Update on Myelodysplastic Syndromes and Myeloproliferative Neoplasms

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Conflict of Interest

• Nothing to disclose
Learning Objectives

• Present the criteria required to establish a diagnosis of MDS and MPN according to the 2016 updated WHO Classification

• Review the revised 2016 WHO categories of MDS and MPN
  – Discuss changes in classification since the 2008 WHO
  – Highlight new genetic information
Myeloid neoplasm classification

- Myelodysplastic syndromes
- Myeloproliferative neoplasms
- Mastocytosis
- Myeloid/lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, FGFR1 and PCM1-JAK2
- Myelodysplastic/myeloproliferative neoplasms
- Acute myeloid leukemia and related entities
- Myeloid neoplasms with germline predisposition
## Myeloid Neoplasms: Major Subgroups and Discriminating Features

<table>
<thead>
<tr>
<th>Group</th>
<th>PB counts</th>
<th>BM cellularity</th>
<th>Hematopoiesis</th>
<th>Maturation</th>
<th>% BM blasts</th>
<th>Morphology</th>
<th>Organo-megaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>Cytopenias</td>
<td>Usually increased</td>
<td>Ineffective</td>
<td>Present</td>
<td>Normal or increased</td>
<td>Dysplasia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>MPN</td>
<td>Cytoses</td>
<td>Usually increased</td>
<td>Effective</td>
<td>Present</td>
<td>Usually normal</td>
<td>Normal except megakaryocytes</td>
<td>Common</td>
</tr>
<tr>
<td>AML</td>
<td>Variable WBC</td>
<td>Usually increased</td>
<td>Ineffective or effective</td>
<td>Usually minimal</td>
<td>&gt;20%; exceptions</td>
<td>Variable</td>
<td>Uncommon</td>
</tr>
<tr>
<td>MDS/MPN</td>
<td>WBC usually increased</td>
<td>Increased</td>
<td>Varies by lineage</td>
<td>Present</td>
<td>Normal or slightly increased</td>
<td>Usually dysplasia in one cell lineage</td>
<td>Common</td>
</tr>
<tr>
<td>MLNE</td>
<td>Eosinophilia</td>
<td>Increased</td>
<td>Effective</td>
<td>Present</td>
<td>Usually normal</td>
<td>Normal</td>
<td>Common</td>
</tr>
</tbody>
</table>
Myelodysplastic syndromes (MDS)

• Clonal hematopoietic stem cell neoplasms with ineffective hematopoiesis and intact maturation
  – Peripheral blood cytopenias
  – Morphologic dysplasia of hematopoietic elements

• Varying propensity to develop maturation arrest in hematopoietic cells, with accumulation of blasts and progression to AML
  – Cutoff of 20% blasts in bone marrow or peripheral blood distinguishes MDS from AML
Myelodysplastic syndromes (MDS)

- Clonal hematopoietic stem cell neoplasm
- Sustained cytopenias: (hemoglobin < 10g/dl, neutrophil count <1.8 x 10^9/L and platelet count <100 x 10^9/L)
- Intact maturation of hematopoietic lineages with ≥10% dysplastic cells in at least one lineage, and increased intramedullary cell death (apoptosis)(ineffective hematopoiesis)
- Variable blast percentage but <20% in blood and bone marrow
- Increased risk of transformation to acute myeloid leukemia
Biologic Spectrum of MDS

- **Indolent “low-grade” subtypes**
  - Low blast counts
  - Typically low risk of progression to AML
  - Morbidity and mortality due to cytopenias and/or complications of infection, bleeding, transfusion

- **Aggressive subtypes**
  - Higher blast counts, genetic instability
  - Often rapidly progress to AML
Dysplasia assessment

- WHO threshold: 10% of cells in any lineage must manifest dysplastic morphology to call that lineage dysplastic
- May be interobserver variability
- Dysplasia is not specific for MDS
- May observe dysplasia in bone marrow of normal volunteers and even more frequently in patients with non-neoplastic cytopenias
Beyond morphology for MDS diagnosis

