**Clinical Features and Risk Stratification of AML**

<table>
<thead>
<tr>
<th>Pragmatic category</th>
<th>Favorable risk</th>
<th>Intermediate risk</th>
<th>Adverse risk</th>
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</thead>
<tbody>
<tr>
<td>Aberration Frequency (%)</td>
<td>Aberration Frequency (%)</td>
<td>Aberration Frequency (%)</td>
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<tr>
<td>t(15;17)</td>
<td>7-12</td>
<td>NK with FLT3-ITD</td>
<td>15-20</td>
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<tr>
<td>t(8;21)</td>
<td>5-8</td>
<td>NK with NPM&lt;sup&gt;mwt&lt;/sup&gt; &amp; no FLT3-ITD</td>
<td>10-17</td>
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<tr>
<td>inv(16)</td>
<td>5-8</td>
<td>NK with APL-RARA &amp; no FLT3-ITD</td>
<td>11q23</td>
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<tr>
<td>t(9;11)</td>
<td>6-12</td>
<td>Other cytogenetic abnormalities not included elsewhere</td>
<td>2-3</td>
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**Current therapies**

- Standard induction cytotoxic therapy (*"3+7"), followed by postremission consolidation
- Allogeneic HSCT should be considered
- Therapy with high dose cytarabine
- Standard induction cytotoxic therapy in t(15;17)
- Anthracycline based chemotherapy
- ATRA as a differentiating agent with HDACi
- iMenin
- iBET/JQ1
- LSK

**Gene**

- FLT3-ITD: 25%-30% (28%-35%); High blast count; Poor prognosis especially in cases with high mutant to WT allele ratio
- FLT3-TKD: 5%-7% (10%-14%); Prognostic impact remains controversial
- NPM1: 25%-30% (40%-65%); M4 blast morphology lacks CD34 expression; HOX gene upregulation; Favorable prognosis in the presence of FLT3<sup>ITD</sup>; Female preponderance
- C-KIT: 5%-5% (4%); 25%-30% in CBF leukemia
- PDK1: 21% (2%); Prognosis unknown
- RUNX1: 5%-13% (5-25%); Enriched in trisomy 13 and FAB M2; Poor prognosis
- WT1: 10% (10-13%); Associated with M0 FAB type; Poor prognosis
- TP53: 2%-4% (~2%); Predominantly in NK-AML; Very poor prognosis

**Ergenic modifications**

- DNMT3A: 20%-25% (22%-35%); Heterozygous RB2 mutations account for 45%-65% of mutations; Poor prognosis in NK-AML
- IDH1/IDH2: 12%-22% (25%-30%); IDH1 & 2 are mutually exclusive; IDH1 mutations enriched in patients with NPM<sup>mwt</sup>; IDH1 is localized in cytoplasm and peroxisomes
- TET2: 7%-15% (15%-23%); Mutually exclusive to IDH1/2 mutations; More prevalent in secondary AML especially MPN

**Cell of Origin and Clonal Evolution Model of Leukemic Stem Cells**

- LSK: Lineage", Sca-1", c-KIT<sup>+</sup> population
- CMP: Common myeloid progenitor
- GMP: Granulocyte macrophage progenitor
- B: B-lineage
- Negative impact
- NS: Not significant
- Colors represent different clones
- Indicates epigenetic mutations
- LSC: Leukemic stem cell
- LSC-SC: Leukemic subclone originating from LSC
- LSC-CS: Leukemic subclone originating from non-LSC
- SC: Leukemic subclone originating from non-LSC
- Self-renewal
Acute myeloid leukemia (AML) is a heterogeneous clonal disorder of hematopoietic stem/progenitor cells characterized by the rapid growth of abnormal white blood cells (blasts) that accumulate in the bone marrow and interfere with the production of normal blood cells. In contrast to the classical French-American-British (FAB) classification based on morphological appearance of blasts and their cytochemistry, the 2008 revised WHO classification of AML incorporates cytogenetic/genetic data that help to define biologically homogenous entities with prognostic and therapeutic relevance. Based on (cyto)genetic features of the AML, patients can be broadly classified into three risk groups, although patient-specific factors (age, performance status, comorbidity, etc.) are also key predictors of outcome. The “3+7” combination of daunorubicin and cytarabine is routinely used as induction chemotherapy for adult patients with AML, except PML-RARα leukemia, whereas molecular profiling is currently guiding postinduction therapeutic strategies. Comparison between adult and childhood AML shows that children have a higher incidence of chromosomal translocation, whereas normal (NK) and complex karyotype (CK)—the latter includes monosomal karyotype (MK)—are associated with dismal prognosis—are more prevalent in adults. While risk classification has advanced in the last decades, treatment of AML, except for t(15;17) leukemia, is only marginally improved, mainly by better supportive care, highlighting the need for novel therapies.

