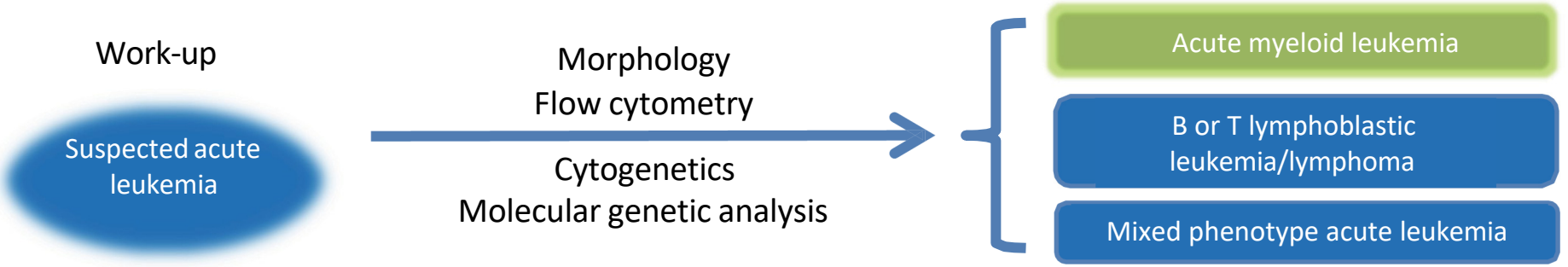
Molecular In My Pocket™...

ONCOLOGY: *Acute Myeloid Leukemia*



Acute Myeloid Leukemia with Defining Genetic Abnormalities

Acute promyelocytic leukemia with *PML::RARA* fusion

- Good prognosis
- t(15;17)(q13.4;q21.2)
- Kidney-shaped or bilobed blasts with granules +/- Auer rods (often multiple)
- Other variants - Cells with regular nuclei, many granules, absence of Auer rods, pelgeroid neutrophils, strong MPO
  - *IRF2BP2::RARA ;* t(1;17)(q42.3;q21.2)
  - *NUMA1::RARA*; t(11;17)(q13.4;q21.2)
  - *NPM1::RARA*; t(5;17)(q35.1;q21.2)
  - *STAT5B::RARA or STAT3::RARA;* t(17;17)(q21.2;q21.2), inv(17), del(17)
  - *ZBTB16::RARA;* t(11;17)(q23.2;q21.2)
  - *TBL1XR1::RARA;* t(3;17)(q26.3;q21.2)
  - *FIP1L1::RARA;* t(4;17)(q12;q21.2)
  - *BCOR::RARA;* t(X;17)(p11.4;q21.2)
- Associated with disseminated intravascular coagulation
- Sensitive to ATRA/arsenic trioxide
  - some variant, such as *ZBTB16::RARA* and *STAT5B::RARA* are ATRA resistant

AML with *RUNX1::RUNX1T1* fusion; t(8;21)(q22;q22.1)

- Good prognosis
- Blasts with basophilic cytoplasm, azurophilic granules and perinuclear hofs; may show pseudo-Chédiak-Higashi granules and/or single, long Auer rods with tapered ends
- Neutrophils may show pseudo-Pelger-Huët nuclei and salmon pink granules
- ≥ 70% have additional karyotypic abnormality: -X, del(9q)
- Presence of *KIT* mutation and CD56 expression associated with worse prognosis; *ASXL1/2, KRAS, NRAS* mutations may also be seen

AML with *CBFB::MYH11* fusion

- Good prognosis
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22)
  - likely need FISH/RT-PCR – subtle rearrangement
- Blasts with abnormal eosinophils (immature eosinophilic/basophilic granules, dense and purple-violet in color)
- Secondary cytogenetic abnormalities include +22 and +8 (each occurring in 10-15% of cases), del(7q) and +21 (in 5%)
- *KIT* mutations in exons 8 and 17 (in 30-40%); worse prognosis
- Other mutations: *NRAS* (in 45%), *KRAS* (in 13%), *FLT3* (in 14%' worse prognosis)

