### Myelodysplastic Syndromes (MDS)

<table>
<thead>
<tr>
<th>Good Prognosis</th>
<th>Intermediate Prognosis</th>
<th>Poor Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core Binding Factor (CBF) AML</td>
<td>Blasts with monocytic differentiation and fine azurophilic granules</td>
<td>With or without monocytic features, often associated with basophilia and multilineage dysplasia</td>
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<tr>
<td>t(8;21)(q22;q22); RUNX1::RUNX1T1</td>
<td>Associated with gingival myeloid sarcoma</td>
<td>inv(3)(q21;q26.2) or t(3;3)(q21;26.2); GATA2, MECOM</td>
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<td>Blasts with salmon/pink granules</td>
<td>More common in children (10% pediatric AML)</td>
<td>Abnormal megakaryocytes</td>
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<td>Predominant in younger patients</td>
<td>Normal Karyotype, mutation status unknown (or rarely negative)</td>
<td>Multilineage dysplasia</td>
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<tr>
<td>&gt;70% of patients show additional chromosome abnormalities including sex chr loss, del(9q)</td>
<td></td>
<td>Common secondary karyotypic abnormalities include -7 (50% cases), del(5q) and complex karyotypes</td>
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<tr>
<td>inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB::MYH11</td>
<td></td>
<td>AML with myelodysplasia related changes (AML-MRC)</td>
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<tr>
<td>Abnormal eosinophils</td>
<td></td>
<td>≥50% dysplasia in ≥2 lineages (if no NPM1 mutation)</td>
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<tr>
<td>Worse prognosis in CBF AMLs when Kit is mutated</td>
<td></td>
<td>History of MDS</td>
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<tr>
<td>Acute Promyelocytic Leukemia (APL) with t(15;17)(q22;q12); PML::RAR</td>
<td>Associated with disseminated intravascular coagulation</td>
<td>MDS-defining cytogenetic abnormality (see MDS section)</td>
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<tr>
<td>-</td>
<td>APL with PML::RAR is sensitive to ATRA/arsenic treatment</td>
<td>Mutations in ASXL1, BCR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2</td>
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<tr>
<td></td>
<td>APL variants like ZBTB16::RAR and STAT5B::RAR</td>
<td>11q23 (non t(9;11), many partners)</td>
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<tr>
<td></td>
<td>fusions are resistant to ATRA</td>
<td>t(9;22) (q34;q11.2); BCR::ABL1</td>
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<td></td>
<td>NPM1 mutation without FLT3-ITD</td>
<td>FLT3-ITD mutation</td>
</tr>
<tr>
<td></td>
<td>AML with in-frame bZIP mutated CEBPA</td>
<td>~20% AML cases</td>
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<tr>
<td></td>
<td>FLT3-ITD mutations occur in 22-33% of cases (unclear prognosis)</td>
<td>ASXL1, TPS3, RUNX1 mutation</td>
</tr>
</tbody>
</table>

### Mutations

- **SF3B1** mutation (strongly correlated with ring sideroblasts)
- With **SF3B1** mutation can diagnose MDS with ring sideroblasts (MDS-RS) with only 5-10% ring sideroblasts rather than 15% without the mutation
- **Chronic Myelogenous Leukemia (CML)**
  - t(9;22)(q34;q11.2); BCR::ABL1
  - Usually M-BCR (p210) breakpoint
  - Rarely m-BCR (p190) or μ-BCR (p230) breakpoints
  - ABL1 kinase mutations confer TKI resistance
  - Particularly T315I
  - Transformation to accelerated phase (AP) or blast phase (BP) often accompanied by extra Ph chromosome, +8, +19, or i(17q)(q10)
  - **Polycythemia Vera (PV)**
    - JAK2 V617F (~95% of cases)
    - JAK2 exon 12 mutation (~5% of cases)
  - **Essential Thrombocytopenia (ET) and Primary Myelofibrosis (PMF)**
    - JAK2 V617F (~50% of cases)
    - CALR exon 9 indel mutations (~30% of cases)
    - MPL W515L (~5% of cases)
  - **Chronic Neutrophilic Leukemia (CNL)**
    - Activating membrane proximal mutations in CSF3R at exon 14, especially T618I and T615A; present in 50-80% of CNL

### Cytogenetics

- **Very Good Prognosis**
  - del(11q)* or -Y
- **Good Prognosis**
  - Normal
  - del(5q)*, del(12p)*, del(20q), double del(5q)
- **Intermediate Prognosis**
  - del(7q)
  - Monosomy 5*
  - Trisomy 8, trisomy 19
  - i(17)(q10)*
  - Monosomy 13* or del(13q)*
  - 2+ independent clones
  - Double any other abnormality
- **Poor Prognosis**
  - Monosomy 7*
  - inv(3), t(3;3), del(3q), 3+ abnormalities
  - Very Poor Prognosis
  - Complex (≥3 abnormalities)*

*MDS defining abnormality

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## Myeloid/Lymphoid Neoplasms associated with Eosinophilia

- **Atypical Chronic Myeloid Leukemia (aCML)**
- **Chronic Myelomonocytic Leukemia (CMML) (MDS/MPN “bridging” category)**

