Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) Updated

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Disclosure of speaker’s interests
(Attilio Orazi)

- (Potential) conflict of interest

- Potentially relevant company relationships in connection with event
  - Sponsorship or research funding
  - Fee or other (financial) payment
  - Shareholder
  - Other relationship, i.e. …

- None

- Company names

✓
MDS/MPN
First introduced by the WHO 2001 (3rd edition)

- Myeloid neoplasms characterized by proliferative features combined with evidence of partially ineffective hematopoiesis and (usually) dysplasia, simultaneously present at disease outset and persistent over time

- MDS/MPN have <20% blasts in PB and/or BM. They are negative for BCR/ABL1 and PDGFR-A,-B, FGFR1 or PCM1-JAK2 rearrangements

Mughal TI, et al. Haematologica. 2015
Orazi A, Germing U. Leukemia. 2008
Anemia (rarely normal Hb*) and dysplasia in one or more lineages, in combination with one or more of the following:

- Leucocytosis (WBC ≥ 13 x10⁹/L)**
- Monocytosis (monocytes ≥ 1 x10⁹/L)
- Thrombocytosis (plts. ≥ 450 x10⁹/L)
- Splenomegaly associated with myeloproliferation***

*No erythrocytosis
** May have normal WBC but usually no absolute neutropenia (<1.8 x10⁹/L)
*** The presence of splenomegaly or fibrosis alone is not a MPN-like qualifying feature
MDS/MPN: Entities

- Chronic myelomonocytic leukemia (CMML)
- Atypical chronic myeloid leukemia \( BCR-ABL1 \) negative (aCML)
- MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
- MDS/MPN, unclassifiable (MDS/MPN,U)
- [Juvenile myelomonocytic leukemia (JMML)]
CMML
CMML: WHO definition

A subtype of MDS/MPN which has monocytosis (PB) as its major defining feature

- Monocytosis $\geq 1 \times 10^9/L$ and $\geq 10\%$ of the WBC
Abnormal monocytes found in CMML
Flow cytometry

Variable/abnormal antigenic expression in monocytes:

- Increased proportion of CD14 pos./CD16 neg. cells

- Aberrant phenotypes with two or more aberrant features, e.g. overexpression of CD56, aberrant expression of CD2 and/or decreased expression of CD14, CD64, HLA-DR, CD13, CD15, or CD36

Cytogenetics

- Normal karyotype (60%)
- If abnormal, overlaps MDS:
  - +8,
  - -7/del(7q),
  - abn. chrom.12
  - complex
Mutations of **SRSF2, TET2, ASXL1; NPM1**

- One of the three above mutations can be identified in at least 90% of CMML cases; other mutations seen less frequently are **SETBP1, RAS, RUNX1, CBL, and EZH2**. They can be helpful diagnostic adjuncts in difficult cases, particularly given the frequently normal karyotype of CMML.

  - **Mughal TI, Haematologica. 2015**

- Co-mutation of **TET2 and SRSF2** is seen in about one-third of CMML cases and is a **predictor of the diagnosis**.

  - **Malcovati L, Blood. 2014**

- **ASXL1** is a **predictor of aggressive disease** behavior and has been incorporated into a prognostic scoring system alongside karyotype and clinicopathologic parameters.

  - **Itzykson R, J Clin Oncol. 2013**

- **NPM1** mutation is seen in a rare subset of CMML (3-5%) and appears to herald a **worst prognosis**.

  - **Peng J, Eur J Haematol. 2015**
Bone Marrow Findings
Bone Marrow

- Hypercellular with high M:E ratio due to increased granulopoiesis (resembles CML); blasts usually <5%
- Typical “morphologic dissociation” between a granulocytic-rich BM and a monocytic-rich PB
- Monocytes are hard to see and to distinguish from myelocytes, metamyelocytes, and band forms

Esterase cytochemistry helps in confirming CMML

CMML
Mean: 13.4% ±17.1

CML
Mean: 0.63% ±0.7

$P = 0.053$

Bone Marrow Biopsy: “myeloproliferative look”
BM examination is **always** necessary

