Chronic myelomonocytic leukemia

Lymphoma Tumor Board

May 26, 2017
CMML has an estimated incidence of less than 1 per 100,000 persons per year
Myeloproliferative neoplasms (MPN) and myelodysplastic syndromes (MDS) define a spectrum of pathology.
Overlap syndromes with features of both MDS and MPN are common

Tariq I. Mughal et al. Haematologica 2015;100:1117-1130
Chronic myelomonocytic leukemia (CMML)

- Increased numbers of monocytes and immature blood cells (blasts) in the peripheral blood and bone marrow
- Abnormal looking cells (dysplasia)
- Shows characteristics of myelodysplastic syndrome (MDS) and myeloproliferative disorder (MPD)
- Splenomegaly is quite common
- Other symptoms include:
  - Anemia
  - Fever
  - Weight loss
  - Night sweats
  - Infection
  - Bleeding
  - Synovitis
  - Lymphadenopathy
  - Pleural effusion, pericardial effusion, and/or peritoneal effusion
- Diagnosis (WHO): Persistent (> 3 months) blood monocytosis (>1,000/µL)
- No Philadelphia chromosome or mutations in PDGFRA or PDGFRB
- Blast count must be <20% and dysplasia of at least one lineage of myeloid blood cell should be present
Diagnostic algorithm for peripheral blood monocytosis

1. Peripheral blood monocytosis: Absolute monocyte count, $>1 \times 10^9/L$
   - $<3$ months:
     - Viral infections
     - Recovering bone marrow
   - $>3$ months:
     - Associated blood smear abnormalities—additional cytopenias/cytosis, Auer rods, and dysplastic granulocytes

2. Bone marrow biopsy to evaluate for CMML and/or related myeloid neoplasms
   - Yes
   - FISH BCR-ABL1: If positive, CML
     - FISH PDGFRA/B: If positive, myeloid neoplasms with PDGFRA/B rearrangement
     - Flow cytometry for CD14/CD16: CD14$^+$/CD16$^-$ monocites, consider CMML
   - No
   - Evaluate for persistent nonclonal causes such as tuberculosis, brucellosis, sarcoidosis, subacute bacterial endocarditis, and connective tissue disorders
     - No
     - CMML excluded
   - Yes
     - Bone marrow biopsy to evaluate for CMML-1

3. Other myeloid neoplasms
   - MDS/MPN-U
   - Atypical CML
   - JMML
   - RARS-T
   - MPN with monocytosis
   - MDS with monocytosis
# Potential diagnostic approach for patients suspected to have a MDS/MPN overlap syndrome

<table>
<thead>
<tr>
<th>Criteria</th>
<th>CMML</th>
<th>aCML</th>
<th>MDS/MPN-U</th>
</tr>
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<tbody>
<tr>
<td>Mean age</td>
<td>72</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>2/1</td>
<td>2/1</td>
<td>2/1</td>
</tr>
<tr>
<td>Mean OS</td>
<td>~3 years</td>
<td>~1 year</td>
<td>~2 years</td>
</tr>
<tr>
<td>Incidence</td>
<td>1/100000</td>
<td>1/100 CML</td>
<td>Unknown</td>
</tr>
<tr>
<td>Monocytosis &gt; 1 G/L at least 3 months +/- bone marrow cell dysplasia</td>
<td>Persistent leukocytosis &gt; 13 G/L + immature circulating myeloid precursors &gt; 10% of leukocytes + Marked dysgranulopoiesis, and - Absent/minimal monocytosis (&lt;1 G/L and &lt;10% of leukocytes) - Absent/minimal basophilia (&lt;2%)</td>
<td>Heterogeneous group of rare myeloid neoplasms with myeloproliferative features &amp; myelodysplastic features that cannot be classified as JMML, CMML, RARS-T, and aCML</td>
<td></td>
</tr>
</tbody>
</table>

A definitive diagnosis of MDS/MPN requires the exclusion of AML; BM blast cells < 20%; CML: lack of BCR-ABL; MLN-Eo: lack of PDGFR/FGFR fusion & eosinophilia; CMML: chronic myelomonocytic leukemia; aCML: acute chronic myeloid leukemia; MDS: myelodysplastic syndromes; MPN-U: myeloproliferative neoplasms; Unknown; AML: acute myeloid leukemia; myeloproliferative neoplasms; BM: bone marrow.

