AML: Understanding your diagnosis and current and emerging treatments

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Disclosures

- Nothing to disclose.

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Objectives

- Understand what is AML
- Understand the symptoms, signs and diagnosis of AML
- Standard treatment options for AML
- Emerging treatments for AML

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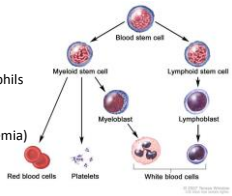
Normal blood cells production

- Hematopoietic "blood-forming" stem cells
- They produce all the
  - White blood cells: neutrophils (if low → neutropenia), lymphocytes, etc
  - Red blood cells (if low anemia)
  - Platelets (if low thrombocytopenia)



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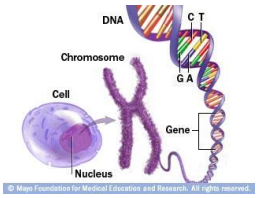
Story of DNA



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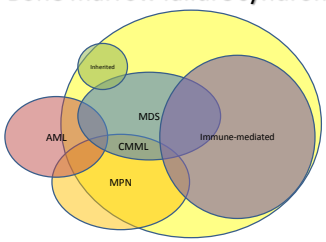
Bone marrow failure syndromes



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What is acute myeloid leukemia (AML)

- a type of blood cancer.
- usually fast-growing and needs to be treated quickly.
- Cancer of early cells that are distend to develop into neutrophils (type of WBC)
- Bone marrow usually shows more than 20% blasts
- 1% of all adult cancer deaths
- Average age at diagnosis is approximately 65 years

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MDS

- MDS is a malignant blood disease
- MDS is a form of bone marrow failure
- Stem cells do no mature as they should → ineffective blood production
- Bone marrow has less than 20% blasts

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Myeloproliferative neoplasms (MPN)

- Polycythemia vera
- Essential thrombocythemia
- Chronic myeloid leukemia (CML)
- Primary myelofibrosis

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Chronic myelomonocytic leukemia (CMML)

- Malignant stem cell disorder with clinical and pathological features of both a myeloproliferative neoplasm (MPN) and myelodysplastic syndrome (MDS).
- Characterized by a peripheral blood monocytosis, bone marrow dysplasia; cytopenias and hepatosplenomegaly.
- High rate of transformation to AML

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Risk factors for AML

- Age
- Male gender (5:3 male:female)
- Previous cancer treatment
- Exposure to radiation
- Dangerous chemical exposure
- Smoking
- Other blood disorders (MDS, MPN, CMML)
- Genetic disorders (eg, trisomy 21; Fanconi anemia; Bloom's syndrome)

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Symptoms of AML

- Feeling very tired and weak
- Bleeding more easily than normal
- Getting sick from infections more easily than normal

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How to get tested for AML

- Complete blood counts (CBC): very high or very low WBC, low RBC, low platelets
- Peripheral blood smear: blasts (immature WBC)
- Bone marrow biopsy: more than 20% blasts

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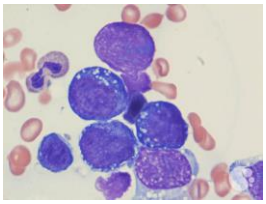
Bone marrow biopsy



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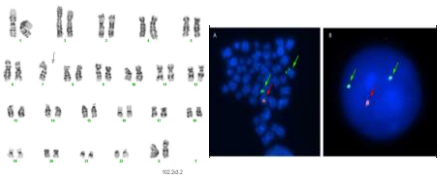
Timothy C Carll, MD; Girish Venkataraman, MD, MBBS
ASH image bank

Cytogenetics and FISH



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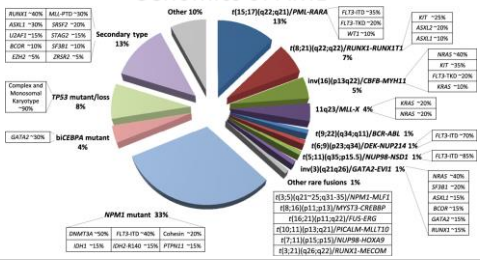
Genomics of AML



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Medinger and Passweg, BJC, 2017

Mutation	Frequency in CN-AML	Mode of action	Prognosis	Target "drugable"	Drugs
NPM1	30–45%	Nucleolar component	Favourable	–	–
DNMT3A	34%	De novo DNA methylation	Inconclusive	–	–
FLT3-ITD	28–34%	Receptor tyrosine kinase for Flt3 ligand	Unfavourable in high ratio (≥0·5)	tyrosine kinase inhibitors	e.g. sorafenib, midostaurin quizartinib
FLT3-TKD	11–14%	Receptor tyrosine kinase for Flt3 ligand	Neutral	–	–
IDH1/*IDH2*	15–30%	Conversion of isocitrate to α-ketoglutarate	Favourable		e.g. AG-221, AG-120
TET2	10%	Conversion of 5 methylcytosine to 5-hydroxy-methylcytosine, mediating demethylation	Inconclusive	–	–
ASXL1	5–16%	Epigenetic regulation by interaction with PRC2	Unfavourable	–	–
CEBPA	10–18%	Haemopoietic transcription factor	Favourable	–	–
RAS	25% *NRAS*, 15% *KRAS*	G-protein associated with receptor tyrosine kinases	Neutral	RAS downstream Inhibitors	–
KIT	20–30% of CBF-AML	Receptor tyrosine kinase for stem cell factor	Unfavourable	Kinase inhibitors	e.g. imatinib dasatinib
KMT2A-PTD	5–10%		20–30% of CBF-AML	Unfavourable	–	–
RUNX1	5–13%	Haemopoietic transcription factor	Unfavourable	–	–
TP53	5–20%	Tumour-suppressor gene	Unfavourable	–	–

