Significance of Multilineage Dysplasia in Acute Myeloid Leukemia

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Hematopathology Unit
Pathology Department
Hospital Clínic Barcelona
Significance of Multilineage Dysplasia in Acute Myeloid Leukemia

1. Introduction

2. MLD in AML with mutated NPM1 & biallelic mutations of CEBPA

3. MLD in de novo AML with intermediate-risk cytogenetics & wild-type NPM1

4. MLD in older patients with AML

5. Implications of MLD for AML diagnosis according to the WHO

6. Conclusions
I. AML with recurrent cytogenetic abnormalities
   - AML with t(8;21)(q22;q22)/RUNX1-RUNX1
   - AML with inv(16) or t(16;16)(p13;q22)/CBFβ-MYH11
   - Acute promyelocytic leukemia [t(15;17) & PML-RAR-α]
   - AML with t(9;11)(p22;q23)/AF9(MLLT3)-MLL
   - AML with t(6;9)(p23;q34)/DEK-CAN(NUP214)
   - AML with inv(3) or t(3;3)(q21;q26)/RPN1-EVI1
   - Megakaryoblastic AML with t(1;22)(p13;q13)/RBM15-MKL1
   - AML with mutated NPM
   - AML with normal karyotype and CEBPA mutation

II. AML with myelodysplasia-related changes

III. Therapy-related AML/MDS

IV. AML, not otherwise specified
   - AML without differentiation
   - AML minimally differentiated
   - AML with differentiation
   - AML myelomonocytic
   - AML monoblastic and monocytic
   - Acute erythroid leukemia
   - Acute megakaryoblastic leukemia

V. Myeloid sarcoma

VI. Myeloid proliferations related to Down syndrome

VII. Blastic plasmacytoid dendritic cell neoplasms
Acute myeloid leukemia
Impact on survival of cytogenetic entities recognized in 2008
WHO classification

WHO 2001: Acute myeloid leukemia with multilineage dysplasia as a new category

- **Definition:**
  - AML (20% blasts)
  - $\geq 50\%$ dysplastic abnormalities in 2/3 hematopoietic cell lines

- **Features:**
  - *de novo* or following a previous MDS or MPN
  - chromosome abnormalities similar to those in MDS
  - older patients, higher proportion to unfavorable cytogenetics
  - unfavorable prognosis, with low response rate to standard treatment and short response duration
**WHO 2008**: acute myeloid leukemia with myelodysplasia-related changes (AML-MRC)

- **Definition**: AML (≥20% blasts BM or PB) with one of these:
  - ≥50% dysplastic abnormalities in 2/3 hematopoietic cell lines
  - Prior history of MDS or MDS/MPN
  - MDS related cytogenetic abnormalities & absence of recurrent genetic abnormalities
WHO 2008: AML-MRC

• Three possibilities for diagnosis:
  – AML arising from previous MDS or MDS/MPN
  – AML with an MDS-related cytogenetic abnormality
  – AML with multilineage dysplasia
Dysplasia assessment*

- **Dysgranulopoiesis**: 25-100 neutrophils
  - hypogranular cytoplasm, hypossegmented nuclei or bizarrely segmented nuclei, cytoplasmic vacuoles
  - MPO deficiency (50%, 20 cells)
- **Dyserythropoiesis**: at least 25 mature erythroblasts
  - megaloblastosis, karyorhexis & nuclear irregularity, fragmentation or multinucleation
  - ring sideroblasts, PAS positivity
- **Dysmegakaryopoiesis**: at least 6 megakaryocytes
  - micromegakaryocytes, normal sized or large megakaryocytes with non-lobulated or multiple nuclei

AML with myelodysplasia-related changes in WHO: concerns

• Its recognition as a separate entity implies the presence of differential biological and clinical features.
• This seems to be confirmed for patients with AML and MLD associated with high risk cytogenetic abnormalities.
• Unclear whether multilineage dysplasia *per se* or other well recognized adverse prognostic factors in AML accounts for its poor clinical outcome.
Prognostic significance of multilineage dysplasia in AML: background

Multilineage dysplasia (MLD) in acute myeloid leukemia (AML) correlates with MDS-related cytogenetic abnormalities and a prior history of MDS or MDS/MPN but has no independent prognostic relevance: a comparison of 408 cases classified as "AML not otherwise specified" (AML-NOS) or "AML with myelodysplasia-related changes" (AML-MRC)