Flow cytometry

- Abnormal flow cytometry patterns predict MDS with good sensitivity and specificity
- WHO 2016 and ELN guidelines do not permit a diagnosis of MDS solely based on flow cytometry
- Considered ‘supportive’ of a diagnosis
- More data needed on findings in reactive conditions
- Flow is important to evaluate for lymphomas that can present with cytopenia mimicking MDS
Beyond morphology for MDS diagnosis

Genetic abnormalities

• Karyotype abnormalities
  – ~50% of MDS cases have a normal karyotype

• Sub-karyotypic genetic alterations
  – Microdeletions, other small imbalances
  – Gene mutations (detected mainly in the clinical realm by next generations sequencing assays)
# MDS-defining cytogenetic abnormalities

<table>
<thead>
<tr>
<th>Unbalanced</th>
<th>Primary MDS</th>
<th>Therapy-related MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>-7 or del(7q)</td>
<td>10%</td>
<td>50%</td>
</tr>
<tr>
<td>del(5q) to t(5q)</td>
<td>10%</td>
<td>40%</td>
</tr>
<tr>
<td>i(17q) or t(17p)</td>
<td>3-5%</td>
<td></td>
</tr>
<tr>
<td>-13 or del(13q)</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>del(11q)</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>del(12p) or t(12p)</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>del(9q)</td>
<td>1-2%</td>
<td></td>
</tr>
<tr>
<td>idic(X)(q13)</td>
<td>1-2%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Balanced</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>t(11;16)(q23;p13.3)</td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>t(3;21)(q26.2;q22.1)</td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>t(1;3)(p36.3;q21.2)</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>t(2;11)(p21;q23)</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>inv(3)(q21q26.2)</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>t(6;9)(p23;q34)</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

+8, -Y, and del(20q) are common in MDS, but can occur in non-neoplastic conditions and are not MDS-defining.
Somatic mutations in MDS

• Increasing availability of sequencing has enabled significant knowledge to be gained in MDS patients
• Great heterogeneity in mutational landscape
• Recurrent genetic alterations in multiple cellular pathways: transcription factors, tumor suppressors, epigenetic modifiers, splicing machinery, etc.
## Somatic mutations in MDS*

<table>
<thead>
<tr>
<th>Genetic mutation</th>
<th>Incidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RNA splicing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– <em>SF3B1</em></td>
<td>25-30%</td>
<td>Strong assoc. w/ RS and LR-MDS, ↑OS, ↓ OS prognosis</td>
</tr>
<tr>
<td>– <em>SRSF2</em></td>
<td>10-20%</td>
<td>↑ risk for AML</td>
</tr>
<tr>
<td>– <em>U2AF1</em></td>
<td>5-10%</td>
<td></td>
</tr>
<tr>
<td><strong>DNA methylation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– <em>TET2</em></td>
<td>20-30%</td>
<td>Assoc. w/ ↓ OS</td>
</tr>
<tr>
<td>– <em>DNMT3A</em></td>
<td>10%</td>
<td>Assoc. w/ MLD and ↑ blasts</td>
</tr>
<tr>
<td>– <em>IDH1/IDH2</em></td>
<td>~5%</td>
<td></td>
</tr>
</tbody>
</table>

*(not all inclusive)*

Papaemmanuil E Blood. 2013;122:3616
# Somatic mutations in MDS*

<table>
<thead>
<tr>
<th>Genetic mutation</th>
<th>Incidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromatin modification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– <em>ASXL1</em></td>
<td>15-20%</td>
<td>↓OS</td>
</tr>
<tr>
<td>Transcription</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– <em>RUNX1</em></td>
<td>10%</td>
<td>assoc. w/ MLD and ↑ blasts</td>
</tr>
<tr>
<td>– <em>NPM1</em></td>
<td>&lt;5%</td>
<td></td>
</tr>
<tr>
<td>DNA repair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– <em>TP53</em></td>
<td>~10%</td>
<td>↑in HG-MDS; ↓OS</td>
</tr>
</tbody>
</table>

*(not all inclusive)*
Can mutations = diagnosis of MDS?