AML with *KMT2A* rearrangement

- ≥80 *KMT2A* fusion partners described, with *MLLT3, AFDN, ELL*, and *MLLT10* being most common; most poor prognosis
- *KMT2A::MLLT3*; t(9;11)(p21.3;q23.3); Intermediate prognosis
- Adults often have high blast counts at presentation, usually with monocytic differentiation
- In children, AML with *KMT2A::MLLT3* and *KMT2A::MLLT10* show megakaryoblastic differentiation and/or low blast counts
- May present with DIC, myeloid sarcoma, gingival hyperplasia
- May need FISH/other molecular techniques for identification due to subtle translocations
- *MECOM* overexpression is common; worse prognosis

AML with *DEK::NUP214* fusion

- Poor prognosis
- t(6;9)(p23;q34.1); mostly sole karyotypic abnormality
- Blasts with/without monocytic features
- Associated with basophilia and multilineage dysplasia
- *FLT3*-ITD mutations are common; may benefit from FLT3 inhibitors

AML with *MECOM* rearrangement

- Poor prognosis
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)
- May have normal or elevated platelet counts, hepatosplenomegaly
- Peripheral blood may include hypogranular neutrophils with pseudo-Pelger-Huët nuclei, giant and hypogranular platelets with bare megakaryocytic nuclei
- Associated with increased dysplastic megakaryocytes with monolobated or bilobed nuclei, and multilineage dysplasia
- Often associated with -7 (>50% of cases), del(5q) and complex karyotypes
- Also associated with mutations of RAS/receptor tyrosine kinase signaling pathways (*NRAS*, *PTPN11*, *FLT3*, *KRAS, NF1*, *CBL*, *KIT*)
- Other associated mutations: *GATA2*, *RUNX1*, *SF3B1*

AML with *RBM15::MRTFA* fusion

- Poor prognosis
- t(1;22)(p13.3;q13.1); mostly sole karyotypic abnormality
- Uncommon; may be congenital
- Infants and children age ≤3 years
- Small and large megakaryoblasts admixed with undifferentiated blasts; dense fibrosis

AML with *BCR/ABL1* fusion

- ≥20% blasts required
- *De novo* AML in patients with no evidence of CML before/after therapy
- Present with less splenomegaly, less basophilia, lower cellularity, fewer dwarf megakaryocytes, normal M:E ratio compared with blast transformation of CML
- Most cases show the p210 fusion (most commonly b2a2 and b3a2 fusions); minority show p190 fusion
- Associated with -7, +8 and complex karyotypes
- May be associated with *NPM1* and *FLT3*-ITD, loss of *IKZF1* and *CDKN2A* and cryptic deletions in *IGH* and *TRG* genes (not seen in blast transformation of CML)

Acute Myeloid Leukemia with Defining Genetic Abnormalities (cont'd)

AML with *NUP98* rearrangement

- >30 fusion partners
- Rearrangement may be cryptic
- Many associated with overexpression of HOXA9; poor prognosis

AML with *NPM1* mutation

- Overall good prognosis; poorer prognosis with presence of *FLT3*-ITD +/- *DNMT3A*
- Blasts often show monocytic features
- Multilineage dysplasia seen in up to 25% of cases
- Usually associated with normal karyotype
- del(9q), +8 seen in 5-15% of cases
- Secondary mutations include *FLT3*, *DNMT3A*, *IDH1/2*, *KRAS*, *NRAS*
- Up-regulation of *HOX* gene

AML with mutated *TP53*

- Very poor prognosis
- Typically associated with complex karyotype
- Although multi-hit *TP53* is required for MDS with mutated *TP53*, in AML and MDS/AML with mutated TP53, any pathogenic TP53 mutation VAF >10% is sufficient.
- Pure erythroid leukemia is typically associated with *TP53* mutations, and these cases should be classified as AML with mutated TP53.

AML with *CEBPA* mutation

- 20% blasts required
- Favorable prognosis
- Includes biallelic (biCEBPA) and single mutations located in the basic leucine zipper region of the gene (smbZIP-*CEBPA*)
- No distinct morphologic features (usually have features of AML with/without maturation)
- Higher expression of HLA-DR, CD7 and CD15
- Presence of bi*CEBPA* should raise possibility of germline mutation
- >70% of cases associated with normal karyotype; del(9q) may also be seen
- *GATA2* mutations seen in 39% of cases, *FLT3*-ITD in 5-9% of cases

Acute myeloid leukemia, myelodysplasia-related (AML-MR)

AML with other defined genetic alterations

- "Landing spot" for emerging or rare entities

Diagnosis requires:

- ≥20% blasts required by WHO; 10% blasts by ICC
- Either: history of MDS or MDS/MPN, or MDS-related cytogenetic abnormality or somatic mutation
- Absence of prior cytotoxic or radiation therapy for unrelated disease or AML-defining recurrent genetic abnormality

4 subclassifications (ICC only)

- AML with myelodysplasia-related cytogenetic abnormalities
- AML and MDS/AML with myelodysplasia-related gene mutations
- AML and MDS/AML with mutated TP53
- AML, NOS

ML-MR-defining cytogenetic abnormalities

- Complex karyotype (≥3 abnormalities)
- del(5q), t(5q)
- -7, del(7q)
- del(11q)
- del(12p)
- -13 or del(13q)
- Isochromosome 17q, del(17p)
- idic(X)(q13)

AML-MR-defining somatic mutations

- *ASXL1*
- *BCOR*
- *EZH2*
- *SF3B1*
- *SRSF2*
- *STAG2*
- *U2AF1*
- *ZRSR2*
- *RUNX1* (ICC only)

Eosinophilia

Myeloid/Lymphoid Neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK)

- Broad range of histologic types – MPN, MDS, MDS/MPN, AML, MPAL, B-ALL, T-ALL
- Eosinophilia common feature but may be absent in some cases
- Sensitive to tyrosine kinase inhibitor (TKI) therapy
- Defining genetic abnormalities
  - *PDGFRA* rearrangement (often del(4)(q12q12); *FIP1L1::PDGFRA*)
  - *PDGFRB* rearrangement (often t(5;12)(q32;p12); *ETV6::PDGFRB*)
  - *FGFR1* rearrangement
  - *JAK2* rearrangement (often t(8;9)(p22;p24.1);*PCM1::JAK2*
  - *FLT3* rearrangement
  - *ETV6::ABL1* fusion (separate from B-ALL with *ETV6::ABL1*) and other *ETV6* rearrangement (*ETV6::FGFR2; ETV6:LYN; ETV6::NTRK3; RANBP2::ALK)*
  - Other MLN-TK (more is accrued): *BCR::RET; FGFR1OP::RET*
- Mostly, long-term survival option is bone marrow transplant

Secondary myeloid neoplasms

Myeloid neoplasms post cytotoxic therapy (MN-pCT)

- Poor prognosis
- Requires a documented history of chemotherapy (e.g. alkylating agents, topoisomerase II inhibitors, antimetabolites, antitubulin agents) or large-field radiation therapy for an unrelated condition
- *De novo* AML with defining genetic abnormality, such as NNPM1 mutation and CBF AML, post cytotoxic therapy should be assigned to this category based on medical history
- Majority AML-pCT and MDs-pCT associated with *TP53* mutations; worse outcomes with biallelic (multi-hit) *TP53* alterations
- Less frequent mutations involving genes such as *PPM1D* or DNA-damage response genes require consideration of a germline predisposition

Myeloid neoplasms associated with germline predisposition

- Myeloid neoplasms with germline predisposition without a pre-existing platelet disorder or organ dysfunction
  - Germline *CEBPA* P/LP variant (CEBPA-associated familial AML)
  - Germline *DDX41* P/LP variant
  - Germline *TP53* P/LP variant (Li-Fraumeni syndrome)
- Myeloid neoplasms with germline predisposition and pre-existing platelet disorder
  - Germline *RUNX1* P/LP variant (familial platelet disorder with associated myeloid malignancy, FPD-MM)
  - Germline *ANKRD26* P/LP variant (Thrombocytopenia 2)
  - Germline *ETV6* P/LP variant (Thrombocytopenia 5)
- Myeloid neoplasms with germline predisposition and potential organ dysfunction
  - Germline *GATA2* P/LP variant (GATA2-deficiency)
  - Bone marrow failure syndromes
    - Severe congenital neutropenia (SCN)
    - Shwachman-Diamond syndrome (SDS)
    - Fanconi anemia (FA)
  - Telomere biology disorders
  - RASopathies (Neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan syndrome-like disorders)
  - Down Syndrome
  - Germline *SMAD9* P/LP variant (MIRAGE syndrome)
  - Germline *SAMD9L* P/LP variant (SAMD9L-related ataxia pancytopenia syndrome)
  - biallelic germline *BLM* P/LP variant (Bloom syndrome)