Miriam Miesner, Claudia Haferlach, Ulrike Bacher, Tamara Weiss, Katja Maciejewski, Alexander Kohlmann, Hans-Ulrich Klein, Martin Dugas, Wolfgang Kern, Susanne Schnittger and Torsten Haferlach
Prognostic significance of multilineage dysplasia in AML: cytogenetics & MDS

- 408 AML adult patients; MLD 31.9%
  - AML-MLD sole (N=90)
  - AML with MDS-related cytogenetics (N=55)
  - AML with history of MDS or MDS/MPN (N=42)

57.6% NPM1+
Prognostic significance of MLD in AML with intermediate risk cytogenetics, \textit{NPM1}-mutated

1. Falini (Blood 2010) (318 cases)
   
   23% MLD

   – \textit{NPM1}-mutated AML with and without MLD showed overlapping immunophenotype and gene expression profile

   – overall and event-free survival did not differ among \textit{NPM1}-mutated AML patients independently of whether they were MLD(+) or MLD(-)
Prognostic significance of MLD in AML with intermediate risk cytogenetics, \textit{NPM1}-mutated

2. Díaz-Beyá, Rozman, Pratcorona, Torrebadell, Camós, Aguilar & Esteve (Blood 2010)
   - No impact of MLD on survival in patients with \textit{NPM1} mutations
   - MLD predicts a poorer survival in patients with \textit{wild-type NPM1}
Prognostic significance of MLD in AML with IR-cytogenetics AML, *NPM1*-mutated

- Multilineage dysplasia in the presence of NPM1 mutation, a normal karyotype and no history of MDS
  - MLD found in 23% de novo NPM1 mutated AML
  - No prognostic significance for MLD (Falini, Blood 2010, Díaz-Beyá, Blood 2010)

- NPM1 mutation in secondary AML cases
  - Lack the favorable prognosis of the novo AML with mutated NPM1 (Schnittger et al, Leukemia 2011, Courville et al, Modern Pathology 2013)
• 6-15% of newly diagnosed AML
• There are no distinctive morphologic features
• 70% of AML with CEBPA have a normal karyotype
• In multivariate analyses, the presence of biCEBPA but not moCEBPA is an independent factor for favorable outcome in AML

• MLD
  • found in 25% CEBPA mutated AML patients
  • No significant survival difference in MLD+ and MLD- subgroups

Swerdlow et al. WHO 2008
Green et al. JCO 2010; 28: 2739
Dufour et al. JCO 2010;28:570
Bacher et al, Blood 2012
Multilineage dysplasia in mutated $NPM1$ and $biCEBPA$ AML

These mutations now supersede the presence of multilineage dysplasia in the classification.
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   - No impact of MLD on survival in patients with *NPM1* mutations
   - MLD predicts a poorer survival in patients with *wild*-type *NPM1*

![Graph A: Mutated NPM1](image)

![Graph B: Wild-type NPM1](image)

62 cases, 13 with MLD
Prognostic significance of MLD in AML with intermediate risk cytogenetics, Wild-type NPM1

- CCC&CETLAM: Group of 10 expert cytologists:

Esther Alonso, Leonor Arenillas, Anna Aventín, Mireia Camós, Teresa Gimenez, Mayda Navarrete, Tomás Navarro, Granada Perea, María Rozman, Esperanza Tuset

on behalf of the Catalan Group of Hematologic Cytology
Prognostic significance of MLD in AML with intermediate risk cytogenetics, Wild-type NPM1

177 cases

- MLD1 (≥50% dysplasia 2-3 series)
- MLD2 (≥50% dysplasia 1 series, ≥30% dysplasia 1 series)

![Pie chart showing distribution of cases]

- No MLD, 80, 43%
- MLD1, 43, 24%
- MLD2, 16, 9%
- Non-evaluable, 43, 24%

![Survival curve graph]
Multilineage dysplasia is associated with a poorer prognosis in patients with de novo acute myeloid leukemia with intermediate-risk cytogenetics and wild-type NPM1

María Rozman · José-Tomás Navarro · Leonor Arenillas · Anna Aventín · Teresa Giménez · Esther Alonso · Granada Perea · Mireia Camós · Mayda Navarrete · Esperanza Tuset · Lourdes Florensa · Fuensanta Millá · Josep Nomdedéu · Esmeralda de la Banda · Marina Díaz-Beyá · Marta Pratcorona · Ana Garrido · Blanca Navarro · Salut Brunet · Jorge Sierra · Jordi Esteve · on behalf of Grup Català de Citologia Hematológica and Spanish CETLAM Group (Grupo Cooperativo Para el Estudio y Tratamiento de las Leucemias Agudas Mieloblásticas)