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Medinger and Passweg, BJC, 2017

WHO Classification

- AML with recurrent genetic abnormalities (which includes specific AML subtypes with defined structural or molecular abnormalities).
- AML with myelodysplasia-related features, without a history of prior cytotoxic therapy
- Therapy-related AML.
- AML, not otherwise specified (NOS), which does not meet the criteria for the categories described above.
- Myeloid sarcoma.

- Acute promyelocytic leukemia (APL)

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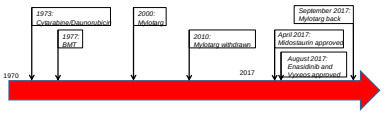
Slow ~~Lack of~~ therapeutic progress…



LLS, Facts and Statistics: From 2006-2012, the 5-year relative survival rates overall were:

AML = 26.8%

ALL = 70.7 %

CML = 65.9 %

CLL = 85.1 %

https://www.lls.org/http%3A/lsorg.prod.acquia-sites.com/facts-and-statistics/facts-and-statistics-overview/facts-and-statistics

Management of Leukemia

- Goals of treatment:
  - Needs careful discussion with the treating physician
  - Achieving a complete remission is necessary for cure and is a reasonable goal for most patients.
  - For some patients, treatment with the intent of achieving CR may be inadvisable because of advanced age, debility, coexisting medical problems, and/or prior treatment.
  - In such circumstances, it may be appropriate to provide supportive care alone (eg, blood transfusions, antibiotics)

Induction Therapy

- Induction therapy: intensive combination chemotherapy to achieve a remission
  - Usually a combination of anthracycline/cytarabine 7+3
  - Given as IV infusion
  - About 4 week hospitalization
  - Requires close monitoring to treat infections and other complications (eg. Tumor lysis syndrome) awaiting blood counts recovery

Adding a third drug

- Midostaurin in AML with FLT3 mutation:
  - Oral medication
  - Improves survival (average 75 months versus 26 months)
- Gemtuzumab ozogamicin (Mylotarg)
  - anti-CD33 antibody linked to the cytotoxic agent, IV infusion
  - Decreases chances of relapse, improves survival
  - Risk of liver toxicity

Therapy related AML

- Newly approved drug is Vyxeos (Liposomal daunorubicin and cytarabine)
- *Induction (first cycle):* Daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 (liposomal) on days 1, 3, and 5
- *Induction (second cycle in patients who do not achieve remission with first cycle):* Daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 (liposomal) on days 1 and 3
- *Consolidation:* Daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 (liposomal) on days 1 and 3

Acute promyelocytic leukemia (APL or APML)

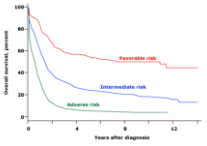
- Special type of AML
- Translocation (15;17)
  - **Low- or intermediate-risk APL** – Initial WBC count ≤10,000 →
    - ATRA: Oral
    - ATO: arsenic trioxide, IV
- **High-risk APL** – Initial WBC count >10,000 → ATRA plus anthracyclin based chemo

Post remission therapy

- Consolidation with chemotherapy:
  - Usually high dose cytarabine IV infusion for 4 or 5 days
  - For up to 4 rounds (cycles) of therapy
- Hematopoietic stem cell transplantation

2017 European LeukemiaNet risk stratification of acute myeloid leukemia by genetics

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3-ITD* or with *FLT3-ITD*low§
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3-ITD*high§
	Wild type *NPM1* without *FLT3-ITD* or with *FLT3-ITD*low§ (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* −5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,† monosomal karyotype‖
	Wild type *NPM1* and *FLT3-ITD*high§
	Mutated *RUNX1*‡
	Mutated *ASXL1*‡
	Mutated *TP53*‖



Hematopoietic stem cell transplantation or BMT

- Finding a donor
- Majority of time it is the only potential cure
- Has high early toxicity
- Finding a donor
- Conditioning regimen
- Graft versus host disease (GVHD)

What if I don't achieve a remission

- Clinical trial
  - Clinicaltrials.gov
  - Beat AML Master Trial
- Targeted therapy
  - Enasidenib (IDHIFA) (IDH2 mutated AML)

Questions