MDS Updated

Robert P Hasserjian, MD
Professor of Pathology
Massachusetts General Hospital and Harvard Medical School
Disclosure of speaker’s interests

Robert P Hasserjian

• **Celgene**: Consulting income
• **Promedior**: Consulting income
Outline of presentation

• Review criteria required to establish a diagnosis of MDS according to the 2016 WHO Classification

• Present the revised 2016 WHO MDS disease categories
  – Distinguishing features of each category
  – Changes from 2008 Classification based on new data
Challenges in MDS diagnosis

- Non-neoplastic causes of cytopenia
  -- Other neoplasms
  -- Inherited
  -- Extrinsic factors

- Does the patient have a neoplasm?
- Should the patient be treated for MDS or should another diagnosis be sought?
- Should the patient receive induction or other intensive chemotherapy with a goal of remission?

Risk-adapted therapy according to prognosis
Case

- 74 year-old man presented with anemia and thrombocytopenia discovered on routine blood work
- Bone marrow biopsy and aspirate performed to ‘rule out MDS’
Components of MDS diagnosis and classification (2016 WHO)

Unexplained cytopenias are a sine qua non of MDS

90% of MDS cases have a demonstrable clonal genetic abnormality

Dysplasia is defining feature of MDS
Information needed to diagnose MDS

- **Clinical history**
  - Full CBC and WBC differential results
  - Knowledge of duration of cytopenias and possible other causes of cytopenia

- **Morphology review**
  - Blood smear
  - Bone marrow aspirate and/or touch prep
  - Bone marrow biopsy

- **Complete bone marrow karyotype**
Complications in defining cytopenia

ANC x 10⁹/L

- <1.0
- 1.1
- 1.2
- 1.3
- 1.4
- 1.5
- 1.6
- 1.7
- 1.8
- 1.9
- ≥2.0

HGB g/dL

- 8.0
- 9.0
- 10.0
- 11.0
- 12.0
- 13.0
- 14.0

Platelets x 10⁹/L

- 80
- 90
- 100
- 110
- 120
- 130
- 140
- 150
- 160
- 170
- 180

WHO 2016 cytopenic thresholds

• ‘Traditional’ original IPSS thresholds still apply as a guideline
  – Absolute neutrophil count $<$1.8 x $10^9$/L
  – Hemoglobin $<$10 g/dL
  – Platelets $<$100 x $10^9$/L

• MDS may be diagnosed with milder cytopenias if definitive diagnostic criteria are present
  – Hemoglobin $<$12/13 g/dL for females/males
  – Platelets $<$150 x $10^9$/L
  – Should use individual laboratory reference ranges
  – Ethnic and conditional variation should be taken into account

Case

- 74 year-old man presented with anemia and thrombocytopenia discovered on routine blood work

- **WBC 4.34 x 10⁹/L**
  - 52% polys (ANC 2.2 x 10⁹/L, 36% lymphs, 11% monos, 1% eos, 0.2 nRBC/100 WBC)

- **HGB 8.8 g/dL (MCV 112.1 fL)**

- **PLT 100 x 10⁹/L**

- Patient is asymptomatic and past medical history is only significant for hypertension

- Bone marrow biopsy and aspirate performed
Dysplasia assessment

• Review peripheral smear, bone marrow aspirate smear, and bone marrow biopsy
• Threshold of 10% of cells in any lineage
• Caveats
  – Poor-quality samples may limit the ability to properly assess for dysplasia
  – Dysplasia is not always reproducible, even among experienced hematopathologists
  – Morphologic dysplasia is not specific for MDS

Megakaryocyte dysplasia

- Small size
- Hypo/mononucleation
- Separated nuclear lobes

Micromegakaryocytes
Granulocytic dysplasia

- Bilobed pseudo Pelger-Huet nucleus
- Nuclear hypersegmentation or other abnormal nuclear shape
- Cytoplasmic hypogranulation or uneven granulation
Erythroid dysplasia

• Cytoplasmic vacuolization
• Megaloblastoid change (nuclear:cytoplasmic asynchrony)
• Bi- or multi-nucleation
• Nuclear budding and nuclear irregularities
Specificity of dysplastic findings

