• 42 patients with aCML reported by EMBT²
  – OS of 51% and RFS 36% at 5 years
  – Offer at time of diagnosis in young fit patients

2. Onida F BJH 2017
MDS/MPN-RS-T (RARS-T)

RS usually signifies ineffective erythropoiesis and mitochondrial iron overload.
Clinical Presentation

• Median age 71-75 years
• Venous Thrombosis (3.9/100 patient years)
  – SF3B1 mutation patients more likely to have thrombosis (20%)
• Anemia
• Bleeding (Von Willebrands Disease)
• Vasomotor symptoms:
  – Migraine headaches
  – Palpitations
  – Paresthesias
  – Atypical chest pain

Patnaik MM Am Journal Hem April 2019
Diagnostic Criteria

- Features of MDS-RS-SLD + sustained elevated platelets (> 450,000) + proliferation of large atypical megakaryocytes
- No history of MDS or MPN except MDS-RS
- No BCR-ABL or PDGFR or PCM1-JAK2
- No t(3,3), inv3 or del5q
- SF3B1 mutation with > 15% RS
Molecular Mutations

• 80% have normal cytogenetics
• In Mayo clinic study 94% of patients had at least one mutation.
• **SF3B1 mutation in 85% of patients**
  – Prognostic significance (6.9 and 3.3 years for those positive and negative respectively, \( P=0.003 \)).
• JAK-2 mutation (33-50%)
• ASXL1 in 20-29% (poor prognosis)
• DNMT3A in 13-15%
• SETBP1 10-13% (poor prognosis)
• TET2 10-25%
- 2 points for abnormal karyotype
- 1 point for ASXL1 or SETBP1
- 1 point for Hb < 10

Low = 0 points (80 months)
Intermediate = 1 point (42 months)
High = 2 or more points (11 months)

Patnaik MM Am Journal Hem 2016
Treatment for MDS/MPN-RS-T

• Management is similar to low risk MDS
• ESA and supportive care early on
• Case reports of lenolinomide to decrease anemia
• ASA for thrombosis prevention
• Cytoreductive therapy controversial due to anemia
  – Hydrea
  – Lenolinomide
  – Interferon
  – Busulfan
• Allogeneic Transplant for refractory cytopenias or progressive disease
MDS/MPN-U

• Dysplastic Feature in at least 1 type of blood cell and <20% blasts in the peripheral blood and marrow

• Prominent myeloproliferative features
  – Plt > 450,000
  – WBC > 13,000
  – +/- splenomegally

• No history of MDS/MPN

• No Cytotoxic or growth factor treatment

• No BCR-ABL or PDGFR

• No isolated del 5q-, t (3,3) or inversion 3 OR

• Not fitting any other categories
Clinical Features of MDS/MPN-U

- Median age 70 yrs
- 72% male
- 35% have splenomegaly
- Majority of patients have diploid cytogenetics (49%) or trisomy 8
- 12% have complex karyotype
- Approximately 25% have JAK-2 mutation

DiNardo C. Leukemia 2014
MD Anderson Study of MDS/MPN-U

• Median OS was 12.4 months (21 months from diagnosis)

• Favorable outcome was associated with
  – Age < 60
  – Thrombocytosis (52.5 months)
  – Lack of circulating blasts
  – < 5% bone marrow blasts.

• MDS-IPSS score provided significant prognostic information while the MF DIPSS did not

• MDS-MPN-U patients had worse survival compared with MDS and PMF.

DiNardo C. Leukemia 2014
Mutational Landscape of MDS/MPNU

- ASXL1, TET2 (21%)
- JAK2 (19%)
- SRSF2 (15%)
- EZH2 (14%)
- U2AF1, RUNX 1, SETBP1 (11%)
- At least 1 mutation was associated with worse OS (11.8 months vs 28.6 months)
- ASXL1/SRSF2 combo was more likely to develop AML

Bose P Letter to the Editor Blood 2018
Treatment

• No standard treatment regimen
• No treatment regimen proven effective
• Combination therapy with Ruxolitinib and Azacitadine is under investigation.
MDS/MPN: Summary

• MDS/MPN has features common to both MDS and MPN
• Diagnosis is often made by a pathologist and though chromosomal and molecular testing.
• The combination of increased WBC and/or platelet counts with anemia can make treatment decisions challenging.
• Hypomethylating agents are commonly employed.
• For younger patients with higher-risk disease and an acceptable co-morbidity index, allogeneic transplant is the preferred treatment.
• Searching for actionable mutations may provide opportunities for targeted therapy.
• Accrual in clinical trials is highly recommended for these rare diseases.
Acknowledgements

• Fred Hutch
  – Joachim Deeg
  – Bart Scott
  – Cecilia Yeung

• Seattle Cancer Care Alliance

• Patients and Caregivers
Questions??

- SETBP1
- IDH1/2
- TET2
- RUNX1
- DNMT3A
- NRAS
- KRAS
- ASXL1
- CBL
- SRSF2
- U2AF1