- AML-M4 and -M5b can simulate CMML in the PB
- CMML-1 in PB can have $\geq 10\%$ blasts in BM (CMML-2) or may be undergoing transformation to AML
- BM flow cytometry can help separating monocytes from blasts
- Karyotype e.g., 11q23 may suggest AML
- Monocytic proliferation can be more pronounced in BM than PB (seen in a subset of oligomonocytic CMML)

Immunohistochemistry in CMML

- Myeloid cells
  - CD68, Lysozyme
- Granulocytes
  - MPX, CD15, [CD56]
- Monocytes
  - CD14, CD68R, [CD56]
- Macrophages
  - CD163, CD68R
- Plasmacytoid dendritic cells
  - CD303, CD123
- Blasts
  - CD34, CD117
CD68R/PG-M1 (high specificity for monocytes)

Mature plasmacytoid dendritic cell (PDC) nodule

CD123 PMs nodules

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>CMML</td>
<td>(19%)</td>
</tr>
<tr>
<td>CML</td>
<td>0</td>
</tr>
</tbody>
</table>

Orazi et al: *Mod Pathol* 2006
Mature plasmacytoid dendritic cells in myeloid neoplasms

- Clonal in nature, closely related to the associated myeloid neoplasm

- Immunophenotype
  - CD303, CD123, CD14, CD43, CD4, CD68, CD68R, CD45RA, CD33 (weakly); CD2 and CD5 can also be positive
  - Granzyme B pos.; TIA-1 and perforin neg.
  - CD56 expression seen only in rare cases
  - Low Mib-1 (Ki-67)
Prognostication
1. CMML dysplastic vs. MPN-like
2. Refined blast count for prognosis

• CMML dysplastic (WBC, <13 x 10^9/L)
• CMML proliferative (≥13 x 10^9/L); this subtype has more frequent RAS or JAK2 mutations and splenomegaly


• CMML-0: <2% blasts in PB; <5% blasts in BM
• CMML-1: 2–4% blasts in PB; 5–9% blasts in BM
• CMML-2: 5–19% blasts in PB; 10–19% in BM, or when Auer rods are present irrespective of the blast count

Storniolo AM, et al. Leukemia. 1990
Prognosis and progression to AML

Cytogenetic risk categories:

– high (complex and monosommal karyotypes)
– intermediate (all other abnormalities)
– low [normal, sole -Y and sole der (3q)]

Median survivals of 3, 20 and 41 months, respectively

CMML with fibrosis
BACKGROUND
Chronic myelomonocytic leukemia (CMML) is a well characterized subtype of myelodysplastic/myeloproliferative neoplasms recognized by the WHO 2008 classification. Bone marrow (BM) fibrosis is seen in nearly 30% of these cases. Although BM fibrosis is an adverse prognostic marker in other myeloid neoplasms, particularly in MDS with fibrosis, no such information is available in relation to CMML. The aim of this study was to investigate the clinicopathological features and prognosis correlates of CMML with fibrosis.

MATERIALS & METHODS
• Pathology records of two institutions were searched for BM of untreated CMML patients with BM fibrosis over an 8 year period (from 4/2007 to 3/2015), as well as for CMML cases lacking fibrosis.
• BM fibrosis was defined using the WHO semi-quantitative “MF” grading system based on a 0-3 scale.
• Cases of CMML with at least MF-1 grade fibrosis (MF>1: 30 cases) were compared to CMML MF-0 (31 cases).
• Myelodysplastic-type CMML (MDS-type; <13 x10^9/L) was compared with myeloproliferative-type (MPN-type; >13 x10^9/L).
• Progression was defined as either: (1) Progression from CMML-1 to CMML-2 or (2) Progression to AML.

