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Hierarchy Model of Hematopoiesis and Leukemogenesis

- **HSC** (Hematopoietic Stem Cell)
- **Myeloid Stem Cell**
- **CD33 +**
- **AML** (Acute Myeloid Leukemia)
- **Erythrocytes**
- **Granulocytes**
- **Platelets**
# Pathophysiology of Acute Leukemia: Determinants of Clinical Presentation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Consequences</th>
<th>Correction</th>
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<tbody>
<tr>
<td>Bone Marrow Failure</td>
<td>Anemia</td>
<td>Restore Normal Hematopoiesis</td>
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<tr>
<td></td>
<td>Bleeding</td>
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<td></td>
<td>Infection</td>
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<tr>
<td>Leukemia Phenotype</td>
<td>Leukostasis</td>
<td>Cytoreduction</td>
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<tr>
<td></td>
<td>Endothelial Damage</td>
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<td></td>
<td>DIC</td>
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<tr>
<td></td>
<td>Extramedullary Tissue Infiltration</td>
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<td></td>
<td>Tumor Lysis Syndrome</td>
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LEUKEMIA BIOLOGY: A SIMPLISTIC VIEW

TWO MAJOR DEFECTS:

- INABILITY TO DIFFERENTIATE
- INABILITY TO DIE IN RESPONSE TO STRESS
Biological Advances: Understanding Cellular Mechanisms → Cancer
Tumor and Host Microenvironment: Growth Factors, Motility Factors, Angiogenic Factors
AML demographics 2006

- New cases = 12,000; deaths = 9,000
- Median age = 68 yrs
- Incidence = 3.8 per 100,000
  - <65 yrs = 2.1 per 100,000
  - >65 yrs = 18 per 100,000
- Chance of developing AML
  - For a 50 yr old = 1 in 50,000
  - For a 70 yr old = 1 in 5,000
### AML: Much work to do

<table>
<thead>
<tr>
<th>Age</th>
<th>CR</th>
<th>DFS</th>
<th>Early Death</th>
<th>OS (median)</th>
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</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>70%</td>
<td>45%</td>
<td>10%</td>
<td>30% (24 mo)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>45%</td>
<td>20%</td>
<td>25%</td>
<td>10% (10 mo)</td>
</tr>
</tbody>
</table>

Based on CALGB, MRC trials in which adults of all ages were eligible

*Slide kindly provided by Dr. Richard Stone*
Cytogenetics | Total | Relapse
---|---|---
inv16/t8;21 | 17 | 10
-5/-7, +8 | 62 | 57
Other | 214 | 157

p<0.001

Adapted by CTLT from Eli Estey, MD.
Why is AML in the older adult so difficult to treat?

**Disease Biology**
- DNA Damage/Toxin Exposure Increases with Age
- Detoxifying Enzyme Activity Decreases with Age
- Immune Surveillance Decreases with Age

**Host Biology**
- Intolerance for Cytotoxic Chemotherapy
DNA REPAIR PATHWAYS

IDENTIFYING CRITICAL GENES IN THE PROCESS OF LEUKEMOGENESIS
Repairing DNA Damage: Lessons Learned from Familial Cancer Syndromes

Selected Familial Leukemia-Prone Syndromes: Lesions in Genes Responsible for Repairing DNA Damage

- Fanconi Anemia (Repair of interstrand DNA crosslinks)
- Xeroderma Pigmentosum (Nucleotide excision repair)
- Bloom Syndrome (RecQ Helicase)
- Ataxia Telangiectasia
- Li-Fraumeni (p53)
Polymorphisms in DNA Repair Genes May Determine Risk, Response, and Toxicity

• XPD Lys751Gln polymorphism $\rightarrow$ increased risk of developing AML with -5q and/or -7q
• ERCC1 8092 C>A polymorphism $\rightarrow$ increased risk for childhood ALL in males
• XPD Gln751/Asp312G haplotype $\rightarrow$ increased CR for adults with AML > age 55
• ERCC1 polymorphisms $\rightarrow$ lung and metabolic tox
• XRCC3 241Met polymorphism $\rightarrow$ decreased risk for liver toxicity
Fanconi Anemia Proteins: A “Master” Switchboard for Repairing of DNA Damage

All 11 FA proteins cooperate in a pathway to:

• Recognize and repair DNA damage due to DNA crosslinking agents (alkylators, platins, mitomycin C)
• Coordinate with other DNA repair proteins (ATM, ATR, Bloom, BRCAs!!) to form complexes that localize to and repair damaged sites
FA Genes as Targets for Inactivation in AML (Kennedy and D’Andrea, JCO, 2006)

Inherited biallelic inactivating mutations → high incidence (~ 30%) of developing cancer by age 40, especially AML with adverse cytogenetics (-7, abnormalities of chromosomes 1q and 3q)

