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

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What is a myeloproliferative neoplasm (MPN)?

- Myeloproliferative neoplasms are diseases in which the bone marrow makes **too many** red blood cells, platelets, or certain white blood cells.
- Common Symptoms include:
  - Headache
  - Shortness of breath
  - Bleeding
  - Dizziness
  - Itchiness
  - Fatigue
  - Weakness
  - Abdominal pain from an enlarged spleen
Symptoms of MPN

• Common myeloproliferative neoplasms include:
  – **Chronic Myeloid Leukemia**- overproduction of white cells
  – **Polycythemia Vera**- an overproduction of red blood cells
  – **Essential Thrombocythemia**- overproduction of platelets
  – **Chronic Neutrophilic Leukemia**- overproduction of neutrophils (a type of white cell)
  – **Chronic Eosinophilic Leukemia**- overproduction of eosinophils (a type of white cell)
  – **Primary Myelofibrosis**- a condition in which bone marrow tissue is gradually replaced by fibrous scar-like tissue, disrupting normal blood cell production.
Comparison of Features of MDS vs. MPN

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

**MPN**
- “Super”-effective blood making
- Increased Blood Counts
- Increased spleen size
- Dysplasia absent
What is MDS/MPN?

• Some problems with blood-cell formation have features of both MDS and MPN.

• 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)
You know, when I was a little stem cell, I didn't know what I wanted to be either.

But I'm so confused.
Pathologists' Challenge

“Dysplasia with fibrosis”

MDS

MDS/MPN

“Fibrotic with Dysplasia”

MPN
CMML
CMML

- Most common of MDS/MPN entities
- Main features is too many monocytes in your blood (at least 1,000 per mm3)
- Bone marrow is hypercellular with monocytosis.
- Dysplasia ≥ 1 cell line but < 20% blasts
- Spleen is often enlarged
- 15-30% of patients go on to develop AML.
- Gene mutations are seen in >90% of patients
  - \( TET2 \sim 60\% \)
  - \( ASXL1 \sim 40\% \)
  - \( SRSF2 \sim 50\% \)
  - \( RAS \sim 30\% \)
  - \( CBL \sim 15\% \)
Symptoms of CMML

• Having too many monocytes also causes many of the symptoms of CMML.
• These monocytes can settle in the spleen or liver, enlarging these organs.
• Weight loss, fever, and loss of appetite
• Low blood counts
Diagnosis of CMML

Per i pheral Blood

Bone Marrow Aspirate
Staging of CMML

• CMML can be divided into 3 categories by blood and marrow blasts count.
  – CMML-0 blood < 2%; marrow <5%
  – CMML-1 blood 2-4% marrow 5-9%
  – CMML 2 blood 5-19% marrow 10-19%

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

• Other poor prognostic features include:
  – Hb < 10
  – Platelet Count < 100
  – Abnormal chromosomes (monosomy 7 or complex)
  – ASXL1 mutation

From Cazzola et al, Hematology Am Soc Hematol Educ Program, 2011
# Prognosis in CMML

<table>
<thead>
<tr>
<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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=386</td>
<td>CMML/MDS n=204</td>
<td>CMML/MPN n=182</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMML-0</td>
<td>&lt;5% blasts n=101</td>
<td>31</td>
<td>48</td>
<td>.03</td>
<td>7%</td>
</tr>
<tr>
<td>CMML-I</td>
<td>5-9% blasts n=204</td>
<td>19</td>
<td>29</td>
<td>.008</td>
<td>18%</td>
</tr>
<tr>
<td>CMML-2</td>
<td>10-19% blasts n=81</td>
<td>13</td>
<td>17</td>
<td>.09</td>
<td>36%</td>
</tr>
</tbody>
</table>

*WBC ≤ vs >13,000 (CMML/MDS vs CMML/MPN)

Schuler et al, Leuk Res 2015
Treatment of CMML

- Most common treatment is Azacitadine or Decitabine
- Overall response rate: 30-40%\(^1\) (up to 70%)
- Complete remission rate: 10-58%
- Overall Survival (OS): 12-37 months
- Prognostic factors 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% \(^3\)

\begin{flushright}
2 Ades *et al*, *Leuk Res*, 2013
3 Fianchi, *et al*, *Leuk Lymphoma*, 2013
\end{flushright}
Transplantation is only cure for CMML

- No randomized trials
- Increasing use of reduced intensity conditioning
  - Other donor sources: haploidentical; double umbilical cord
- Fred Hutch Study (n=85)\(^1\)
  - 10-yr overall and relapse-free survival: 40% and 38%, respectively
  - Increasing age, higher co-morbidity index, and poor-risk cytogenetics were associated with increased mortality and 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

\(^1\)Eissa H et al, Biol Blood Bone Marrow Transplant, 2011
\(^2\)Symeonidis et al, Br J Haematol, 2015
Atypical CML
Atypical CML

- Similar to CML but no Philadelphia chromosome = cannot treat with Gleevec or Tasigna
- < 2 cases for every 100 cases of CML
- Median age 70; Male predominance
- Symptoms: Fatigue, night sweats, splenomegaly
- Diagnosis is pathologic
  - too many neutrophils but no basophilia or monocytosis.
- Treatment of choice is bone marrow transplant.
White Blood Cell Dysplasia (Dysgranulopoiesis)

- Hypogranularity
- Hypolobation
- Hyperlobation
- Pseudo-Pelger Huet cells

Normal neutrophil

Hyperlobation

Hypogranularity

Pseudo-pelger Huet; hypolobation
CML vs Atypical CML

CML

Atypical CML

More lobulated

Tinge of blue
Atypical CML: Disease Course

• The largest series of WHO-defined aCML: 55 cases from an Italian cohort.
• Overall median survival: 25 months.
• Transformation to AML occurred in 22 patients (40%), with a median time from diagnosis of 18 months.
• Predictors of shorter survival:
  – Older age (>65 years)
  – Female gender
  – WBC count (>50x10^9/L)
  – Presence of immature circulating cells.