Table I. CMML MF-0 vs. MF ≥1: subtypes and clinical findings

<table>
<thead>
<tr>
<th>Feature</th>
<th>MF-0 (N=31)</th>
<th>MF≥1 (N=30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (Range)</td>
<td>70.0 (41-90)</td>
<td>66.3 (23-87)</td>
<td>0.2</td>
</tr>
<tr>
<td>M</td>
<td>19 (61%)</td>
<td>19 (63%)</td>
<td>0.86</td>
</tr>
<tr>
<td>F</td>
<td>12 (39%)</td>
<td>11 (37%)</td>
<td>0.1</td>
</tr>
<tr>
<td>CMML Category</td>
<td></td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>1</td>
<td>26 (84%)</td>
<td>28 (93%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5 (16%)</td>
<td>1 (33%)</td>
<td>0.52</td>
</tr>
<tr>
<td>CMML Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS-type</td>
<td>14 (45%)</td>
<td>16 (53%)</td>
<td>0.6</td>
</tr>
<tr>
<td>MPN-type</td>
<td>17 (55%)</td>
<td>14 (47%)</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td></td>
<td></td>
<td>0.04*</td>
</tr>
<tr>
<td>Y</td>
<td>11 (35%)</td>
<td>18 (60%)</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>20 (65%)</td>
<td>11 (37%)</td>
<td></td>
</tr>
<tr>
<td>Median Time to Disease Progression Not Reached</td>
<td>45.8</td>
<td>0.03*</td>
<td></td>
</tr>
<tr>
<td>Median overall survival (m)</td>
<td>24.1</td>
<td>19.2</td>
<td>0.5</td>
</tr>
<tr>
<td>SCT</td>
<td>9 (29%)</td>
<td>10 (33%)</td>
<td>0.93</td>
</tr>
<tr>
<td>N</td>
<td>18 (58%)</td>
<td>19 (63%)</td>
<td>0.93</td>
</tr>
<tr>
<td>NA</td>
<td>4 (13%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died of disease</td>
<td>8 (26%)</td>
<td>13 (43%)</td>
<td>0.35</td>
</tr>
<tr>
<td>No evidence of disease</td>
<td>14 (45%)</td>
<td>10 (33%)</td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>9 (29%)</td>
<td>7 (23%)</td>
<td></td>
</tr>
</tbody>
</table>

Table II. BM and PB findings in CMML MF-0 vs. MF ≥1

<table>
<thead>
<tr>
<th>Feature</th>
<th>MF-0 (N=31)</th>
<th>MF≥1 (N=30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BM Cellularity (Range)</td>
<td>79 (40-100)</td>
<td>87 (40-100)</td>
<td>0.02*</td>
</tr>
<tr>
<td>BM Megakaryocytes</td>
<td></td>
<td></td>
<td>0.006*</td>
</tr>
<tr>
<td>Increased</td>
<td>12 (39%)</td>
<td>21 (70%)</td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>3 (10%)</td>
<td>5 (17%)</td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>16 (51%)</td>
<td>4 (13%)</td>
<td></td>
</tr>
<tr>
<td>Mean BM Smear Blasts (Range)</td>
<td>4.23 (0-16)</td>
<td>4.43 (0-10)</td>
<td>0.81</td>
</tr>
<tr>
<td>Mean BM Smear Monocytes (Range)</td>
<td>18 (3-48)</td>
<td>17 (2-69)</td>
<td>0.79</td>
</tr>
<tr>
<td>Mean BM WBC (x 10^9 cells/ l) (Range)</td>
<td>17.2 (3.7-53.1)</td>
<td>30.7 (3-170)</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean PB Blasts (%)</td>
<td>0.4 (0-8)</td>
<td>0.8 (0-3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Mean Abs Mono (x 10^9 cells/ l) (Range)</td>
<td>4.6 (0.6-22.8)</td>
<td>10.7 (0.7-131.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>Mean Hgb (g/ dl) (Range)</td>
<td>10.8 (5.0-14.9)</td>
<td>10.7 (6.4-15.0)</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean MCV (fl) (Range)</td>
<td>91.0 (69-114)</td>
<td>91.2 (74-117)</td>
<td>0.95</td>
</tr>
<tr>
<td>Mean Plt (x10^9 cells/ L) (Range)</td>
<td>113 (12-296)</td>
<td>90 (12-266)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

CONCLUSIONS
• Patients with CMML associated with BM fibrosis have higher marrow cellularity, increased megakaryopoiesis, more frequent splenomegaly and a significantly shorter median time to disease progression, when compared to those without BM fibrosis.
• Assessing BM fibrosis in CMML is important.
• Similar to MDS, its presence identifies a distinct subgroup of CMML patients which may require a more aggressive treatment.