Tariq I. Mughal et al. *Haematologica* 2015;100:1117-1130
Peripheral blood and bone marrow findings in CMML
Chronic myelomonocytic leukemia-1 (CMML-1)
Chronic myelomonocytic leukemia-1 (CMML-1)
# Features of MDS vs. CMML

<table>
<thead>
<tr>
<th>Feature</th>
<th>MDS</th>
<th>CMML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytopenias present</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Splenomegaly present</td>
<td>No</td>
<td>Yes (50% of cases)</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>Rare</td>
<td>Yes (frequency unknown)</td>
</tr>
<tr>
<td>AML transformation rate</td>
<td>30% of cases</td>
<td>30% of cases</td>
</tr>
<tr>
<td>Median survival</td>
<td>30 months</td>
<td>12-19 months</td>
</tr>
<tr>
<td>Preferred prognostic tool</td>
<td>IPSS/IPSS-R</td>
<td>Unknown</td>
</tr>
<tr>
<td>Treatment options</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-- Hematologic improvement</td>
<td>HMA, lenalidomide NA</td>
<td>HMA Hydroxyurea, topotecan</td>
</tr>
<tr>
<td>-- Splenomegaly</td>
<td>Azacitidine</td>
<td>None</td>
</tr>
<tr>
<td>-- Disease modification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stem cell transplant options</td>
<td>Allogeneic</td>
<td>Allogeneic</td>
</tr>
</tbody>
</table>

CMML, chronic myelomonocytic leukemia; HMA, hypomethylating agents; IPSS, International Prognostic Scoring System; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; NA, not applicable.
Treatment of CMML

- Remains challenging as there are few trials investigating CMML as a clinical entity
- Foundation of treatment is supportive care – directed by patients’ co-morbidities
- Blood transfusions and ESA administration are used to raise hemoglobin levels in patients with symptomatic anemia
- Hypomethylating agents (HMAs) are a non-transplant treatment option
  - Azacitidine is approved by the FDA and European Medicines Agency for treatment of CMML, and indicated for high risk non-proliferative CMML with 10-19% marrow blasts
  - Decitabine is also approved by the FDA for CMML and all subtypes of MDS
- Hydroxyurea can be used in the myeloproliferative form of CMML to reduce WBC
- Topotecan, both as single-agent therapy and in combination with cytarabine, was found to have activity in patients with CMML in multiple studies performed at the MD Anderson Cancer Center – enthusiasm for this agent has waned, however
- Some patients can progress rapidly to secondary AML
- Hematopoietic stem cell transplantation is currently the only curative treatment for CMML and secondary AML arising from CMML
  - Often not possible due to late stage disease and co-morbidities
Mayo Clinic risk-adapted algorithm for the management of patients with CMML

CMML

Age <65 y

Molecular Mayo Model risk stratification

Symptomatic: low & intermediate-1
- MPN-like features
  - Hydroxyurea
    - Clinical trials
- MDS-like features
  - ESA
    - Hypomethylating agents
      - Clinical trials

Intermediate-2 & high risk
- Donor available
  - Acceptable HSCT comorbidity index
    - Yes
      - Allogenic stem cell transplant
        - Myeloablative if age <55 years
        - Reduced intensity for age >55 years
    - No
      - 1. Observation
      - 2. Hydroxyurea
      - 3. ESA
      - 4. Hypomethylating agents
      - 5. Clinical trials
      - 6. Supportive care

Age ≥65 y
Survival in CMML circa 2002

Survival in CMML circa 2002 – association with selected laboratory variables

Survival in CMML circa 2002 - association with risk classification

Survival of CMML patients is associated with WBC

**A**

**B**

MP-CMML: WBC ≥ 13,000/μL
MD-CMML: WBC < 13,000/μL

Alignment of gene mutations, karyotype information, and CMML category for 275 patients

Manja Meggendorfer et al. *Blood* 2012;120:3080-3088
OS of patients with CMML according to SRSF2 mutations

Manja Meggendorfer et al. Blood 2012;120:3080-3088

©2012 by American Society of Hematology
Clusters of gene mutations in CMML

Itzykson et al., J Clin Oncol 2013; 31:2428-2436
A simplified prognostic score for CMML that includes ASXL1 mutations

Leucocytosis (>15) | Absence | Presence
Age (>65) | 0 | 3
Anemia | 0 | 2
Thrombocytopenia (<100) | 0 | 2
ASXL1 mutation | 0 | 2

Low < 4
Intermediate 4-8
High >8

Adapted, with permission, Itzykson et al. J Clin Oncol, 2013, in press

Tariq I. Mughal et al. Haematologica 2015; 100:1117-1130
Early clonal dominance (CD34+/CD38− cells) in CMML compared to MPN

- Early clonal dominance in HSC compartment
- Linear acquisition of mutations, starting with epigenetic and splicing genes
- Growth advantage to the more mutated cells with differentiation

Tariq I. Mughal et al. Haematologica 2015;100:1117-1130
Schematic description of genotypic diversity in patients with MDS and MPN

Tariq I. Mughal et al. Haematologica 2015;100:1117-1130
Emerging molecular fingerprints of MDS and MPN

Tariq I. Mughal et al. Haematologica 2015;100:1117-1130
References