Bone Marrow Failure and Acute Leukemia: More mutations, more problems 6/18/13

Rebecca Olin, MD, MSCE

BIOGRAPHY:

Rebecca Olin MD MSCE is an Assistant Professor of Clinical Medicine at UCSF. After undergraduate work at Amherst College, she received her MD degree from University of Pennsylvania School of Medicine. She subsequently completed residency training in Internal Medicine and fellowship in Hematology/Oncology, both also at University of Pennsylvania. During fellowship she also received a Masters degree in Clinical Epidemiology, with a focus both on clinical trial development and outcomes research. She has been at UCSF as an Assistant Professor since 2009, and has a clinical practice which focuses on acute leukemia, myelodysplastic syndromes and other hematologic disorders, as well as stem cell transplantation. Her research area of interest is in evaluating quality of life and functional status in older stem cell transplant recipients, with a goal of learning more about how to make stem cell transplant safer.

BIBLIOGRAPHY:


Bone Marrow Failure Syndromes and Acute Leukemia: “More mutations, more problems”

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UCSF Mini Medical School
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Huntington Disease
- Progressive neurological disorder
- Typical onset in 30's, progresses over 10-20 years until death
- Genetically inherited – 50% chance
- No treatment, no cure

Overview
- Review of normal hematopoiesis (blood development)
- Bone Marrow Failure Syndromes
  - Aplastic Anemia
  - Fanconi Anemia
  - Dyskeratosis Congenita
- Acute Leukemias
  - Acute Myeloid Leukemia
  - Acute Promyelocytic Leukemia
- Hematopoietic Stem Cell Transplantation
Laboratory Values (Review)
- We order a “CBC” = Complete Blood Count
- RBC = red blood cells (erythrocytes)
- Platelets
- WBC = white blood cells
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Basophils
  - Eosinophils

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Acquired Aplastic Anemia
- “Aplastic” = failure to develop
- “Aplastic anemia” is a misnomer because it is not just about anemia
- Failure of the bone marrow to make enough cells of all three lineages
  - Failure to make blood
  - Aka “The Empty Marrow”
  - Disorder of the bone marrow stem cell

Clinical Presentation
- Rare disease: <5 cases per million people per year
- Clinical presentation is based on the deficiency of each of the cell lines
  - Low white blood cells: fever, susceptibility to infection
  - Low red blood cells: fatigue, pallor, shortness of breath
  - Low platelets: bleeding, bruising

Diagnosis
Causes of Aplastic Anemia
- Chemicals – eg pesticides
- Medications – wide variety
- Viruses – hepatitis, HIV, parvovirus
- Radiation
- Inherited predisposition
- MAJORITY ARE UNKNOWN
  - “idiopathic”

Aplastic Anemia is an Autoimmune Disease
- Patient’s own T-cells (T lymphocytes) are attacking the bone marrow stem cell
- Treatment is based on suppressing the T-cells

Treatment of Aplastic Anemia
- Anti-thymocyte Globulin (ATG)
- Cyclosporine

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Fanconi Anemia
- Inherited genetic disease
- Aplastic anemia, leukemia
- Susceptibility to cancers
- Other physical abnormalities: short stature, skin findings, abnormality of thumbs, small head
- 60% have some physical abnormality (40% do not)
- Mean age of diagnosis is 6 years, but some in 20’s, 30’s

Fanconi Anemia Genes

Shimamura 2010
DNA Damage

Up to one million events per cell per day!

DNA Repair

Fanconi Anemia: Diagnosis

- Blood lymphocytes are cultured with a DNA cross-linking chemical (MMC, DEB)
- Normal cells can repair the damage, FA cells cannot

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Dyskeratosis Congenita

- Inherited syndrome
  - Aplastic anemia
  - Cancers
  - Lung fibrosis and liver cirrhosis
  - Other physical abnormalities: abnormal nails, lacy rash, white patches in mouth, premature grey hair
  - 75% have some physical abnormality (25% do not)
  - Mean age of diagnosis is 14 years, but some up to 50s, 60s

Shimamura 2010
Telomeres

- Every time a cell divides, a very small amount of DNA at the ends of chromosomes is not replicated and therefore lost.
- Telomeres are "martyrs" to protect coding genetic material from being lost – telomeres get shorter instead.

Telomere Maintenance

- Enzyme complex called telomerase, containing both proteins and RNA.