Heterozygous Carriers → high incidence of breast/ovarian, pancreatic (esp. FANCD1/BRCA2), low incidence of AML (FANCA missense mutations)

Somatic inactivation of FANC genes in AML:
- Deletions/mutations: FANCA, FANCD1, FANCG
- Methylation: FANCA, FANCC, FANCF, FANCG
GENES AND ENVIRONMENT: A LEUKEMOGENIC COMBINATION
# AML: A Prototype Environmental-Occupational Malignancy

## Etiologic Factors

<table>
<thead>
<tr>
<th></th>
<th>% AML</th>
<th>Genetic Abnormalities</th>
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</thead>
<tbody>
<tr>
<td>Env/Occ Exposure</td>
<td>~30-35%</td>
<td>-5/5q, -7/7q, 3q26</td>
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<tr>
<td>Benzene, Petroleum,</td>
<td></td>
<td>t(8;21), +8, +21</td>
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<tr>
<td>Organic solvents,</td>
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<td></td>
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<tr>
<td>Arsenical Pesticides,</td>
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<tr>
<td>Radiation</td>
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## Therapeutic Agents

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<tr>
<th></th>
<th>~20%</th>
<th>Genetic Abnormalities</th>
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</thead>
<tbody>
<tr>
<td>DNA Damaging Agents</td>
<td></td>
<td>-5/5q, -7/7q, 3q26</td>
</tr>
<tr>
<td>Topo-II Directed Drugs</td>
<td></td>
<td>AML-1 mutation (21q22)</td>
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<tr>
<td></td>
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<td>Translocations (11q23)</td>
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</tbody>
</table>
Benzene: The Classical Environmental Hematotoxin

• 1930’s: 1st association between benzene and bone marrow disorders
• 1950’s: Direct link between chronic exposure and acute leukemia demonstrated in long-term study from Turkey when benzene-based adhesives were first used (Askoy 1972)
Selected Mechanisms of Benzene Hematotoxicity

- Intermediary benzene metabolites → direct DNA damage → activate p53 and, in turn, p21 → cell cycle arrest (Yoon, Exp Hematol 2001)
- Hydroquinone causes selective deletion of chromosome 7 (by FISH) in CD34+ marrow cells (Stillman, Exp Hematol, 2000)
- Low level airborne exposure to benzene (gas station attendants, police) → altered methylation of p15 (↑) and MAGE ↓ (Bokati, Ca REs 2007)
NAD(PH): QUINONE OXIDOREDUCTASE (NQO1)

- NQO1 gene located on chromosome 16q23
- Induced by antioxidants → protects against oxidative stress
- Inactivated by $^{609}C \rightarrow T$ polymorphism
Intersection of Benzene and $^{609}\text{C} \rightarrow \text{T}$ NQ01 Polymorphism

- NQO1 detoxifies marrow-genotoxic benzene metabolites (phenols, benzoquinones) to less toxic hydroxyquinone metabolites
- Inactivating $^{609}\text{C} \rightarrow \text{T}$ associated with >7-fold increased RR for benzene poisoning (Rothman, Ca Res, 1997)
- Low exposure (<1ppm) → decrease in WBC, platelets, colony-forming progenitors; most toxicity in $^{609}\text{C} \rightarrow \text{T}$ NQO1 and/or fully active MPO (converts benzene to toxic quinones) (Lan, Science, 2004)
More Evidence Tying $^{609}\text{C} \rightarrow \text{T}$ to Increased Risk of Leukemia

- ↑ frequency low or null NQO1 activity in all acute leukemias: for *de novo* leukemias, highest frequency seen in *de novo* AML with *inv(16)* (Smith, Blood 2001)
- ↑ prevalence in AMLs with -5/-7 and T-AML, with greatest prevalence in homozygotes (Larson, Blood 1999)
- ↑ risk 11q23 (*MLL* gene)-rearranged infant ALL (Smith, Blood 2002) or infant ALL without *MLL* rearrangements (Lanciotti, Leukemia 2005)
GLUTATHIONE S-TRANSFERASES (GSTs)

- Family of isoenzymes (α, μ, ρ, Θ) that detoxifies anthracyclines and epipodophyllotoxins (VP16): induced by oxidative stress (DNA and lipid damage by reactive oxygen species)
- Null polymorphisms are common for each subfamily
- Epidemiologic relationships between “null” μ or Θ genotypes and increased risk for developing CLL and MDS – relationships with genesis of treatment-related AML and de novo childhood ALL not so clear
GST Polymorphisms May Relate to Chemotherapy Drug Metabolism and Clinical Outcome

- Homozygous deletions in GSTM1 and/or T1 → drug resistance and short overall survival in AML (Voso, Blood 2002) but not in childhood ALL (Davies, Blood 2002)
- High blast glutathione levels → ↑ risk of relapse in childhood ALL (Kearns, Blood 2001)
- Null GST-T1 genotype → increased early death (toxicity) in AML (Naoe, Leukemia 2002)
- SWOG multiple AML therapies → no clear impact of GST polymorphisms on toxicity, early mortality achievement or duration of remission (Weiss, Leukemia 2006)
Treatment-Related AML After Treatment for Breast Cancer