<table>
<thead>
<tr>
<th>Morphological abnormalities</th>
<th>Cutoff values</th>
<th>AUC</th>
<th>Cohen's K-coefficient (inter-observer agreement)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythroid lineage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Megaloblastoid changes</td>
<td>&gt; 5%</td>
<td>0.814, (P &lt; 0.001)</td>
<td>0.83</td>
</tr>
<tr>
<td>Bi- or multinucularity</td>
<td>&gt; 3%</td>
<td>0.679, (P &lt; 0.001)</td>
<td>0.87</td>
</tr>
<tr>
<td>Nuclear lobulation or irregular contours</td>
<td>&gt; 5%</td>
<td>0.698, (P &lt; 0.001)</td>
<td>0.84</td>
</tr>
<tr>
<td>Pyknosis</td>
<td>&gt; 3%</td>
<td>0.674, (P &lt; 0.001)</td>
<td>0.81</td>
</tr>
<tr>
<td>Cytoplasmic fraying</td>
<td>≥ 7%</td>
<td>0.602, (P &lt; 0.001)</td>
<td>0.82</td>
</tr>
<tr>
<td>Ring sideroblasts</td>
<td>&gt; 5%</td>
<td>0.650, (P &lt; 0.001)</td>
<td>0.95</td>
</tr>
<tr>
<td>Ferritin sideroblasts</td>
<td>≥ 15%</td>
<td>0.719, (P &lt; 0.001)</td>
<td>0.92</td>
</tr>
<tr>
<td>Erythroid lineage</td>
<td>≥ 30%</td>
<td>0.670, (P &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td><strong>Granulocytic lineage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloblasts</td>
<td>&gt; 5%</td>
<td>0.723, (P &lt; 0.001)</td>
<td>0.92</td>
</tr>
<tr>
<td>Auer rods</td>
<td>≥ 1%</td>
<td>0.524, (P = 0.001)</td>
<td>0.90</td>
</tr>
<tr>
<td>Pseudo Pelger–Hüet anomaly</td>
<td>≥ 3%</td>
<td>0.714, (P &lt; 0.001)</td>
<td>0.87</td>
</tr>
<tr>
<td>Abnormal nuclear shape</td>
<td>≥ 5%</td>
<td>0.814, (P &lt; 0.001)</td>
<td>0.86</td>
</tr>
<tr>
<td>Neutrophil hypogranulation</td>
<td>≥ 7%</td>
<td>0.700, (P &lt; 0.001)</td>
<td>0.81</td>
</tr>
<tr>
<td>Megakaryocytic lineage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micromegakaryocytes</td>
<td>&gt; 5%</td>
<td>0.916, (P &lt; 0.001)</td>
<td>0.88</td>
</tr>
<tr>
<td>Small binucleated megakaryocytes</td>
<td>&gt; 5%</td>
<td>0.845, (P = 0.001)</td>
<td>0.81</td>
</tr>
<tr>
<td>Megakaryocytes with multiple separated nuclei</td>
<td>&gt; 5%</td>
<td>0.750, (P &lt; 0.001)</td>
<td>0.84</td>
</tr>
<tr>
<td>Hypolobated or monolobar megakaryocytes</td>
<td>&gt; 5%</td>
<td>0.646, (P &lt; 0.001)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Della Porta MG et al. Leukemia 2015;29:66
Non-MDS conditions associated with cytopenia and >10% dysplasia

• Drugs/toxins
  – Recent (<6 months) chemotherapy
  – Heavy alcohol intake

• Metabolic deficiencies: B12, folate, copper

• ‘Stress erythropoiesis’ due to hemoglobinopathy or acquired/congenital hemolytic anemias

• Infections, especially HIV and Hepatitis C

• Autoimmune diseases

• Concurrent neoplasms
  – Infiltrating marrow, especially hairy cell leukemia and myeloma
  – Rarely paraneoplastic dysplasia from remote tumor

Castello A et al. Haematologica 1992;77:392
Case: Peripheral blood smear
Case: Bone marrow aspirate smear

Iron stain on bone marrow aspirate is negative for ring sideroblasts
Case: Bone marrow biopsy
Case:
Further information

• Reticulocyte count: 8%
  – Coombs negative
• No iron, B12 or folate deficiency
• LDH 1312 U/L
• Flow cytometry: No lymphoma
• Peripheral blood PNH study: Large percentage of red cells, monocytes and granulocytes have GPI-protein deficiency
Case Final diagnosis

Hypercellular marrow with erythroid hyperplasia and GPI-protein loss, consistent with paroxysmal nocturnal hemoglobinuria

Diagnostic features of a myelodysplastic syndrome are not recognized

Correlate with pending cytogenetics and molecular genetic studies (54-gene panel)
# MDS-defining cytogenetic abnormalities (WHO 2016)

<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>-5 or del(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>
<tr>
<td>Balanced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(11;16)(q23;p13.3)</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>t(3;21)(q26.2;q22.1)</td>
<td>2%</td>
<td></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>

~50% of MDS have a normal karyotype

+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

Some genetic abnormality is present in ~90% of MDS cases
Bone marrow karyotype:

45, X,-Y [15]/46,XY [5]

-Y abnormality in isolation is not diagnostic of MDS; could part of the normal aging process
Case: 54-gene NGS panel for myeloid neoplasm-associated mutations

- Single nucleotide variant: TP53 p.Tyr163Cys, c.488A>G

Case Final diagnosis revisited. . .