¹ Breccia et al, Haematologica, 2006
SETBP1 Mutation in 30% of Atypical CML

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

SETBP1- = 77 months
SETBP1+ = 22 months
p=0.01
MDS/MPN-RS-T (RARS-T)
MDS/MPN RARS-T Symptoms

- Like RARS in MDS but with too many platelets (> 450,000).
- Patients can be divided into low risk (0 factors) and high risk (1 or 2 factors), based on age >60 years and history of blood clot.
- Low risk patients benefit from low dose aspirin therapy (81–100 mg).
- Bone marrow transplant is reserved for patients with blood counts not responding to transfusions or progressive disease.
Pathologic features of MDS/MPN RARS-T

Peripheral blood:
Increased platelets & dysplastic neutrophil

BM aspirate:
dysplastic Red blood cells

BM aspirate:
ringed sideroblast

Cytogenetics: normal
Myeloid mutation panel: SF3B1 & JAK2 V617F

From Cazzola et al, Hematology Am Soc Hematol Educ Program, 2011
MDS/MPN-RS-T (RARS-T)

• SF3B1 mutation in 72% of patients.
  – Prognostic significance (6.9 and 3.3 years for those positive and negative respectively, \( p = 0.003 \)).

• Can be distinguished from RARS by JAK-2 mutation.
  – RARS-T 60% of patients vs 0% in RARS
  – Patients with JAK-2 mutation have better prognosis.

• Two-hit Hypothesis
  – SF3B1 leads to RARS, JAK-2 leads to the -T

Broseus Leukemia 2013
MDS/MPN-U
**MDS/MPN-U**

- Dysplastic feature in 1 type of blood cell
  - <20% blasts in PB and BM
- Prominent myeloproliferative features
  - Plt > 450x10^9/L
  - WBC >13x10^9/L
  - ± splenomegaly
- OR
- de novo disease with mixed MPN and MDS features and not fitting any other category

- No history of MPN/MDS
- No cytotoxic or growth factor tx
- No BCR-ABL, PDGFRA, PDGFRB, FGFR1
- No isolated del 5q, t(3;3), or inv 3(q21q26)
MD Anderson Study of MDS/MPN-U

- 85 patients with MDS/MPN-U
- Patients with treated with HMA (n = 36), an immunomodulator (n = 13) or stem cell transplant (n = 5)
- Median OS was 12.4 months
- Favorable outcome was associated with
  - Age < 60
  - Thrombocytosis (52.5 months)
  - Lack of circulating blasts
  - < 5% bone marrow blasts.
- MDS-MPN-U patients had worse survival compared with MDS and PMF.
- No treatment regimen proved effective
- Combination therapy with Ruxolitinib and Azacitadine is under investigation.

DiNardo C. Leukemia 2014
The Future of Treatment in MDS/MPN
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
TADA Study

• 28 enrolled patients (median age was 66.5 years)
• Treatment: thalidomide, arsenic trioxide, dexamethasone, and ascorbic acid [TADA]
• 15 patients had MDS/MPN-unclassifiable, 8 patients had chronic myelomonocytic leukemia type 1, and 5 patients had PMF.
• With a median follow-up of 5.7 months, 21 patients (75%) completed the 12-week course of therapy, and 6 patients (29%) responded to TADA.
• At 24.1 months (15 evaluable patients), median PFS was 14.4 months, and the median overall survival was 21.4 months.
# Targeted Therapy Considerations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Disease Entity</th>
<th>Therapy</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2 V617F</td>
<td>CMML (5-10%) RARS-T (60%), aCML (7%)</td>
<td>JAK inhibitor</td>
<td>Ruxolitinib</td>
</tr>
<tr>
<td>CSF3R T618I</td>
<td>CMML (&lt; 5%), aCML (&lt; 10%)</td>
<td>JAK inhibitor</td>
<td>Ruxolitinib</td>
</tr>
<tr>
<td>RAS pathway (e.g. PTPN11, RAS, CBL, NF1)</td>
<td>CMML (24-37%), aCML (27-54%), MDS-MPN-U (4-16%)</td>
<td>MEK inhibitor</td>
<td>Trametinib</td>
</tr>
<tr>
<td>SF3B1</td>
<td>CMML (5-10%), RARS-T (72%), MDS/MPN-U (1%)</td>
<td>TGF-B ligand trap</td>
<td>Luspatercept</td>
</tr>
<tr>
<td>Other splicing gene mutations (e.g. SRSF2)</td>
<td>CMML (50%), MDS/MPN-U (2%)</td>
<td>Splicing modulator</td>
<td>H3B-8800</td>
</tr>
<tr>
<td>IDH 1/2</td>
<td>CMML (&lt; 2%)</td>
<td>IDH 1/2 inhibitor</td>
<td>Enasidinib</td>
</tr>
<tr>
<td>CD30+</td>
<td>CMML (30-40%)</td>
<td>Anti-CD30</td>
<td>Brentuximab Vedotin</td>
</tr>
</tbody>
</table>
Studie Open at FHCRC/SCCA

• Randomized study of Guadecitabine in patients who are refractory to azacitabine and decitabine.
  – Open for patients with MDS and CMML.
• H3B-800
  – Will include patients with MDS and CMML.
• Brentuximab Vedotin (SWOG)
  – Will include patients with CMML and systemic mastocytosis.
MDS/MPN: Summary

• MDS/MPN has features common to both MDS and MPN
• Diagnosis is often laboratory and 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

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Questions??