- A subset of healthy older individuals harbor MDS-type mutations in hematopoietic cells
  - Top genes include: **DNMT3A, TET2, ASXL1, TP53, JAK2, SF3B1**
  - Associated with increased risk of subsequent hematologic malignancy
    - but many patients never develop MDS even after years of follow-up
  - Designated as “Clonal Hematopoiesis of Indeterminate Potential” (CHIP) in the absence of cytopenias
  - or “Clonal Cytopenia of Undetermined Significance” (CCUS) in the presence of cytopenias

<table>
<thead>
<tr>
<th></th>
<th>CHIP</th>
<th>CCUS</th>
<th>MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonality</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>--</td>
<td>--</td>
<td>+</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>--</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

CHIP

• Appears to be a precursor state to MDS
  – Analogous to the relationship of MGUS to myeloma and monoclonal B-lymphocytosis to CLL
• Most patients with CHIP do not develop MDS
• CHIP phenomenon precludes the current use of mutations in isolation to diagnose MDS
• Specific mutation patterns and high mutant allele frequency may confer higher risk of MDS
  – Mutant allele fraction ≥10%
  – Spliceosome gene mutation
  – *TET2, DNMT3A* or *ASXL1* mutation with at least one other mutation

Malcovati L et al. Blood 2017;129:3371
WHO 2016 MDS Classification

- MDS with single lineage dysplasia
- MDS with multilineage dysplasia
- MDS with ring sideroblasts
  - MDS-RS with single lineage dysplasia
  - MDS-RS with multilineage dysplasia
- MDS with isolated del(5q)
- MDS, unclassifiable
- MDS with excess blasts
- Refractory cytopenia of childhood (RCC)(provisional)
Updates in MDS Classification

• Molecular testing for *SF3B1* mutations useful in cases with ring sideroblasts
• One additional cytogenetic abnormality allowed for MDS with “isolated” del 5q
• Molecular testing for *TP53* mutations useful for prognosis
• Cases formerly fulfilling criteria for AEL, myeloid/erythroid will often become MDS-EB
MDS with ring sideroblasts (MDS-RS)

- Now includes single lineage and multilineage dysplasia categories
- Usually requires $\geq 15\%$ ring sideroblasts; however the diagnosis can be made with $\geq 5\%$ in the presence of $SF3B1$ mutation
- Secondary causes of ring sideroblasts must be excluded
MDS with ring sideroblasts; *SF3B1* association

- Strong association of MDS-RS with *SF3B1* mutation
  - Seen in ~70% of MDS-RS cases
  - Probable early event in disease development
- *SF3B1* is a spliceosome gene
- Favorable clinical outcome

Cumulative probability of survival

MDS with isolated del(5q)

• Updates
  – No adverse effect on clinical outcome with one additional cytogenetic abnormality except -7 and del(7q)
  – The presence of a TP53 mutation is associated with an inferior response in patients treated with lenalidomide
MDS with isolated del(5q): Key tips

- Diagnosis as MDS with “isolated” del(5q) even in the presence of a single additional cytogenetic abnormality (except -7 and del(7q))
- Testing for TP53 mutation is recommended in these patients
Change in blast counting in 2016 WHO

- Blasts in bone marrow are counted as % of total cells, not as % of non-erythroid cells
  - Change from WHO 2008
  - Previously blast %, with >50% erythroid precursors, calculated out of the non-erythroid cells
  - Patients previously diagnosed as acute erythroid leukemia (AEL) may not require intensive chemotherapy

Effect of change in blast counting?

• Myeloid neoplasms with ≥50% erythroids but with myeloid blasts <20% of all cells are now classified as MDS.
  – Many cases previously diagnosed as AEL are no classified as MDS-EB.

• Pure erythroid leukemia remains as an AML subtype (AML, NOS)
  – Malignant proliferation of proerythroblasts
What testing should be performed in the bone marrow workup of MDS?