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International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts

Hervé Dombrain,1 John F. Seymour,2 Aleksandra Butrym,3 Agnieszka Wierzbowska,4 Dominik Selleslag,5 Jun Ho Jang,6 Rajat Kumar,7 James Cavenagh,8 Andre C. Schuh,9 Anna Candoni,10 Christian Récher,11 Irvindeep Sandhu,12 Teresa Bernal del Castillo,13 Haifa Kathrin Al-Ali,14 Giovanni Martinelli,15 Jose Falantes,16 Richard Noppeney,17 Richard M. Stone,18 Mark D. Minden,9 Heidi McIntyre,19 Steve Songer,19 Lela M. Lucy,19 C. L. Beach,19 and Hartmut Döhner20

Table 1. Demographics and disease characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Azacitidine (n = 240)</th>
<th>Common CCR arm</th>
<th>LDAC (n = 158)</th>
<th>IC (n = 44)</th>
<th>Combined CCR (n = 240)</th>
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<td>Age, years</td>
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<td>57-91</td>
<td>65-90</td>
<td>65-93</td>
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<td>AML classification</td>
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<td>Not otherwise specified</td>
<td>153</td>
<td>63.5</td>
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<tr>
<td>With myelodysplasia-related changes</td>
<td>75</td>
<td>31.1</td>
<td>64</td>
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<td>With therapy-related myeloid neoplasms</td>
<td>8</td>
<td>3.3</td>
<td>2</td>
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<td>With recurrent genetic abnormalities*</td>
<td>3</td>
<td>1.2</td>
<td>2</td>
<td>4</td>
<td>5</td>
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<td>Prior MDS</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>49</td>
<td>20.3</td>
<td>11</td>
<td>24.4</td>
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<td>Secondary</td>
<td>3</td>
<td>1.2</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

**AML classification**

- Not otherwise specified: 153
- With myelodysplasia-related changes: 75
- With therapy-related myeloid neoplasms: 8
- With recurrent genetic abnormalities*: 3
- Prior MDS: 49

**Prior MDS**

- Yes: 49
- Secondary: 3

**Initial AML**

- Median: 52
- Min-max: 29-141

**Plasma = IN[T]**

- Median: 90
- Min-max: 22-141

**ANC** = absolute neutrophil count; **Hg** = hemoglobin; **WBC** = white blood cell.

*Excluding the principal entities of AML with APL/H and AML with CEBPA mutation (number data not available).

**Prior central review**

- Patients were randomly assigned on the basis of local pathology assessment of baseline BM aspirate, which was subsequently reviewed by the central pathologist in a small number of cases; baseline blast count was <30%, prior central review.

**No requirement MOC Clinical Practice Guidelines, 2013 (1 abnormal karyotype and 2 CCR patients were missing cytogenetic data).**

**In some cases, maximum WHO values were higher than predicted according to the WHO value of +5 or +7(5). Values shown here are the last over-losing value before randomization, which may have been obtained after the screening WHO value used for study entry.
Azacitidine (AZA) Versus Conventional Care Regimens (CCR) in Older Patients with Newly Diagnosed Acute Myeloid Leukemia (>30% Bone Marrow Blasts) with Morphologic Dysplastic Changes: A Subgroup Analysis of the AZA-AML-001 Trial

John F Seymour, MBBS, FRACP, PhD¹, Hartmut Döhner, MD², Aleksandra Butrym, MD³*, Agnieszka

Response was similar with AZA vs CCR in patients with AML-MRC

*According to IWG 2003 criteria; ORR = overall response rate; CR = complete response; CRi = CR with incomplete blood count recovery; PR = partial response SD = stable disease; PD = progressive disease; NE = not evaluable

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   - AML with mutated NPM
   - AML with normal karyotype and biCEBPA mutation

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   - AML myelomonocytic
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V. Myeloid sarcoma

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VII. Blastic plasmacytoid dendritic cell neoplasms
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   - AML with t(6;9)(p23;q34)/DEK-CAN(NUP214)
   - AML with inv(3) or t(3;3)(q21;q26)/GATA2 ,MECOM
   - Megakaryoblastic AML with t(1;22)(p13;q13)/RBM15-MKL1
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VII. Blastic plasmacytoid dendritic cell neoplasms
AML with $t(6;9)(p23;q34);DEK-NUP214$

- Multilineage dysplasia, basophilia
AML with inv(3) or t(3;3)(q21.3;q26.2);GATA2, MECOM