Hypercellular marrow with erythroid hyperplasia and GPI-protein loss, consistent with paroxysmal nocturnal hemoglobinuria

Diagnostic features of a myelodysplastic syndrome are not recognized

*In light of the NGS results, do we need to amend the diagnosis to MDS?*
“Clonal Hematopoiesis of Indeterminate Potential” (CHIP)

• A proportion of apparently healthy older individuals harbor somatic MDS-type mutations in hematopoietic cells
  – *DNMT3A, TET2, ASXL1, TP53, JAK2, SF3B1*
  – Associated with increased risk of subsequent hematologic malignancy and death from other causes
  – Many patients never develop cytopenias or MDS even after many years of followup

• CHIP phenomenon precludes the current use of mutations in isolation to diagnose MDS

Flow cytometry assessment of MDS

- 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 an MDS diagnosis
- Important to rule out lymphoma

So what is sufficient to diagnose MDS in a cytopenic patient according to WHO 2016?

<table>
<thead>
<tr>
<th>Observation</th>
<th>Sufficient to diagnose MDS in a cytopenic patient?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplastic morphology (≥10%)</td>
<td><strong>Yes</strong>, provided possible secondary causes of cytopenia and dysplasia are excluded clinically</td>
</tr>
<tr>
<td>Excess marrow blasts (≥5%)</td>
<td><strong>Yes</strong>, provided marrow recovery or growth factor effect are excluded</td>
</tr>
<tr>
<td>Cytogenetic abnormality</td>
<td><strong>Yes</strong>, provided it is on the WHO list of ‘approved’ abnormalities (excluding +8, -Y, del20q)</td>
</tr>
<tr>
<td>Flow cytometry abnormality</td>
<td><strong>No</strong>, but can support an MDS diagnosis suspected by other observations</td>
</tr>
<tr>
<td>MDS-type mutation</td>
<td><strong>No</strong>, these can be found in normal individuals (“clonal hematopoiesis of indeterminate potential”); may support an MDS diagnosis suspected by other observations</td>
</tr>
</tbody>
</table>
Morphologic diagnosis of MDS is still a ‘balancing act’

- Morphologic dysplasia
  - ↑ Lineages involved
  - ↑ Number of dysplastic forms
  - ↑ Severity of dysplasia
- Severity and persistence of cytopenia(s)
- Unexplained ↑ MCV
- Flow cytometry abnormalities
- MDS-type mutations

- Younger patients
- Co-morbid conditions
- Paucity of clinical history
Case Final diagnosis revisited. . .

Hypercellular marrow with erythroid hyperplasia and GPI-protein loss, consistent with paroxysmal nocturnal hemoglobinuria

Diagnostic features of a myelodysplastic syndrome are not recognized

Loss of Y chromosome and $TP53$ mutation, consistent with clonal hematopoiesis; recommend clinical follow-up
# Prognostic schemes in MDS

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dysplasia</strong></td>
<td>Yes: single versus multilineage and ring sideroblasts</td>
<td>No</td>
</tr>
<tr>
<td><strong>Cytopenias</strong></td>
<td>Yes: Pancytopenia is only defining feature</td>
<td>Yes: both number and depth of cytopenias</td>
</tr>
<tr>
<td><strong>Blast % in blood</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Blast % in bone marrow</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Karyotype</strong></td>
<td>Yes: isolated del(5q) is the only defining feature</td>
<td>Yes, 5 prognostic groups</td>
</tr>
<tr>
<td><strong>Molecular genetic abnormalities</strong></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Flow cytometry abnormalities</strong></td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Revised International Prognostic Scoring System of MDS

Greenberg PL et al. Blood 2012;120:2454
Bone marrow blast percentage strongly influences overall survival in MDS

- 2% blast threshold is not part of WHO 2016
- Precise blast count should be specified in report so that IPSS-R can be applied
- Elevated blood blasts can upstage some MDS cases with <5% marrow blasts to MDS-EB!