### Myeloid/Lymphoid Neoplasms associated with Eosinophilia

- **PDGFRα rearrangement** (often del(4)(q12;q12); FIP1L1:PDGFRα)
- **PDGFRβ rearrangement** (often t(5;12)(q31–33;p12); ETF6:PDGFRβ)
- **FGFR1 rearrangement** (various partners)
- **t(8;9)(p22;p24.1);PCM1::JAK2**
- **ETV6::FLT3 fusion**

### Other Entities

- **BCL::ABL1 like B-ALL**
  - Lacks BCR::ABL1 translocation
  - TIS51B and EFR rearrangement
  - KIT mutations
  - CDKN2A/B or IKZF1 deletion/mutation
- **Other translocations involving tyrosine kinases**

### T-cell Neoplasms

- **B-cell Neoplasms**

### B-lymphoproliferative disorders

#### Chronic Myelomonocytic Leukemia (CMML) (MDS/MPN “bridging” category)
- Frequent mutations: TET2 (~50%), SRSF2 (~30-50%), ASXL1 (40-50%, poor prognosis if missense mutations are excluded), KRAS and NRAS (myeloproliferative phenotype), SETBP1 (poor prognosis), JAK2 (not specific)

#### Atypical Chronic Myeloid Leukemia (aCML)
- Overlap MDS/MPN neoplasm
- **BCR::ABL1 negative**
- **Cyto genetics**: +8, i(17q), -7, del(7q), del(20q), +9, del(13q)
- **Molecular genetics**: SETBP1 mutation (~20-30%, exon 4 mutations with DI68N most common, associated with -7 and i(17q), ASXL1 (65%), SRSF2, TET2 (~40%), KRAS, NRAS, EZH2, ETNK1, CBL, JAK2 (~10-30%), SF3B1 (~1%, T618I most common), CALR (rarely or never present)

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- **FGFR1 rearrangement** (various partners)
- **t(8;9)(p22;p24.1);PCM1::JAK2**
- **ETV6::FLT3 fusion**

#### T-Lymphoblastic Leukemia/Lymphoma (T-ALL)
- **Translocations involving T-cell receptor (TCR); error during TCR gene rearrangements**
- **NUP214-ABL1 strictly associated with T-ALL <6% cases**
- **MYC rearrangements (~6% cases)**
- **NOTCH1 (70% cases); CASK2A/B (cryptic deletions >70%) mutations**
- Early T-precursor Acute Lymphoblastic Leukemia (ETP ALL)
- **FLT3, NRAS/KRAS, DNMT3A, IDH1/2**
- **Anaplastic Large Cell Lymphoma, ALK-negative (ALCL, ALK-)**
  - Subset have rearrangement at 6p25 (region with DUSP22 and IRF6 - good prognosis)
  - TP53 rearrangement - poor prognosis
- **Anaplastic Large Cell Lymphoma, ALK-positive (ALCL, ALK+)**
  - Chromosome translocations involving ALK gene at 2p23
  - t(2;5)(p22;q35); ALK-NPM1
  - Other ALK rearrangements

#### Lymphosarcomatoid Lymphoma/Lymphoma (T-ALL)
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  - Chromosome translocations involving ALK gene at 2p23
  - t(2;5)(p22;q35); ALK-NPM1
  - Other ALK rearrangements

#### Lymphoplasmycytoid Lymphoma (LPL) and IgM Monoclonal Gammopathy of Unknown Significance (MGUS)
- **6q23 deletion most common cytogenetic finding in LPL**
- **MYD88 p.L265P (~90% of cases)**
- **CXCR4 mutation (~30% of LPL, ~20% of IgM MGUS)**
- **ALK-positive large B-cell lymphoma**
  - t(2;17)(p23;q22); TCL1A
- **High-grade B-cell lymphoma**
  - **MYC rearrangement**
  - **BCL2 rearrangement and/or BCL6 rearrangement**
- **Diffuse large B-cell lymphoma, NOS**
  - **Activated B cell type**
    - **BCL2 rearrangements/NOTCH2 mutations**
    - **MYD88 & CD79B mutations**
    - **NOTCH1 mutations**
  - **Germinal center B cell type**
    - **IGH;BCL2 & EZH2 mutations**

#### Mantle Cell Lymphoma (MCL)
- **t(11;14)(q13;q32); IGH/MYC**
- **Common secondary abnormalities: loss of 1p, 13q, 17p**
- **Two translocations are more common in grade 3B tumors**
- **Mantle Cell Lymphoma (MCL)**
  - **t(11;14)(q13;q32); IGH/MYC**
  - **Common secondary abnormalities: loss of 1p, 13q, 17p**
  - **Two translocations are more common in grade 3B tumors**

#### Burkitt Lymphoma (BL)
- **MYC rearrangements**
  - **t(8;14)(q24;q32); IGH/MYC**
  - **t(2;8)(p21;q24); IGH/MYC**
  - **t(8;22)(q24;q11); IGL/MYC**

#### Lymphoplasmacytoid Lymphoma (LPL)
- **IgM MGUS**
- **IgM monoclonal gammopathy of unknown significance (MGUS)**
- **6q23 deletion most common cytogenetic finding in LPL**
- **MYD88 p.L265P (~90% of cases)**
- **CXCR4 mutation (~30% of LPL, ~20% of IgM MGUS)**
- **ALK-positive large B-cell lymphoma**
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