• Megakaryocytic dysplasia
Cytogenetic alterations are the main prognostic factor in AML

AML-MLD NOT includes some AMLs with MLD:

- AML with recurrent cytogenetic abnormalities
  - Good prognosis
    - AML with mutated *NPM1*
    - AML with biallelic mutations of *CEBPA*
  - Bad prognosis
    - AML with t(6;9)(p23;q34); *DEK-NUP214*
    - AML with inv(3) or t(3;3)(q21;q26); *GATA2, MECOM*

- Therapy-related AML
MYELOID NEOPLASMS WITH ERYTHROID PREDOMINANCE (≥50% BM CELLS). WHO 2008

• Blast percentage (BM aspirate)
  – 5-19% → MDS with excess blasts
  – ≥20% of all nucleated cells (ANC) → AML
    • Exception erythroleukemia: ≥20% blasts from non-eritroid cells

• Degree of dysplasia (BM aspirate)
  – ≥10% per lineage for MDS
  – ≥50% per lineage for AML with myelodysplasia-related changes

• 3 overlapping entities:
  – MDS with excess blasts and erythroid predominance
  – AML with myelodysplasia-related changes
  – Erythroleukemia
MYELOID NEOPLASMS WITH ERYTHROID PREDOMINANCE (≥50% BM CELLS)

Refractory anemia with excess blasts
5-19% blasts (ANC)  
≥10% dysplastic abnormalities in 1-3 hematopoietic cell lines

AML with myelodysplasia-related changes
≥20% blasts (ANC)  
≥50% dysplastic abnormalities in ≥2 hematopoietic cell lines

Erythroleukaemia (erythroid/myeloid, M6a FAB)
≥50% erythroid precursors  
≥20% myeloblasts in the non-erytroid cells (NEC)
MYELOID NEOPLASMS WITH ERYTHROID PREDOMINANCE (≥50% BM CELLS)

Erythroleukemia cases with blasts <20% from all nucleated BM cells & MDS

- similar genetic alterations
- similar prognosis

- Wang SA et al, Mod Pathol 2008
- Hasserjian R et al, Blood 2010
- Bacher et al, Haematologica 2011
- Calvo X et al, Mod Pathol 2016

WHO 2016:
Blasts ≥20% (ANC) → AML (MLD)
Blasts 5-19% (ANC) → MDS with excess blasts
### MYELOID NEOPLASMS WITH ERYTHROID PREDOMINANCE (≥50% BM CELLS): WHO 2016

#### Table 16. Diagnostic approach to myeloid neoplasms when erythroid precursors comprise ≥50% of BM nucleated cells

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>≥50%</td>
<td>NA</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>Therapy-related myeloid neoplasm</td>
<td>Therapy-related myeloid neoplasm</td>
</tr>
<tr>
<td>≥50%</td>
<td>≥20%</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
<td>AML with recurring genetic abnormality</td>
<td>AML with recurring genetic abnormality</td>
</tr>
<tr>
<td>≥50%</td>
<td>≥20%</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>AML with myelodysplasia-related changes</td>
<td>AML with myelodysplasia-related changes</td>
</tr>
<tr>
<td>≥50%</td>
<td>≥20%</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>AML, NOS, acute erythroid leukemia (erythroid/myeloid type)</td>
<td>AML, NOS (non erythroid subtype)</td>
</tr>
<tr>
<td>≥50%</td>
<td>&lt;20%, but ≥20% of nonerythroid cells</td>
<td>No</td>
<td>No*</td>
<td>NA</td>
<td>AML, NOS, acute erythroid leukemia (erythroid/myeloid subtype)</td>
<td>MDS†</td>
</tr>
<tr>
<td>≥50%</td>
<td>&lt;20%, and &lt;20% of nonerythroid cells</td>
<td>No</td>
<td>No*</td>
<td>NA</td>
<td>MDS†</td>
<td>MDS†</td>
</tr>
<tr>
<td>≥80% immature erythroid precursors with ≥30% proerythroblasts</td>
<td>&lt;20%</td>
<td>No</td>
<td>No*</td>
<td>NA</td>
<td>AML, NOS, acute erythroid leukemia (pure erythroid type)</td>
<td>AML, NOS, acute erythroid leukemia (pure erythroid type)</td>
</tr>
</tbody>
</table>

**NOTES**: AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; NA, not applicable.

*Cases of AML (t(8;21)(q22;q22.1); RUNX1-RUNX1T1, AML with inv(16)(p13.1q22) or t(16;15)(p13.1;q22); CBFB-MYH11 or APL with PML-RARA, may rarely occur in this setting with <20% blasts and those diagnoses would take precedence over a diagnosis of AML, NOS, or MDS.