Fig. 1. BM biopsy of a patient with CMML and BM fibrosis. A,B,C (H&E) , D reticulin stain showing MF-2 fibrosis.

Fig. 2. Kaplan-Meier analysis of disease progression. CMML patients with MF≥1 showed a shorter overall median time to disease progression by Kaplan-Meier survival analysis (45.8 months vs not reached; p=0.03, log rank test) compared to MF-0 patients.

Fig. 2. Kaplan-Meier analysis of progression by BM fibrosis

Table II. BM and PB findings in CMML MF-0 vs. MF ≥1

Kaplan-Meier analysis of progression by BM fibrosis

Petrova-Drus K et al. Mod Pathol 2016; 29:368A
Oligomonocytic CMML
70 year old male pt. with anemia and thrombocytopenia (PB)

Hb 9.6, MCV 106 fl; WBC 5.7 x10^9/L; monocytes 12% (0.7 x10^9/L). Plts. 92 x10^9/L
Bone marrow aspirate
Oligomonocytic chronic myelomonocytic leukemia: can the threshold for peripheral blood monocytois be lowered?

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Background

Based on the 2008 WHO Classification, chronic myelomonocytic leukemia (CMLL) is characterized by persistent peripheral blood (PB) monocytois (>1x10^9/L), with monocytes comprising >10% of the PB leukocytes and the presence of dysplasia in one or more hematopoietic lineages. We have encountered cases that have relative monocytois in bone marrow (BM) or PB and dysplasia, but ≤1x10^9/L PB monocytes. These cases are typically diagnosed as myelodysplastic syndrome (MDS) or myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN, U). Since distinction of CMLL from MDS is clinically important, we undertook a study to better characterize these cases provisionally termed oligomonocytic CMLL (OM-CMLL).

Materials and Methods

Thirty four cases from three large institutions were selected based on the 2008 WHO criteria and presence of >10% monocytes in BM and/or >10% PB monocytes with absolute monocyte count of 0.5-1x10^9/L. Clinical and pathologic information was compared to 10 patients with conventional CMLL and 10 patients with MDS. Whole exome sequencing of selected cases is currently in progress.

Results

- There were 24 men and 10 women with a median age of 62 (range 19-87) years.
- 7/34 (20%) patients had therapy-related OM-CMLL.
- 5/34 (15%) had organomegaly.
- At presentation, compared to control CMLL, OM-CMLL patients had significantly
  - lower mean WBC (4.2x10^9/L vs 23x10^9/L, p<0.01).
  - lower absolute number of PB monocytes (0.7x10^9/L vs 4.25x10^9/L, p<0.01).
  - Lower BM monocytes (7.5% vs 13.2%, p<0.05).
  - PB monocyte percentage was similar for OM-CMLL and control CMLL (18.4% vs 22.2%, p=0.67).
- At presentation, compared to control MDS, OM-CMLL patients had a similar mean WBC
  - the percentage of PB and BM monocytes was significantly higher (p<0.01).
- The remaining CBC values, presence of BM fibrosis, and degree of dysplasia were similar in the three groups (OM-CMLL, CMLL control and MDS control).
- Abnormal karyotype was seen in 46% of OM-CMLL vs 10% CMLL controls and 28% MDS controls.
- Limited mutational analysis of OM-CMLL demonstrates:
  - JAK2 mutation in 1/16 cases (6%).
  - N-RAS mutation in 3/18 cases (17%).
  - DNMT3A mutation in 3/13 cases (23%).
  - 10/34 (30%) patients with OM-CMLL progressed to overt CMLL a median of 3 (range 1-58) months after diagnosis.
  - At last follow-up, 14/34 OM-CMLL patients (44%) had died of disease, with a median survival of 16 (range 3-126) months.