- **Peripheral Blood**
  - CBC
  - Cytologic review with differential count (% blasts)

- **Bone marrow aspirate**
  - Cytologic review with differential count (% blasts)
  - % dysplasia and lineage(s) affected
  - Iron stain
What testing should be performed in the bone marrow workup of MDS?

- Bone marrow core biopsy
  - Cytologic review/assess concordance with aspirate findings
- Flow cytometry may be helpful but not required
  - Flow blast % should not replace morphologic %
- Immunohistochemistry for blasts
  - Bone marrow aspirate % is the gold standard
  - Exceptions: aspirate is suboptimal, morphologic discordance
  - Caveat: not all blasts are CD34 positive
What genetic testing should be performed in the bone marrow workup of MDS?

- Cytogenetics required on all cases
  - Detect del(5q), complex, other
- FISH testing generally not indicated if adequate karyotype (20 metaphases)
- *SF3B1* mutation
  - MDS-RS still defined by iron stain, but mutation analysis allows diagnosis if only a small number of ring sideroblasts are present
- *TP53* mutation in del(5q)
- Molecular testing (NGS) has utility
Myeloproliferative neoplasms

• Clonal hematopoietic stem cell disorders
• Characterized by effective hematopoiesis and proliferation of one or more of the erythroid, granulocytic or megakaryocytic lineages
• Variable blast percentage but < 20% in blood and bone marrow
• Often organomegaly
• Variable propensity to develop fibrosis and AML
WHO 2016 Classification of MPNs*

- Chronic myeloid leukemia, *BCR-ABL1*-positive
- Chronic neutrophilic leukemia
- Polycythemia vera
- Primary myelofibrosis
- Essential thrombocythemia
- Chronic eosinophilic leukemia, NOS
- Myeloproliferative neoplasm, unclassifiable

Mastocytosis is now its own category

Chronic myeloid leukemia, \textit{BCR-ABL1} positive: Updates

- Name change from WHO 4\textsuperscript{th} edition (2008) “myeloid”
- New definition of lymphoid blast crisis
  - Any lymphoblast(s) in the PB raise concern for blast crisis
  - Cases with >5\% lymphoblasts in the BM should be diagnosed as blast crisis
- Resistance to TKI treatment is included in the definition of disease progression

\textbf{Lymphoid blast phase}
Chronic myeloid leukemia, *BCR-ABL1* positive

- Most often diagnosed in chronic phase
- Hallmark genetic abnormality: \( t(9;22)(q34.1;q11.2) \), *BCR-ABL1*
- Targeted therapy against tyrosine kinase (ABL)
Chronic myeloid leukemia, \textit{BCR-ABL1} positive

- Disease monitoring
  - Quantitative \textit{BCR-ABL1} transcript levels
  - Goal: complete cytogenetic remission by 12 months
  - Goal: major molecular remission by 12-18 months (3 log reduction; <0.1%)
Chronic myeloid leukemia, *BCR-ABL1* positive

- Disease progression
  - Evidence of morphologic evolution
  - Evidence of laboratory evolution
  - Evidence of genetic evolution
  - Development of resistance to TKI therapy
    - Mutation testing
CML, accelerated phase

Any one or more of the following hematologic/cytogenetic criteria or response-to-TKI criteria:

- Persistent or increasing WBC (>10 X 10⁹/L), unresponsive to therapy
- Persistent or increasing splenomegaly, unresponsive to therapy
- Persistent thrombocytosis (>1000 X 10⁹/L), unresponsive to therapy
- Persistent thrombocytopenia (<100 X 10⁹/L) unrelated to therapy
- 20% or more basophils in the PB
- 10-19% blasts* in the PB and/or BM
- Additional clonal chromosomal abnormalities in Ph+ cells at diagnosis that include "major route" abnormalities (second Ph, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype, or abnormalities of 3q26.2
- Any new clonal chromosomal abnormality in Ph+ cells that occurs during therapy