†Classify based on myeloblast percentage of all BM cells and of PB leukocytes and other MDS criteria.
WHO 2008: acute myeloid leukemia with myelodysplasia-related changes (AML-MRC)

- Definition: AML (20% blasts BM or PB) with one of these:
  - ≥50% dysplastic abnormalities in 2/3 hematopoietic cell lines
  - Prior history of MDS or MDS/MPN
  - MDS related cytogenetic abnormalities & absence of recurrent genetic abnormalities
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  - Prior history of MDS or MDS/MPN
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WHO 2016: acute myeloid leukemia with myelodysplasia-related changes (AML-MRC)

- **del (9q)**
  - Associated with *NPM1* & *biCEBPA*
  - Lack of prognostic significance

---

**Table 18. Cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes when ≥20% PB or BM blasts are present and prior therapy has been excluded**

<table>
<thead>
<tr>
<th>Cytogenetic abnormalities</th>
</tr>
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<tbody>
<tr>
<td>Complex karyotype (3 or more abnormalities)</td>
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<tr>
<td>Unbalanced abnormalities</td>
</tr>
<tr>
<td>- 7/del(7q)</td>
</tr>
<tr>
<td>- del(5q)/t(5q)</td>
</tr>
<tr>
<td>- i(17q)/t(17p)</td>
</tr>
<tr>
<td>- 13/del(13q)</td>
</tr>
<tr>
<td>- del(11q)</td>
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<tr>
<td>- del(12p)/t(12p)</td>
</tr>
<tr>
<td>- idic(X)(q13)</td>
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<tr>
<td>Balanced abnormalities</td>
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<tr>
<td>- t(11;16)(q23.3;p13.3)</td>
</tr>
<tr>
<td>- t(3;21)(q26.2;q22.1)</td>
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<td>- t(1;3)(p36.3;q21.2)</td>
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<td>- t(3;5)(q25.3;q35.1)</td>
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The updated WHO classification of hematological malignancies

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

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The World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues was last updated in 2008. Since then, there have been numerous advances in the identification of unique biomarkers associated with some myeloid neoplasms and acute leukemias, largely derived from gene expression analysis and next-generation sequencing that can significantly improve the diagnostic criteria as well as the prognostic relevance of entities currently included in the WHO classification and that also suggest new entities that should be added. Therefore, there is a clear need for a revision to the current classification. The revisions to the categories of myeloid neoplasms and acute leukemia will be published in a monograph in 2016 and reflect a consensus of opinion of hematopathologists, hematologists, oncologists, and geneticists. The 2016 edition represents a revision of the prior classification rather than an entirely new classification and attempts to incorporate new clinical, prognostic, morphologic, immunophenotypic, and genetic data that have emerged since the last edition. The major changes in the classification and their rationale are presented here. (Blood. 2016; 127(20):2391-2405)
WHO 2016: acute myeloid leukemia with myelodysplasia-related changes (AML-MRC)

AML with myelodysplasia-related changes

The category of AML with myelodysplasia-related changes has been retained, but is refined to better incorporate cases with features suggesting a poor prognosis. As mentioned, the presence of multilineage dysplasia alone will not classify a case as AML with myelodysplasia-related changes when a mutation of NPM1 or biallelic mutation of CEBPA is present. In cases lacking these mutations, the morphologic detection of multilineage dysplasia (defined as the presence of 50% or more dysplastic cells in at least 2 cell lines) remains a poor prognostic indicator and is sufficient to make a diagnosis of AML with myelodysplasia-related changes. A history of MDS remains as an inclusion criterion for this category as does the presence of an MDS-related cytogenetic abnormality with 1 exception: del(9q) has been removed as a defining cytogenetic abnormality for AML with myelodysplasia-related changes because of its association with NPM1 or biallelic CEBPA mutations and its apparent lack of prognostic significance in those settings. Table 18 lists the cytogenetic abnormalities that now define AML with myelodysplasia-related changes.
Conclusions

• MLD in AML has diagnostic, prognostic & therapeutic implications
• MLD in AML has well-defined assessment criteria
• MLD should be evaluated and reported in all newly-diagnosed AML cases
• This information must be integrated with clinical, immunophenotypic, genetic and molecular information for a correct WHO-2016 categorization
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