

# 2012 Update on Myeloid Neoplasms: Myelodysplastic Syndrome and Acute Myeloid Leukemia

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# Speaker Profile

- Professor of Pathology, University of Utah School of Medicine
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- Disclosures
  - Ownership/equity interest that is unrelated to this presentation
    - AvanSci Bio, LLC; Board of Managers
    - DecipherGenX, Inc.; President/COO



# Objectives

- Understand the pathophysiology of myelodysplastic syndromes and acute myeloid leukemia
- Review the current (WHO 2008) diagnostic criteria and classification of these disorders
- Understand the approach to the practical laboratory diagnosis of these disorders



# 2008 WHO Classification of the Myeloid Neoplasms

- Myeloproliferative Neoplasms (MPN)
- Myeloid/Lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1*
- Myelodysplastic syndrome (MDS)
- MDS/MPN
  - Includes CMML and the provisional category of RARS-T
- Acute myeloid leukemia (AML)



# Myelodysplastic Syndromes (MDS)



# MDS, General Features

- Clonal stem cell disorder with ineffective hematopoiesis, cytopenias and dysplasia of one or more cell lineages
- Frequent cytogenetic and/or mutational abnormalities
  - 50% with abnormal karyotypes
  - 50% with somatic mutations (including 50% of normal karyotype MDS cases)
- Typical presentation: elderly adult with sustained, unexplained anemia, leukopenia and/or thrombocytopenia
- De novo or secondary (usually therapy-related)
- Risk-based rate of progression to AML



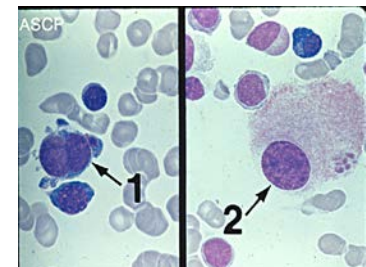
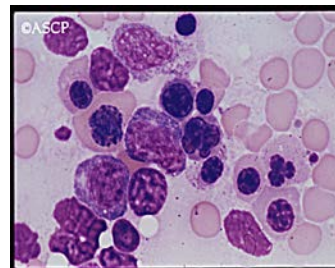
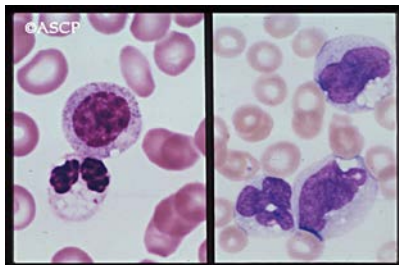
# Revised (2008) WHO Classification of MDS

- Refractory cytopenia with unilineage dysplasia (RCUD)
- Refractory anemia with ring sideroblasts (RARS)
- RC with multilineage dysplasia (RCMD)
- RA with excess blasts (RAEB-1, RAEB-2)
- MDS with isolated del(5q) (5q- syndrome)
- MDS, unclassifiable
- Refractory cytopenia of childhood (RCC, provisional)
- MDS, therapy-related



# Approach to MDS Diagnosis

- Complete history, CBC with peripheral blood smear evaluation, bone marrow aspirate and biopsy, cytogenetics and FISH
- Minimum criteria:
  - Absence of de novo AML recurrent cytogenetic abnormalities
  - At least 2 of the following:
    - Sustained, unexplained cytopenia(s)
    - Dysplasia in 2 or more lineages (except in RCUD, RARS and 5q-syndrome)
    - Clonal cytogenetic abnormality(s)
    - $\geq 5\%$  blasts in the bone marrow





# Differential Diagnosis of MDS

- Megaloblastic anemias (folate and/or B12 deficiencies)
- Copper deficiency
- Zinc toxicity
- Arsenic toxicity
- Chemotherapy-associated effects
- Chronic viral infections (including HIV)
- Congenital dyserythropoietic anemia (especially in children and adolescents)
- Sideroblastic anemia (congenital, acquired)
- Aplastic anemia
- Paroxysmal nocturnal hemoglobinuria
- Low blast count AML



# Genetics of MDS

- Chromosomal copy number abnormalities (additions, deletions) especially of 5, 7, 8, 20
- Recurrent mutations in genes associated with:
  - DNA histone function (*EZH2, ASXL1, UTX*)
  - DNA methylation (*DNMT3A, IDH1, IDH2, TET2*)
  - Active areas of research on pathogenesis pathways and potential therapeutic interventions
- Rare finding of *FLT3* and/or *NPM1* mutations