Cellular Consequences of Telomere Erosion

- Increased cell senescence.
**Treatment of BMF Syndromes**

- Aplastic anemia → stem cell transplant
  - Only fixes the bone marrow problem, not the problem in other body tissues
- Cancers → chemotherapy per cancer type
- Problem: very sensitive to side effects of chemotherapy (FA in particular)
- Require intensive screening programs to detect cancers, and unique stem cell transplant approaches

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**Spectrum of Telomere Diseases**

**Dyskeratosis Congenita: Diagnosis**

![Graph showing telomere length over age](image)

**Graph showing telomere length over age**
Acute Myeloid Leukemia (AML)

- Most common acute leukemia in adults
- Chronic lymphocytic leukemia (CLL) is most common
- 3-5 cases of AML per 100,000 people per year

Clinical presentations:
- Low blood counts
- Leukostasis – “sludging”

AML: Definition and Causes

- Definition of AML: >20% blasts in bone marrow
  - <5% = normal
  - 5-20% = myelodysplastic syndrome (MDS), a precursor to AML
- Causes: largely unknown
  - Prior chemotherapy
  - Prior radiation
  - Certain chemicals eg benzene
  - Genetic disorders eg Fanconi

AML: Sub-classification and Prognosis

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Chromosomal Abnormality in Leukemia Cells</th>
<th>Molecular Abnormality in Leukemia Cells</th>
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<tr>
<td>Favorable</td>
<td>inv(16)</td>
<td>Normal with NPM1</td>
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<tr>
<td></td>
<td>t(8;21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(15;17) - APL</td>
<td></td>
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<tr>
<td>Intermediate</td>
<td>Normal</td>
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<tr>
<td></td>
<td>Other abnormalities</td>
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<tr>
<td>Unfavorable</td>
<td>Loss of 5</td>
<td></td>
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<tr>
<td></td>
<td>Loss of 7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemotherapy-related Complex (≥3)</td>
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</table>

Molecular Diversity of AML with Normal Chromosomes

Dohner 2010
Process of Treating AML

- Phase 1: Induction
  - reduce the number of leukemia cells in the body by orders of magnitude
  - goal: remission
  - = chemo

- Phase 2: Consolidation
  - get rid of every single last leukemia cell in the body
  - goal: cure
  - = more chemo or stem cell transplant

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Acute Promyelocytic Leukemia (APL)

- Defined by existence of t(15;17) translocation
- Function of PML not well understood
- Function of RAR proteins is to bind certain genes, promote normal differentiation of cells
- Abnormal RARα has abnormal function
APL: Prognosis

- Used to be worst prognosis acute leukemia
- Survival <1 month without treatment
- Since the development of targeted therapies against PML-RAR, is now the best form
  - All-trans retinoic acid (ATRA)
  - Arsenic

Evolution of APL Treatment

Chemotherapy 1990's, 2000's
Chemotherapy plus ATRA 2000's
Chemotherapy, ATRA plus arsenic 2010's
ATRA plus arsenic (no chemo?)

APL and Bleeding

- APL commonly presents with bleeding problems
  - DIC, or disseminated intravascular coagulation
  - Due to release of granules from promyelocytes, which affect blood's clotting proteins
  - DIC can worsen during initial treatment, as promyelocytes die and dump granules
  - Early death rate from bleeding complications is 10-30%

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What is a Stem Cell Transplant?

- It's not a surgery
- Consists of chemotherapy (+/- radiation) followed by infusion of hematopoetic (blood) stem cells into a vein
First, Some Terminology

- How is a “stem cell transplant” different from a “bone marrow transplant”?  
- Basically, it’s two terms for the same thing  
- It has to do with how we get them out

More Terminology: Autologous vs Allogeneic

- There are two kinds of stem cell transplant:
  - Autologous – “Derived or transferred from the same individual’s body”
  - Allogeneic – “Being genetically different although belonging to or obtained from the same species”

- DIFFERENT:
  - Philosophy / rationale
  - Diseases and disease scenarios
  - Level of risk

Autologous SCT

- Goal is to administer very high doses of chemotherapy
  - If some is good, more is better
  - Problem is, healthy bone marrow cells are destroyed

Allogeneic SCT

- Works in two ways
  1) Replace bad bone marrow (and/or cancer) with good bone marrow
  2) Use the new immune system to recognize any remaining cancer cells as foreign and attack them

Autologous SCT

- Administer high doses of chemotherapy = KILL CANCER
- Infuse stem cells to “rescue” / regenerate bone marrow
- Low blood counts

Allogeneic SCT

- Administer high doses of chemotherapy = KILL CANCER
- Infuse donor stem cells to regenerate bone marrow
- Donor stem cells recognize and KILL CANCER
- Donor stem cells recognize patient “host” and attack = Graft Versus Host Disease
- Immune Suppressive Medications
Stem Cell Source

- Sibling donor – 25%
- Umbilical cord blood
- Half-matched donor: 50% if sibling, 100% if parent or child

Matched unrelated donor

SCT Cures Disease and Saves Lives

Thank you for your attention!