Conclusions

- At least a subset of OM-CMLL is likely to represent an early phase of CMLL, since 30% of patients developed CMLL.
- Therapy-related disease appears more frequent in OM-CMLL compared to CMLL or MDS (p<0.01).
- Since up to 90% of conventional CMLL cases have TET2, ASXL1 or SRSF2 mutations, genomic analysis is in progress in order to attempt to further characterize the mutational profile of OM-CMLL.
Diagnostic criteria for CMML (Update 2016)

- Persistent PB monocytosis $>1 \times 10^9/L$ and $> 10\%$ of the WBC
- Not meeting WHO criteria for $BCR-ABL1$ pos. CML, PMF, PV or ET $^a$
- No rearrangement of $PDGFRA$, $PDGFRB$, $FGFR1$, or $PCM1-JAK2$
- Fewer than 20\% blasts (include promonocytes) in the PB and BM
- Dysplasia in $> 1$ myeloid lineage(s). If absent, the diagnosis of CMML may still be made if the other requirements are met, and an acquired cytogenetic or molecular genetic abnormality $^b$ is detected, --or-- if the monocytosis has persisted for at least 3 months and all other causes of monocytosis have been excluded.

$^a$Cases of MPN can be associated with monocytosis or they can develop it during the course of the disease. These cases may simulate CMML. In these rare instances, a previous documented history of MPN excludes CMML, while the presence of MPN features in the bone marrow and/or of MPN-associated mutations ($JAK2$, $CALR$ or $MPL$) tend to support MPN with monocytosis rather than CMML. $^b$The presence of mutations in genes often associated with CMML (e.g. $TET2$, $SRSF2$, $ASXL1$, $SETBP1$) in the proper clinical contest can be used to support a diagnosis. It should be noted however, that some of the mutations can be age related or be present in subclones. Therefore caution would have to be used in the interpretation of these genetic results.

Atypical CML \textit{BCR-ABL1} neg. (aCML)
aCML has an abysmal prognosis

Peripheral blood smear in aCML

Note the severe dysgranulopoiesis and the abnormal chromatin clumping.
Atypical chronic myeloid leukemia as defined in the WHO classification is a JAK2 V617F negative neoplasm.

aCML: *SETBP1* and *ETNK1* mutation(s) in the absence of *CSF3R* mutation


Differential diagnosis of aCML

aCML vs. Chronic Neutrophilic Leukemia (CNL)
aCML vs. MPN-associated neutrophilia
CNL vs. aCML

CNL
• Neutrophilia with no significant dysplasia (toxic granulations)

aCML
Neutrophilia with immature myeloid cells and dysplasia

CSF3R (90%)
additional SETBP1 +/- (50%)

SETBP1 (15-32%)
ETNK1 (9%); in one third of these, coexists with SETBP1; CSF3R (<10%)
Diagnostic criteria for aCML, BCR-ABL1 negative (update 2016)

- Leukocytosis $\geq 13\times 10^9$/L due to neutrophilia
- Granulocytic precursors (promyelocytes, myelocytes and metamyelocytes) $\geq 10\%$ of WBC
- Dysgranulopoiesis (may include abnormal chromatin clumping)
- No basophilia; basophils usually $< 2\%$ of PB leukocytes; No monocytosis; monocytes $< 10\%$ of PB leukocyte; Less than 20$\%$ blasts in the blood and bone marrow
- No $BCR-ABL1$, $PDGFRA$, $PDGFRB$ or $FGFR1$, or $PCM1-JAK2$
- No PMF, PV or ET*

*Cases of MPN, particularly those in AP and/or in PV/ET myelofibrosis, if neutrophilic, may simulate aCML. A previous history of MPN, the presence of MPN features in the bone marrow tend to exclude a diagnosis of aCML. MPN-associated mutations in $JAK2$, $CALR$ or $MPL$ tend also to exclude a diagnosis of aCML. Conversely, a diagnosis of aCML is supported by the presence of $SETBP1$ and/or $ETNK1$ mutations. The presence of a $CSF3R$ mutation is uncommon in aCML and if detected should prompt a careful morphologic review to exclude an alternative diagnosis of CNL or of other myeloid neoplasm.
MDS/MPN features in MPN