# Progression to AML

- Clinical low-grade and high-grade forms of MDS
  - Either relatively stable disease (years), or develop clonal cytogenetic evolution and progression to AML (months)
- International Prognostic Scoring System (IPSS) Risk Groups (n=4) provides some predictability
  - # of cytopenias, % of BM blasts, and karyotype
  - Risk of Progression to AML: Low (5.7 yr.), Intermediate-1 (3.5 yr.), Intermediate-2 (1.2 yr.), High (0.4 yr.)
  - But limited by heterogeneity within categories
- Genetic profiling to refine IPSS risk categories is underway



# Treatment of MDS

- Only BMT is potentially curative, everything else is palliative at this point
- Treatment decisions depend upon many factors:
  - Age, performance status, IPSS risk stratification, patient wishes, degree of cytopenias and required support (transfusions), is it de novo or secondary MDS
- Transfusion support, growth factors (especially EPO), iron chelation therapy (deferasirox), immunomodulators (lenalidomide) and/or DNA methyl transferase inhibitors (azacitidine, decitabine)
  - Lenalidomide is first-line treatment of the 5q- Syndrome, and may be considered in selected other patients
  - DNMT inhibitors have shown promise in high-risk MDS



# Myelodysplastic/ Myeloproliferative Neoplasms

What happened to CMML between  
WHO 2001 and WHO 2008?



# MDS/MPN Overlap Syndromes

- Chronic myelomonocytic leukemia (CMML)
- Atypical CML, *BCR-ABL 1* negative (aCML)
- Juvenile myelomonocytic leukemia (JMML)
- MDS/MPN, unclassifiable
  - Includes the provisional entity of “Refractory Anemia with Ring Sideroblasts and thrombocytosis (RARS-T)”



# CMML

- Diagnostic criteria:
  - Persistent monocytosis, absence of *BCR-ABL1*, no rearrangement of *PDGFRA* or *PDGFRB*, <20% blasts in the PB/BM, and at least one of the following:
    - Dysplasia in  $\geq 1$  cell line(s), clonal cytogenetic abnormality, OR unexplained monocytosis >3 months
  - CMML-1 = <5% PB blasts (includes promonocytes) and <10% BM blasts
  - CMML-2 = 5-19% PB blasts, 10-19% BM blasts or any blast count with Auer rods present
  - WBC <  $13 \times 10^9/L$  (CMML-MDS like), or  $\geq 13$  (CMML-MPN like)

# Diagnostic work-up of CMML

- CBC and peripheral blood smear evaluation
- BM aspirate/biopsy
  - Morphologic evaluation for dysplasia, fibrosis
  - Flow cytometry to confirm % promonocyte and monoblast phenotype
  - Cytogenetics and FISH
    - Clonal karyotypic abnormalities other than t(9;22)
    - +8, -7 and/or del7q
    - Lack of *BCR-ABL 1*, *PDGFRA*, *PDGFRB*





# Somatic Mutations in CMML

- Common mutations of possible clinical significance:
  - *TET2* (frequent marker of myelomonocytic clonal dominance)
  - *ASXL1* (associated with progression to AML?)
  - *RUNX1* (progression to AML?)
  - *EZH2* (poorer prognosis?)
  - *CBL* (myelomonocytic clones, uncertain?)
- Recent evidence points to abnormalities of DNA splicing pathways having a major role in CMML



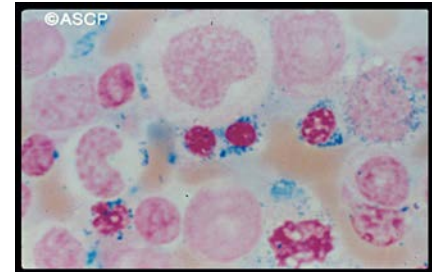
# Treatment and Prognosis

- Hydroxyurea or Azacitidine; Decitabine for CMML-2
- Only BMT is potentially curative
- Poor prognostic risk factors (IPSS)
  - CMML-2, WBC  $\geq 13,000$  (CMML MPN-like), hemoglobin  $< 10\text{g/L}$ , platelet count  $< 100 \times 10^9/\text{L}$
  - Cytogenetics:
    - Low risk= NK, -Y only
    - High risk= +8, abnormalities of 7, complex karyotype
    - Intermediate risk= any other abnormality
- Poor overall survival (months-few years)