"Provisional" Response-to-TKI Criteria

- Hematologic resistance to the first TKI (or failure to achieve a complete hematologic response** to the first TKI) or
- Any hematological, cytogenetic or molecular indications of resistance to two sequential TKIs or
- Occurrence of two or more mutations in BCR-ABL1 during TKI therapy

Large clusters or sheets of small, abnormal megakaryocytes, associated with marked reticulin or collagen fibrosis in biopsy specimens may be considered as presumptive evidence of AP, although these findings are usually associated with one or more of the criteria listed above. *The finding of bona fide lymphoblasts in the blood or marrow, even if less than 10%, should prompt concern that lymphoblastic transformation may be imminent and warrants further clinical and genetic investigation; 20% or more blasts in blood or bone marrow, or an infiltrative proliferation of blasts in an extramedullary site is CML, blast phase. **Complete hematologic response: WBC <10x10⁹/L, Platelet count <450 x 10⁹ /L, no immature granulocytes in the differential, and spleen non-palpable.
Chronic neutrophilic leukemia: Updates

• The CSF3R mutation is strongly associated with chronic neutrophilic leukemia
• Membrane proximal mutation: T615A, T618I
• Truncating mutation
• CSF3R is often co-mutated (SETBP1, ASXL1)

Chronic neutrophilic leukemia

- Peripheral blood white blood cell count \( >25 \times 10^9/L \)
  - Segmented neutrophils plus banded neutrophils constitute \( >80\% \) of the white blood cells
  - Neutrophil precursors (promyelocytes, myelocytes, and metamyelocytes) constitute \( < 10\% \) of the white blood cells
  - Myeloblasts rarely observed
  - Monocyte count \( < 1 \times 10^9/L \)
  - No dysgranulopoiesis
Chronic neutrophilic leukemia

- Hypercellular bone marrow
  - Neutrophil granulocytes increased in percentage and number
  - Neutrophil maturation appears normal
  - Myeloblasts constitute <5% of the nucleated cells
Chronic neutrophilic leukemia

- Does not satisfy WHO criteria for BCR-ABL 1-positive chronic myeloid leukemia, polycythaemia vera, essential thrombocythaemia, or primary myelofibrosis
- No rearrangement of PDGFRA, PDGFRB, or FGFR1, or PCM1-JAK2 fusion
- CSF3R T6181 or another activating CSF3R mutation OR Persistent neutrophilia (>3 months), splenomegaly, and no identifiable cause of reactive neutrophilia including absence of a plasma cell neoplasm or, if a plasma cell neoplasm is present, demonstration of clonality of myeloid cells by cytogenetic or molecular studies
Exemplary case
**CNL versus aCML**

**CNL**
- Neutrophilia lacking significant left shift or granulocytic dysplasia

**Atypical CML**
- Neutrophilia with left shift and significant granulocytic dysplasia

Majority *CSFR3* mutation

<10% *CSFR3* mutation
New data incorporated into the WHO 2016 classification of the classic \textit{BCR-ABL1} negative MPNs: PV, ET, PMF

- The discovery of novel molecular findings in particular the \textit{CALR} mutation
- Revise major and minor diagnostic criteria
  - To improve diagnosis
  - To enable discrimination amongst the various early disease presentations (PV)
  - To provide standardized morphologic criteria of MPNs
ET, PV, PMF: Distinct diseases with different natural history

Mutations and MPN Subtypes

- **JAK2**
  - >95% of PV have a *JAK2* V617F mutation (exon 14), remaining harbor exon 12 mutation
  - 50-60% of PMF and ET have *JAK2* V617F mutation
- **CALR**
  - 20-30% of PMF and ET have *CALR* exon 9 mutations
- **MPL**
  - 5-10% of PMF and ET have *MPL* exon 10 mutation

Remaining cases are noted as “triple-negative”
Survival

- **ET**: Survival is the longest for triple-negative and shortest for *MPL*-mutated patients. Median survival: 19 years for *JAK2* and 20 years for *CALR*-mutated cases
- **PMF**: Triple negative median survival 2.3 years; *CALR* mutated 15.9 years
- **PV**: Median survival 13.7 years