**Molecular Mechanisms, Recurrent Gene Mutations, and Targeted Therapies in AML**

PML-RARα from t(15;17) that exclusively associates with FAB-M3 (acute promyelocytic leukemia, APL) forms transcriptionally repressive complexes with retinoic X receptor (RXR), histone deacetylases (HDACs), enhancer of zeste (EZH2), and DNA methyltransferase (DNMT). All-trans retinoic acid (ATRA), which dissociates repressor complexes from PML-RARα and mediates its subsequent degradation, can effectively induce differentiation of APL cells. In combination with chemotherapy, ATRA achieves a 5 year overall survival of approximately 80%. While As2O3, which degrades PML-RARα, is commonly employed to treat relapsed patients, other targeted therapeutic agents, including HDAC inhibitors and RXR agonists, are being developed.

The hallmark gene located at 11q23 has over 60 different fusion partners in AML. Wild-type MLL encodes a SET domain containing H3K4 histone methyltransferase but the SET domain is invariably replaced by the partner proteins in MLL fusions. All MLL fusions retain MLL’s N terminus that recruits Menin and the polymerase associated factor complex (PACf), which are critical for DNA binding, gene expression, and cellular transformation. Importantly, the fusion partners themselves recruit a variety of protein complexes involved in transcriptional elongation (p-TETF) and/or histone methylation, e.g., DOT1L (H3K79) or PRMT1 (H4R3), resulting in aberrant transcriptional activation. Several novel targeted strategies are emerging for 1q23 AML, including inhibition of Menin, DOT1L, PRMT1, the histone acetylation reader BRD4, and LSD1 (although the mechanisms underlying the efficacy of LSD1 inhibition remain unclear).

Genes encoding core binding factors including AML1/RUNX1 and CBFI are the most frequently rearranged ones in AML. Both core binding factor fusions complex with transcriptional repressors, such as HDACs and NCoR, to suppress expression of normal hematopoietic potential, thus providing HDAC inhibitors as potential therapeutic agents. AML1-ETO fusions may also recruit transcriptional coactivators such as PRMT1 and histone acetyltransferase (HAT) CBP that are critical for transformation.

Going beyond microarray analyses, next-generation sequencing has been unravelling the vast genetic heterogeneity in AML and improving risk stratification, especially for NK-AML. This has led to the discovery of not only several candidate genes that could be classified under the conventional two-hit model (e.g., signaling and transcription factors) of myeloid leukemogenesis but also those involved in epigenetic regulation, spliceosome machinery, and the cohesin complex. Interestingly, some of the mutations identified in NK-AML such as those in FL3T and c-KIT are also recurrent in AML with translocations. Several kinase inhibitors (e.g., FLT3i and dasatinib), anti-CD33 antibody conjugate gemtuzumab ozogamicin (GO), and hypomethylating agents are currently in clinical trials. The role of epigenetic modulation in AML has only started to be unravelled, even though the therapeutic benefit of hypomethylating agents in low blast AML predates our knowledge of the existence of these epigenetic regulator mutations.

**Cell of Origin and Clonal Evolution Model of Leukemic Stem Cells**

The cell of origin for AML stem cells is still unclear. However, studies using mouse models have shown that both hematopoietic stem cells (HSCs) and progenitor cells can be targeted by initiating events, such as MLL fusions and PML-RARα, to generate preleukemic stem cells (pre-LSCs) and, subsequently, LSCs with acquisition of additional cooperative events (e.g., FLT3). The origin of LSCs can influence the leukemia type and lineage, although the cellular origin’s role in treatment response remains to be determined. LSCs possess self-renewal ability and can give rise to short-lived progenies, which form the bulk of the leukemic population in the patient. LSCs and leukemic progenies can further evolve into different subclones by acquiring additional mutations, leading to multiple (epi)genetically different leukemic clones with various clone sizes in the patient at the time of diagnosis. After chemotherapy, the bulk of leukemic cells is eradicated, leading to clinical remission; however, chemoresistant LSCs persist in the patient at low levels. With time, LSCs, which may be shaped by the treatment, can give rise to different progenies again, reinitiating the disease. Thus, the dominant clone at the time of relapse may not necessarily be the same as the one at diagnosis. Self-renewal is a common feature shared by LSCs and HSCs. Pathways such as β-catenin and PTEN, which have differential effects on LSCs versus normal HSCs, may be key targets to eradicate LSCs.

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**REFERENCES**