# MDS/MPN, U

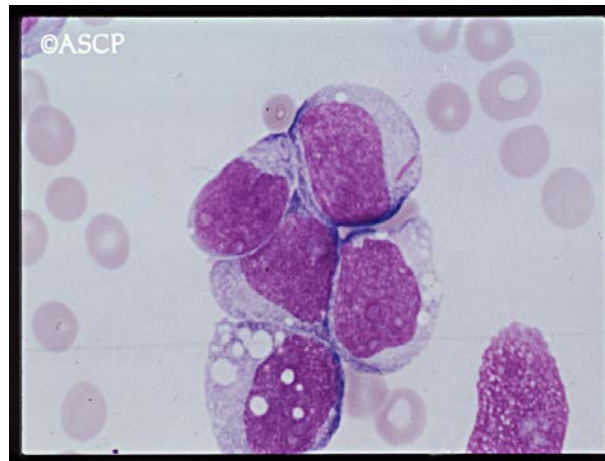
## Provisional entity RARS-T:

- Refractory anemia with dysplasia and RS ( $\geq 15\%$ )
- $< 5\%$  blasts in the BM
- Platelet count  $\geq 450 \times 10^9/L$
- Large, atypical megakaryocytes
- Absence of  $del5q$ ,  $t(3;3)$ , or  $inv3$
- Distinguishable from essential thrombocythemia by the presence of ring sideroblasts
  - Disordered mitochondrial iron transport and heme synthesis results in the RS formation
- Frequent *JAK2* or *MPL* mutations (60-80%)
- Prognosis similar to MDS-RARS but less favorable than ET



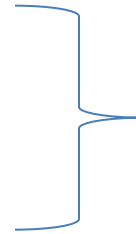
# Acute Myeloid Leukemia

## Genetic analysis and classification



# Diagnosis & Classification Criteria

Morphology (PB, BM)  
Cytochemistry  
Immunophenotype



Determining blast counts and lineage, maturational status, dysplasia, and effectiveness of hematopoiesis

Cytogenetics  
Karyotyping, FISH  
Mutation status  
PCR, NGS, expression  
arrays



Identify recurring cytogenetic abnormalities

Identify established mutational risk factors

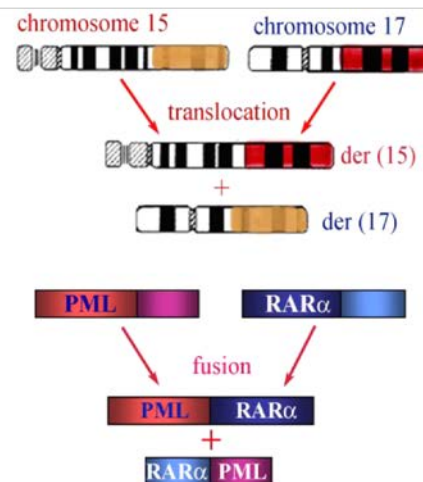
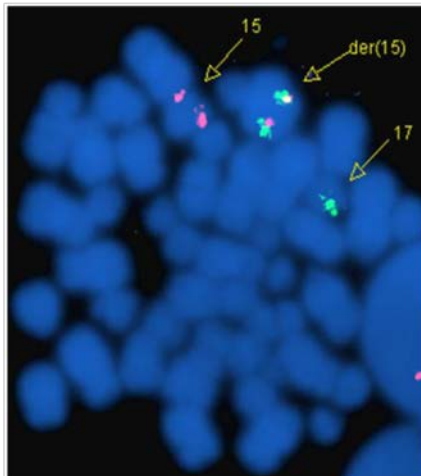
Establish the genetic baseline