Greenberg PL et al. Blood 2012;120:2454
Prognostic influence of cytogenetic abnormalities in MDS

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Cytogenetic abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>Single del(11q) or -Y</td>
</tr>
<tr>
<td>Good</td>
<td>Normal del(5q) (single or with 1 other)</td>
</tr>
<tr>
<td></td>
<td>Single del(12p) or del(20q)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>+8, i(17q), +19, single del(7q)</td>
</tr>
<tr>
<td></td>
<td>Any other single or double</td>
</tr>
<tr>
<td>Poor</td>
<td>-7, inv(3), t(3q), del(3q)</td>
</tr>
<tr>
<td></td>
<td>del(7q) with 1 other</td>
</tr>
<tr>
<td></td>
<td>3 separate abnormalities</td>
</tr>
<tr>
<td>Very poor</td>
<td>4 or more separate abnormalities (complex)</td>
</tr>
</tbody>
</table>

Main new data incorporated into 2016 WHO Classification of MDS

• Significance of point mutations
  – Large body of information confirm significant impact of mutations on prognosis
  – Most data is still too immature to determine how to incorporate mutations into the existing primarily morphologic classification

• New data help refine definitions of MDS with isolated del(5q) and MDS with ring sideroblasts

• Elimination of acute erythroid leukemia, with inclusion of most cases in MDS with excess blasts
MDS classification: new terminology

WHO 2016

- MDS with single lineage dysplasia (MDS-SLD)
- MDS with multilineage dysplasia (MDS-MLD)
- MDS with ring sideroblasts
  - MDS-RS with single lineage dysplasia (MDS-RS-SLD)
  - MDS-RS with multilineage dysplasia (MDS-RS-MLD)
- MDS with isolated del(5q)
- MDS, unclassifiable (MDS,U)
- MDS with excess blasts (MDS-EB)
- *Refractory cytopenia of childhood (RCC)(provisional)*

WHO 2008

- Refractory cytopenia with unilineage dysplasia (RCUD)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- Refractory anemia with ring sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia and ring sideroblasts (RCMD-RS)
- MDS with isolated del(5q)
- MDS, unclassifiable (MDS,U)
- Refractory anemia excess blasts (RAEB)
- *Refractory cytopenia of childhood (RCC)(provisional)*
MDS with ring sideroblasts: strong association with *SF3B1* mutation

- RNA splicing factor
  - Mutated in 70-80% of MDS with >15% ring sideroblasts
  - Very rare in MDS lacking ring sideroblasts
- Appears to be an early founding mutation
- Associated with longer survival in MDS patients

SF3B1 mutation is associated with highly differential gene expression

Includes downregulation of ABCB7 gene due to altered exon usage

New handling of MDS with ring sideroblasts in WHO 2016

• MDS with ring sideroblasts (MDS-RS) is broadened to include:
  – “Traditional” RARS (single erythroid lineage dysplasia)
  – Cases with multilineage dysplasia (MDS-RS-MLD)
  – Cases with SF3B1 mutation and ≥5% RS
    • If SF3B1 mutation status is negative or unknown, ≥15% RS is required

• Presence of SF3B1 mutation or RS does not affect MDS with excess blasts or isolated del(5q)
MDS with isolated del(5q)
MDS with isolated del(5q): new data

No adverse effect with one additional cytogenetic abnormality

TP53 mutation confers poor prognosis to del(5q) patients treated with lenalidomide

MDS with isolated del(5q) in 2016

- Dysmegakaryopoiesis, one or two cytopenias, and del(5q) on karyotype

- One additional cytogenetic abnormality, except -7 or del(7q)
- Ring sideroblasts or SF3B1 mutation
- JAK2 mutation
- Low or high platelets

- Granulocytic dysplasia
- TP53 mutation

- Pancytopenia
- ≥ 1% PB blasts
- ≥ 5% BM blasts
- -7, del(7q), or ≥ 2 other cytogenetic abnormalities
Reorganization of low-grade MDS

2008 WHO

- RCUD
- RARS
- RCMD (+/- RS)
- MDS isolated del(5q)

2016 WHO

- MDS-SLD
- MDS-RS (+/- MLD)
- MDS-MLD
- MDS isolated del(5q)

Key:
- ≥5% RS + SF3B1 mutation
- Multilineage dysplasia + ≥15% RS or ≥5% RS/SF3B1 mutation
- del(5q) + one additional abnormality
MDS, unclassifiable (MDS-U): diseases ‘on the fence’ between other entities

- Pancytopenia, but only one dysplastic lineage or del(5q)
  MDS-SLD/5q- or MDS-MLD?