Monocytosis
Neutrophilia with dysplasia
Monocytosis in PMF and Polycythemia Vera

Monocytic progression of PMF

Earlier (2002) BMB

Polycythemia Vera with aCML-like neutrophilic progression

WBC > 25 x10⁹/L ; FISH for BCR-ABL1 neg.; Karyotype: 46, XY

Boiocchi et al. Mod Pathol. 2015;28:1448-57
“The Overlaps”

Well defined and not so well defined entities
True *gray zone* between PMF and CMML

Monocytosis $> 1.0 \times 10^9/$L and ambiguous BM morphology
Combination of mutations: *MPL* 44%; *ASXL1* 43%; *EZH2* 51%; *TET2* (2 frameshift mutations) 42% and 48%; *SRSF2* 46%; *NRAS* 25%.

Chapman JR et al, Mod Pathol 2017, in press
Myeloid neoplasms associated with isolated isochromosome 17q
Myeloid neoplasms with isolated 17q

- Neutrophilia with monolobated forms
- In a proportion of the cases leukocytosis is CMML-like or aCML like
Myeloid neoplasm with isolated 17q

Courtesy of Dr. Carlos Bueso-Ramos, MD Anderson
MPN with isolated 17q

Hypercellular BM with variable morphology e.g., pleomorphic megakaryocytes “PMF-like” have been reported (McClure RF et al. Br J Haematol, 1999)
MDS/MPN with isolated isochromosome 17q

• Its appropriate categorization is uncertain at this time

• Although a proportion of cases meet the criteria for CMML, aCML, MPN-AP/BP, MDS or AML, others may be appropriately categorized as MDS/MPN-U

• High frequency of mutations in ASXL1, SETBP1, SRSF2, NRAS, TP53

The overlap syndrome promoted to full entity

MDS/MPN-RS-T*

*Formerly, Refractory Anemia with Ring Sideroblasts and Thrombocytosis (RARS-T)
MDS/MPN-RS-T

- Combination of MDS-RS and MPN-like features clinically, morphologically and at molecular level
- May progress from RARS
- *SF3B1* mutation (80% - similar to MDS-RS)
- *JAK2* pos. in up to 60% (unclear prognostic role)
- *MPL W515K/L* 5%; *CALR* rare
- *BCR/ABL1* neg.
- Karyotype variable

Diagnostic criteria for MDS/MPN-RS-T (update 2016)

- Anaemia associated with erythroid lineage dysplasia with or without multilineage dysplasia; **≥15% ring sideroblasts** in BM; <1% blasts in PB and <5% blasts in BM
- Persistent thrombocytosis with platelet count **≥450 x 10⁹/L**
- **Presence of a SF3B1 mutation**
- No BCR-ABL1 fusion gene, or PDGFRA, PDGFRB, FGFR1, PCM1-JAK2; no (3;3)(q21;q26), inv(3)(q21q26) or del(5q)**
- No history of MPN, MDS (except MDS-RS), or other type MDS/MPN
- In the absence of SF3B1 mutation, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic/myeloproliferative features

*A diagnosis of MDS/MPN-RS-T is strongly supported by the presence of SF3B1 mutation together with a mutation in JAK2 V617F, CALR or MPL genes

**In a case which otherwise fulfills the diagnostic criteria for MDS with isolated del(5q)

Mutational Analysis in MDS/MPN

• Useful in differential diagnosis:
  – in establishing MDS/MPN-RS-T
  – in separating aCML from CNL
  – in excluding MPN
  – in supporting a highly suspected diagnosis (e.g. early phase disease not meeting all the diagnostic thresholds)

• Provide powerful prognostic info (several mutations are prognostically detrimental)

• Limited value for confirmation of clonality; analogy with MDS in relation to CHIP and CCUS (too few studies)
In conclusion

- Cytogenetics and molecular genetics are key diagnostic elements in some myeloid neoplasms. However, the MDS/MPNs are still clinicopathologically defined entities with specific diagnostic algorithms based on careful multiparametric integration.
- Mutational analysis provides diagnostic support and helps in accurate prognostication.
- Once the diagnostic role of genetic abnormalities is better clarified, a redefinition of disease boundaries (and a new Blue Book) will follow.
Thank you for your attention!