Impact therapeutic decision making



# AML Diagnostic Criteria

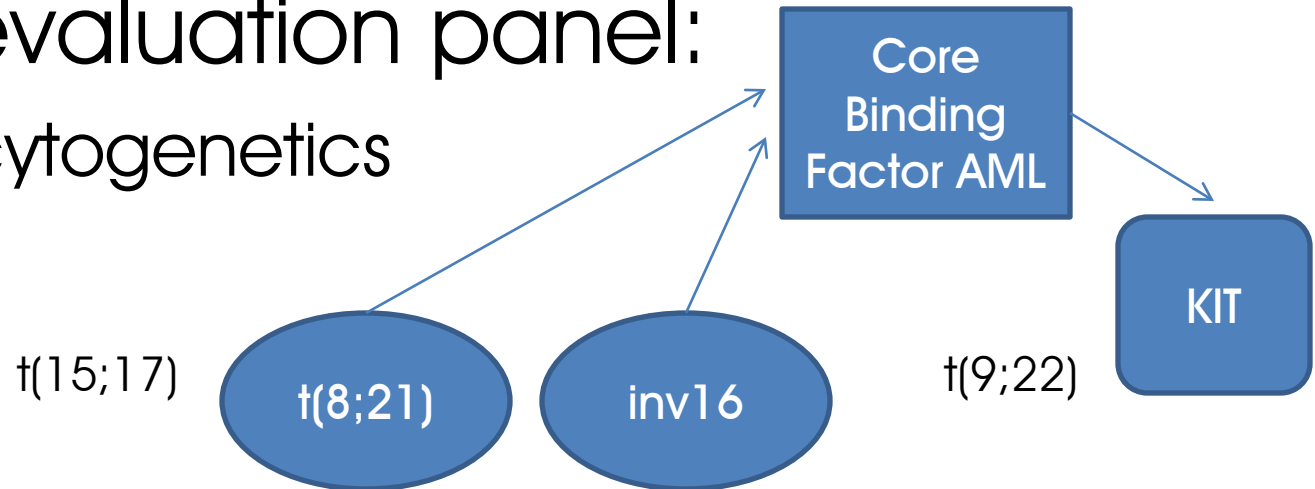
- A clonal stem cell disorder with  $\geq 20\%$  blasts in the blood or bone marrow, OR the presence of one of the following recurring genetic abnormalities regardless of blast count:
  - $t(8;21)(q22;q22)$ ;  $inv(16)(p13.1;q22)$  or  $t(16;16)(p13.1;q22)$ ; and  $t(15;17)(q22;q12)$



# Genetic Analysis in AML

Typical evaluation panel:

- Classic cytogenetics
- FISH



- Molecular Testing

*FLT3, NPM1, CEBPA, (DNMT3A, IDH1, IDH2)*

\* Emerging/investigational mutational factors

# Sequencing the AML Genome?

- Whole genome sequencing of AML\* leads to estimates of 500-1000 somatic mutations
  - Most are not considered to be primary “AML driver mutations”
  - Sequencing does not capture gene expression profiles or epigenetic changes that also contribute to leukemogenesis

\* Mardis ER, et al. *NEJM* 2009;361:1058-66.





# Integrated Genetic Profiling in AML

- Mutational analysis of 18 genes in 398 patients < 60 years old
  - 97.3% of the patients had at least one mutation
- The findings were then validated in an independent set of 104 patients
- Identified independent genetic predictors of outcome that improved risk stratification
- Improved outcomes seen with *DNMT3A* and *NPM1* mutations, and *MLL* translocations
- Suggested a future role for AML mutational profiling as well as emphasizing the complex nature of the disease

Patel JP, et al. NEJM 2012;366:1079-89



# AML and Related Neoplasms

## Classification

- AML with recurrent genetic abnormalities
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, NOS
  - Includes the French-American-British (FAB) subtypes
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm



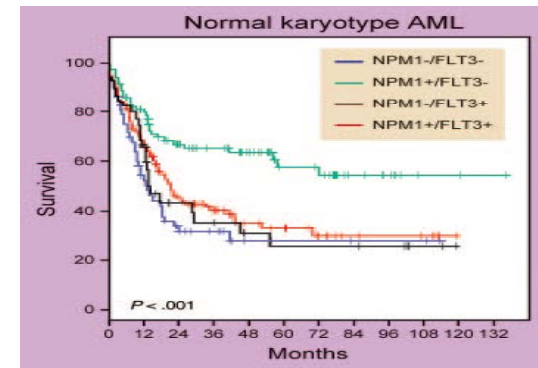
# AML with Recurrent Genetic Abnormalities

- Additional entities introduced in the 2008 WHO classification
  - t(9;11)(p22;q23) *MLLT3-MLL*
  - t(6;9)(p23;q34) *DEK-NUP214*
  - inv(3(q21;q26.2) or t(3;3)(q21;26.2) *PRN1-EVI1*
  - t(1;22)(p13;q13) *RBM15-MKL1*
  - Provisional entity: AML with mutated *NPM1*
  - Provisional entity: AML with mutated *CEBPA*
- *FLT3* mutations are frequently associated with other genetic abnormalities, and should be determined in cases of AML