- 1970’s: Case reports of women < age 60 who received chemo but no XRT → AML (Davis, Cancer 1972)
- 1980’s: AML RR post-breast cancer therapy: 2.4 local XRT alone, 10 alkylators alone; 17.4 alkylators + XRT (Curtis, NEJM 1992)
- 1990’s: ↑ AML risk with DNA intercalators Epirubicin (+ alkylators: Pederson-Bjerrgaard, JCO 1992; Praga, JCO 2005) and Mitoxantrone (+ XRT: Carli, Leukemia 2000; Chaplain JCO, 2000) – risks are dose-dependent
- 1990’s (NSABP trials): AML risk relates to CY dose (in CY/Adr combo), XRT, and use of G-CSF
BREAST CANCER AND AML: A “LOCAL” PERSPECTIVE

• Among 230 women ages 18-86, 33 (14.3%) have a history of breast cancer and an additional 47 (20.3%) have positive family history (mainly breast/ovarian, also heme and/or multiple ca’s)

• Of the 33 women with AML and Hx breast cancer:
  – 19 (58%) < 60 at breast ca Dx (med 51, range 36-76)
  – 20 (61%) did not have chemotherapy:
    • 8 → no chemo or XRT, 12 → XRT only
    • 4 → chemo only, 9 → chemo + XRT
Therapy-Related AML: Could We Predict Who Is At Risk?

Development of T-AML appears to be increased in patients with:

- Defective expression of mismatch repair proteins → microsatellite instability (Ben-Yehuda, Blood 1996; Zhu, Blood 1999; Rund, Leukemia 2005)
- Variant polymorphisms in HLX1 (homeobox gene) and Rad51 (DNA repair) (Kawad, Blood 2006)

In contrast, the CYP3A4 1*B genotype may confer protective effect against T-AML (Rund, Leukemia 2005)
Clinical trials are important because:

• At the present time, we don’t have a reasonable “standard of care” because we are not curing nearly enough people

• Clinical trials with new ideas and new drugs that offer a chance to do better
  – What we have learned from clinical trials in years past is the basis for what we do today (and we are better than we were 2-3 decades ago!)

• What we learn from today’s trials will help us to develop more effective approaches tomorrow
TYPES OF CLINICAL TRIALS

• Risk Assessment → Prevention
• Early Detection and Diagnosis
• Treatment
  – Primary Disease
  – “Secondary Prevention” (Adjuvant Therapy, Minimal Residual Disease/Maintenance)
  – Recurrent/Refractory/Metastatic Disease
• Quality of Life
  – Quantity vs. Quality – how can we measure that?
  – What is the cost to the person and to society?
“Secondary” Leukemia Research Agenda: Molecular Epidemiology

Define pathways/processes leading to loss of cell cycle regulation, inappropriate cell survival and net genomic instability

– Genetic Susceptibility (Host response to Toxins and DNA Damage)
  • DNA Repair Genes and Pathways
  • Pharmacogenomics (Intracellular toxin metabolism)

– “Epigenetic” Factors
  • DNA damage $\rightarrow$ altered gene expression through methylation and/or histone deacetylation
“Secondary” Leukemia Research Agenda: Clinical Epidemiology

• Define populations at risk for leukemogenesis: A *folie a deux* between genetics and environment
  – Longitudinal studies to quantitate dose-risk relationships for leukemogenic agents
  – Serial monitoring of “at risk” populations to identify “leukemia intitiation”
“Secondary” Leukemias: Clinical Interventions

• Prevention for patients at high risk
  – Screening for predisposition → intervene before cumulative genetic damage ensues: Vaccines???
  – Avoid specific agents in patients with susceptibility to certain types of DNA damage

• Innovative treatment approaches
  – Epigenetic modulation
  – Overcome pro-survival pathways
  – Inhibit DNA repair pathways
CHALLENGES TO TRANSLATIONAL CLINICAL RESEARCH:
Common Misconceptions

Patient samples grow on trees
Man is related to any/all:
Isolated cells are just like cells in their natural habitat
Patients, like inbred mice, are all the same
Insurance companies really have the patient’s interest at heart
IRBs protect all of us from the bad, mad doctors who just want to “spearmint” on those poor, unsuspecting patients
The FDA makes thoughtful decisions about drug safety and efficacy
Why should clinical research cost anything? After all, the patients are already there
A MAJOR CHALLENGE FOR ALL AREAS OF MEDICINE

How do we get the best medicine *to EVERYONE, not just those who can pay or be paid for?*

*What is the best medicine? In the setting of inadequate cure rates, it is a clinical trial that offers the possibility of doing better!*