Understanding AML
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First Let’s Look at Our Blood…

Bone Marrow: The Blood Cell Factory

Blood: 3 Major Cell Types

ADDITIONAL RESOURCES
- www.keckmedicine.org/rare-blood-diseases
  Video “How to Read Your CBC”

How Does a Factory Making 310,000,000,000 cells Daily Function for 80+ Years?????
1. **Needs Ingredients**: proteins, iron, oxygen, B12, Folate, copper, etc.
2. **Needs Stimulus**: Erythropoietin – from the kidneys stimulates Red Cell Production
   GCSF – from blood vessel lining, immune cells stimulates WBC Production
   Thrombopoietin – from the liver stimulates Platelet Production
3. **Needs Source**: STEM CELLS

RED CELLS: Carry oxygen to all the organs

PLATELETS: Help heal cuts or nicks on SKIN, MUCOSA (gums, nose, gut)

WHITE BLOOD CELLS: fight infection, help with healing
ACUTE MYELOID LEUKEMIA

• **1855** Alfred Donne: “There are conditions in which white cells seem to be in excess in the blood. I found this fact so many times, it is so evident in certain patients, that I cannot conceive the slightest doubt in this regard….The blood of this patient showed such a number of white cells that I thought his blood was mixed with pus....”

Acute Myeloid Leukemia Defined

• >20 “BLASTS” in blood or bone marrow
• Usually associated with worsening anemia and thrombocytopenia
• Often requires bone marrow biopsy to diagnose

WHO CRITERIA FOR AML
**Defective HSCs lead to defective blood cell production**

- Decreased/Defective (“Ineffective”) Red Cell Production = **ANEMIA**
  - Fatigue, shortness of breath, weakness, fainting, heart attack, stroke
- Decreased/Defective Platelet Production = **Thrombocytopenia**
  - Bruising, gum bleeding, nose bleeding, red dots on skin (petechiae)
- Decreased/Defective White Blood Cell Production = **Neutropenia**
  - Infections, fatigue, poor wound healing

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**WHY DOES AML HAPPEN?**

- Genetic/Molecular defect in DNA affecting **HEMATOPOIETIC STEM CELLS (HSCs)**
  - Sometimes (50%) we can see this DNA defect in the karyotype (i.e. 46XX, 45XX, -5q)
  - Sometimes (90%) we can only see the DNA defect with special molecular studies (e.g. TET2 mutation, IDH2 mutation)

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**What Causes AML?**

- Acquired DNA damage…
  - Chemotherapy
  - Benzene/chemicals
  - Radiation
  - Immune Dysregulation?
  - MAJORITY: IDIOPATHIC
- People are living longer after chemo…

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**How Do We FIND Mutations?**  **3 Levels of Gene Testing:**

1. **CYTOGENETICS** – usually done in MPN patients on their bone marrow sample
2. **FISH** – can be used to detect a mutation that may be missed by cytogenetics
3. **PCR** – most sensitive, relies on amplification of the DNA present in the sample

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**There Are Different Types of Mutations**
Progress in defining the molecular landscape of AML. Timing of the identification of leukemic fusion genes and mutations underlying the pathogenesis of AML. David Grimwade et al. Blood 2016;127:29-41


NEW CASES 2016: 19,550

Projected relative 5-year survival in AML according to age and time period, with follow-up on December 31, 2006. Gunnar Juliusson et al. Blood 2012;119:3890-3899

AML Risk Stratification

AGE > 65 = poorer response to induction chemotherapy
Treatment-related AML more likely to have complex cytogenetics
Post-MDS/MPN AML = poorer response to traditional chemotherapy

Figure 2: Age-Specific Incidence Rates for Acute Myeloid Leukemia, 2006 - 2010

Source: US Dept of Health and Human Services, Centers for Disease Control and Prevention 2018

CPX-351 (Vyxeos) – Liposomal ARA-C + Daunorubicin

Published in: Jeffrey E. Lancet; Geoffrey L. Uy; Jorge E. Cortes; Laura F. Newell; Tara L. Lin; Ellen K. Ritchie; Robert K. Sture; Stephen A. Strickland; Donna Hogge; Scott R. Solomon; Richard M. Stone; Dale L. Bixby; Jonathan E. Kolitz; Gary J. Schiller; Matthew J. Wieduwilt; Daniel H. Ryan; Antje Hoering; Kamali Banerjee; Michael Chiarella; Arthur C. Louie; Bruno C. Medeiros; Journal of Clinical Oncology 2018, 36, 2684-2692. DOI: 10.1200/JCO.2017.77.6112

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AML with FLT3+: 7+3 + Midostaurin

AML: Why Does Allo-SCT Work?

Engages a healthy immune system (Donor’s) in fighting the aberrant cells (Recipient’s) = “graft vs. leukemia”

AML Therapy >65 yo

Methyl Groups Silence Tumor Suppressor Genes – Cancers are Highly Methylated

2 FDA-approved Hypomethylating Agents:
- VIDAZA (5-azacytidine)
- DACOGEN (decitabine)

1 Novel HMA in Clinical Trials:
- SGI-110

2017-07-11(H 기간)
Active Clinical Trials

- **Frontline Guadecitabine Falls Short in Phase III AML Study**
- **Venetoclax** (Bcl-2 inhibitor) Promising results in Phase ½
  - CPX-351 + venetoclax in R/R or Untreated (MD Anderson)
  - Venetoclax and azacitidine for non-elderly (Univ Colorado)
  - Venetoclax + cabimetinib & Venetoclax + Dinaciclib
- **IDH1 inhibitor** (USC)
- **PARP inhibitor + Decitabine** (USC)
- **Flt3 inhibitors** (USC/UCLA/COH)
- **Lintuzumab-Ac225** (UCLA)
- Immune checkpoint inhibition

**QUESTIONS?**