# Therapeutic & Prognostic Decision Making

- AML with t(15;17)
  - All-trans retinoic acid (ATRA), plus cyto-reduction or arsenic trioxide
- Core Binding Factor (CBF) AML
  - Significantly higher response rates and long-term survival probabilities
  - Further evaluation for activating *KIT* mutations (in ~30%) open up the potential for tyrosine-kinase inhibitor therapy
- AML with *NPM1* mutations
  - Favorable prognosis
  - 25-35% of AML; 45-65% of NK-AML
- AML with *FLT3* mutations (in 20% of AML)
  - Worse prognosis
  - Clinical evaluation for *FLT3* inhibitor therapy or HSCT
- AML with *CEBPA* mutation (10-18% of NK-AML)
  - *CEBPA* double mutations (*CEBPA<sup>dm</sup>*) have a favorable prognosis



# Monosomal Karyotype AML

- Newly recognized
- Clone of at least 2 autosomal monosomies, or a single autosomal monosomy (other than of X or Y) and at least one structural abnormality
- ~10-15% of AML, increases with age
- Rarely seen with *FLT3* or *NPM1* , but frequently seen with *TP53* alterations
- Poor response to treatment
  - BMT recommended if possible



# AML with Myelodysplasia-Related Changes

- Includes patients with:
  - AML arising in previous MDS or MPS/MPN
  - AML with specific MDS-associated cytogenetic abnormality
  - AML with multi-lineage dysplasia (>50% of cells in  $\geq 2$  cell lineages)
- Doesn't include cases with prior cytotoxic therapy for an unrelated disease, or cases with the "recurring" AML cytogenetic abnormalities
- More common in the elderly
- ~25-30% of all AML cases (50% of adult AML?)



# Therapy-related Myeloid Neoplasms

- Alkylators, radiotherapy, and/or topoisomerase II inhibitors; usually within 1-6 years
- Based upon blast count and morphology:
  - t-MDS
  - t-MDS/MPN
  - t-AML
- But, best considered as a single biologic disease with a dismal prognosis (5 year survival < 10%)
- ~90% have recurrent genetic abnormalities,



# Genetics of Therapy-related Myeloid Neoplasms

- Genetic lesions similar to de novo MDS, but in different frequencies
  - *TP53* (17p) mutations are infrequent in de novo, but common (25-30%) in secondary MDS
  - *RUNX1* (21q) and *N/KRAS* (1p/12p) mutations are more common in secondary MDS than in de novo
  - Balanced translocations of *RUNX1* (21q) and *MLL* (11q23) are more common in radiation-induced MDS
  - del5 and del7 are more common in alkylator-induced MDS
- Similar to de novo AML genetics, but have worse outcomes than the de novo counterparts
  - Except for inv(16), t(16;16) or t(15;17)





# Myeloid Proliferations Related to Down Syndrome

- Transient abnormal myelopoiesis in 10% of DS
  - Median age of diagnosis = 5 days
  - Leukocytosis with increased blasts; variable RBC and platelet values
  - Myeloid blasts with frequent CD7, CD56, CD41 and CD61 expression (megakaryoblast-like)
  - Trisomy 21 with *GATA1* and *JAK2* mutations
  - Usually resolves spontaneously, but 10-15% later develop a myeloid neoplasm
  - Hepatic dysfunction/fibrosis is a poor prognostic sign
- Myeloid leukemia associated with DS
  - High risk of AML, especially AML-M7, in first 4 years of life
  - Usually preceded by myelodysplasia
  - Relatively good prognosis, especially in < 4 years of age

# Myeloid Sarcoma

- Extramedullary proliferation of myeloblasts
  - Variable expression of CD13, CD14, CD33, CD34, CD64, CD68, CD117, myeloperoxidase, and/or lysozyme
- May or may not be associated with concurrent disease of the bone marrow
- Diagnostic of AML
  - More common in pediatric AML
  - More common in monoblastic and myelomonocytic leukemias



# Blastic Plasmacytoid Dendritic Cell Neoplasm

- History of uncertain histiogenesis
  - “Blastic NK-cell lymphoma,” “CD4+/CD56+ hematodermic neoplasm”
- Confirmed to be of plasmacytoid dendritic cell origin, related to myeloid cells
- Cutaneous, bone marrow and blood involvement by non-descript blasts
- CD4, CD56 and CD123 expression, variable CD7 and CD33, without B, T, NK or myelomonocytic specific markers
- ~60% have non-recurrent genetic abnormalities
- Very aggressive clinical course
- Only BMT offers a chance of long-term survival



# Summary

- The myeloid neoplasms encompass a broad range of disorders
- Accurate diagnosis and treatment requires a combination of morphologic and genetic features
- New entities will continue to be added as we better understand the molecular genetic basis of pathogenesis



# Thank you for your attention

## Questions?