- Clonal cytogenetic abnormality, but no dysplasia
  CCUS or MDS?

- 1% blood blasts*, but <5% marrow blasts
  MDS-SLD/MLD or MDS-EB?

*Measured on at least 2 separate occasions

Margolskee E et al. AJCP (in press).
Unilineage dysplasia <5% BM blasts <2% PB blasts

1% PB blasts documented on at least 2 occasions

Pancytopenia (ANC <1.8, HGB <10, PLT <100)

Del(5q) alone or with 1 other abnormality

≥5% RS and SF3B1 mutation or ≥15% RS

MDS-U

MDS-SLD

MDS del(5q)

MDS-RS-SLD
Multilineage dysplasia <5% BM and <2% PB blasts

1% PB blasts documented on at least 2 occasions

Del(5q) alone or with 1 other abnormality

≥5% RS and SF3B1 mutation or ≥15% RS

Pancytopenia (ANC <1.8, HGB <10, PLT <100)

MDS-U

MDS del(5q)

MDS-RS-MLD

MDS-MLD
Special situations in MDS

• Hypoplastic MDS
  – About 10% of cases
  – Differential diagnosis with aplastic anemia
  – CD34 and CD61 immunostains of biopsy

• MDS with fibrosis
  – 10-15% of cases
  – Differential diagnosis with MPN and MDS/MPN
  – CD34 and CD61 immunostains of biopsy
  – Adverse prognosis

MDS with excess blasts (MDS-EB)

- ≥5% blasts in marrow or ≥2% blasts in blood
  - Subdivided into MDS-EB-1 and MDS-EB-2 based on marrow and blood blast levels

- Increased blasts are a very strong indicator of aggressive behavior in MDS, independent of cytogenetics, cytopenias, and mutations

- CD34 immunostaining useful in cases with fibrosis or poor aspirate

• Aspirate blast count is ‘gold standard’
• CD34 immunostaining of biopsy is critical if aspirate is compromised and is useful in all possible MDS cases
New WHO 2016 recommendations for blast counting

- Blasts in BM are always counted as % of total cells, never as % of non-erythroid cells

- Myeloid neoplasms with \( \geq 50\% \) erythroids and \(<20\%\) blasts are now classified as MDS-EB, even if blasts are \( \geq 20\% \) of the non-erythroid cells
  - Merges most cases previously diagnosed as acute erythroleukemia (erythroid/myeloid) into MDS-EB
  - Pure erythroid leukemia remains as an AML subtype
  - Malignant proliferation of *immature erythroblasts*

Most acute erythroleukemia patients do not appear to benefit from intensive chemotherapy

AEL patients not receiving stem-cell transplant

Wang SA et al. Mod Pathol 2016;29:1221
MDS in children

• Refractory cytopenia of childhood (~50%)
  – Usually hypocellular, important differential diagnosis with aplastic anemia
  – Usually normal karyotype or -7 (20% of cases)
  – Mutations are less common than in adult MDS (22% of cases) and have a different profile
    • SETBP1, ASXL1, NRAS/KRAS, RUNX1, BCOR/BCORL

• ‘Conventional’ types of MDS (~50%)
  – Classify as for adult MDS
  – MDS-RS and isolated del(5q) are very rare in children

Diagnosis of MDS in children

Diagnostic features of MDS (cytopenia, >10% dysplasia)
- Dysplastic erythroids and micromegakaryocytes
- Clusters of erythroid precursors in biopsy
- <5% BM blasts, <2% PB blasts
- Hypocellular (usually)

Therapy-related MDS
- History of cytotoxic therapy

MDS-EB
- ≥5% BM blasts or ≥2% PB blasts

Refractory cytopenia of childhood
- Not fulfilling any of the above features

Classify as for adult MDS

- All of the above diagnoses should be modified in the setting of a known germline predisposition, e.g.
  - Refractory cytopenia of childhood with germline GATA mutation
  - MDS with excess blasts associated with Fanconi anemia
Conclusions: MDS diagnosis and classification should optimally incorporate multiple modalities

• There is no ‘magic’ single test to confirm or exclude a diagnosis of MDS
• Prognosticating MDS
  • Blood counts
  • Blasts (blood and marrow) and dysplasia
• Cytogenetics
• Mutational profile
• Expression profile, epigenome, microenvironment