Comparative BM features

**PV**
- Hypercellular with panmyelosis with a spectrum of megakaryocyte size

**ET**
- Normocellular with giant, hyper-lobulated megakaryocytes

**PMF**
- Hypercellular with ranulocytic hyperplasia with significant megakaryocyte atypia
Value of Megakaryocytes

CML

PMF

PV

ET
Criteria for Polycythemia Vera*

• Major
  – Elevated hemoglobin concentration (> 16.5 g/dl in men; > 16.0 g/dl in women) or Elevated hematocrit (> 49% in men; > 48% in women) or Increased red blood cell mass (> 25% above mean normal predicted value)
  – Bone marrow biopsy showing age-adjusted hypercellularity with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (size differences)
  – Presence of JAK2 V617F or JAK2 exon 12 mutation

• Minor
  – Subnormal serum erythropoietin level

*The diagnosis requires either all 3 major or the first 2 major and the minor criterion.
MPN: Polycythemia Vera

BM: Spectrum megakaryocytes, panmyelosis; Bld: erythrocytosis, low serum erythropoietin level
Criteria for PMF, prefibrotic/early stage
(All major + ≥ 1 minor criteria)*

- **Major**
  - Atypical meg hyperplasia without fibrosis, with increased cellularity, granulocytic proliferation, and often decreased erythropoiesis
  - Does not meet criteria for PV, CML, MDS or other myeloid neoplasm
  - *JAK2, MPL, or CALR* mutation or, presence of another clonal marker, or absence of minor reactive BM reticulin fibrosis

- **Minor**
  - Palpable splenomegaly
  - Leukocytosis ≥ 11 x 10⁹/L
  - Anemia not attributed to a comorbid condition
  - Increase in serum LDH above reference range

*For a diagnosis of overt phase PMF: presence of either reticulin and/or collagen fibrosis grades 2 or 3; Leukoerythroblastosis represents one more minor criterion
MPN: Primary Myelofibrosis

BM: pleomorphic megakaryocytes; Bld: LER
Criteria for Essential Thrombocythemia

Major

1. Platelet count $\geq 450 \times 10^9 /L$
2. Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; very rarely MF-1 reticulin fibrosis
3. WHO criteria for $BCR-ABL1$ positive chronic myeloid leukemia, polycythaemia vera, primary myelofibrosis, or other myeloid neoplasms are not met
4. $JAK2$, $CALR$, or $MPL$ mutation

Minor

Presence of a clonal marker or
Absence of evidence of reactive thrombocytosis

The diagnosis of essential thrombocythaemia requires that either all major criteria or the first 3 major criteria plus the minor criterion are met.
MPN: Essential Thrombocythemia

BM: hyperlobulated megas; Bld: ↑↑ plts
Key take-away points: MDS

• Molecular testing for SF3B1 mutations useful in cases with ring sideroblasts
  – Threshold lowered to ≥ 5% rings if SF3B1 positive
• One additional cytogenetic abnormality allowed for MDS with “isolated” del 5q
  – Cannot be -7, del(7q) or MDS-related abnormality
• Cases formerly fulfilling criteria for AEL, myeloid/erythroid will often become MDS-EB
  – Alert clinician to monitor carefully for progression to overt AML
  – Test for NPM1 and MLL mutations; if positive suggest evolving AML
• Molecular testing for TP53 mutations useful for prognosis
Key take-away points: MPN

- Inclusion of novel molecular findings in addition to *JAK2* and *MPL* mutations; in particular the *CALR* mutation provides proof of clonality, and has diagnostic and prognostic importance.
- *CSF3R* mutation and its strong association with CNL.
- PV was likely under-diagnosed using the previous WHO 2008 hemoglobin/hematocrit cutoffs; New cut-offs and BM morphology improve diagnosing early PV.
- Only one minor criterion to diagnose pre-PMF.
- Various minor refinements.
Questions?