Camp Rainbow
Why is it called DBA “101”?
<table>
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<th>Syndrome</th>
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These disorders are the “Inherited Bone Marrow Failure Syndromes” (IBMFS).
Questions

1. How many are new to a DBA meeting?
2. How many have been here before?
3. How many have DBA and are 18 years of age or older?
4. How many think that the diagnosis of DBA was initially missed by one or more physicians?
5. How many were called “TEC” initially?
Diamond and Blackfan

Louis K Diamond, 1902-1999
Kenneth D Blackfan 1883-1941
What Symptom led to DBA?

1. Physical findings (e.g. thumbs, cleft palate)
2. Endocrine (e.g. short stature)
3. Hematology (e.g. anemia)
4. Family member
Some of the Topics for this week

- Background
- Genetics
- Treatment
- Stem cell transplantation
- Cancer risk
- Clinical trials
- Iron overload
- Drug screening
Diamond-Blackfan Anemia

- Normochromic, usually macrocytic anemia, developing in infancy (large red cells)
- Reticulocytopenia (no early red cells)
- Marrow erythroblastopenia (no precursors)
- Normal or slightly decreased leukocytes (white cells)
- Normal or increased platelets
- Increased fetal hemoglobin (Hb F)
- Increased red cell adenosine deaminase (ADA)
- ~25% with physical findings: short, abnormal thumbs, etc
Supportive Criteria for DBA

- **Major**
  - Mutation in a DBA gene (ribosomal?)
  - Family history of DBA

- **Minor**
  - Increased red cell Adenosine Deaminase (ADA)
  - Typical physical abnormalities
  - Increased fetal hemoglobin (% Hb F)
  - Other IBMFS ruled out

Vlachos et al, Br J Haematol 2008
Sources of Data

- Literature review
- Prospective cohort at the NCI
- DBAR

Biases:
- Volunteerism
- Selection (publication, enrollment)
- Information (incomplete records, self-report)
- Survival
NIH, Bethesda; and NCI, Rockville

A mere 13 miles
NCI’s Inherited Bone Marrow Failure Syndromes Study 02-C-0052, www.marrowfailure.cancer.gov

- Family Study
  - Fanconi Anemia
  - Dyskeratosis Congenita (DC)
  - Diamond-Blackfan Anemia
  - Shwachman-Diamond Syndrome

- Questionnaires
- Medical Record Review
- Consultation

- Evaluation at the NIH Clinical Center, or at home
  - Hematology Team
  - Genetic Counseling
  - Subspecialists
  - Biospecimens
Type of Study at the NCI

- Natural history: the course over time
- Epidemiology: the sum of the factors controlling the presence or absence of a complication
- Not “treatment”: we do not do SCT or clinical trials
- Thorough evaluation at the NIH or at home
- Expert review of medical records
- Clinical research
- Consultation, advice
- No cost to family or insurance
DBA Literature: Age at Diagnosis

Median age at diagnosis 2.5 mo; 90% by 2 and 99% by 10 years

Shimamura and Alter: Blood Reviews 2010
DBA Literature Physical Abnormalities

Shimamura and Alter: Blood Reviews 2010
Glossary

- Chromosome: structure of nucleic acids and protein, carries genes
- Allele: alternative form of a gene
- Gene: unit of heredity
- Pathogenic variant: deleterious variant, mutation
- VOUS: VUS, variant of unknown significance
- SNP: single nucleotide polymorphism
- Genotype: heritable genetic identity
- Phenotype: physical characteristics
Examples

One Chromosome

Two Identical Chromatids
One is an exact copy of the other and each contains one DNA molecule.

p arm – short arm structure

Centromere – constricted point of the chromosome

q arm – long arm structure

DNA molecule – long string like DNA molecule formed into a compact structure by proteins called histones.
Genetic Terminology

- Autosome: Not X or Y
- XX: female    XY: male
- Autosomal dominant: one pathogenic variant from one parent
- X-linked recessive: male, with variant on X
- *De novo* mutation: new mutation in the offspring, parents are normal
DBA Inheritance

Dominant

X-linked Recessive

Affected

Normal

Carrier

Affected
What are the Tests?

- Red cell adenosine deaminase (ADA)
- Sequencing of all cloned genes in a “panel”
- NextGen sequencing: exome, GWAS, etc
DBA Genes, N >20
DBA Genes, N >20

- RPL5
- RPL11
- RPL15
- RPL18
- RPL26
- RPL27
- RPL31
- RPL35
- RPL35A
- RPL36
- RPS7
- RPS10
- RPS15A
- RPS17
- RPS19
- RPS24
- RPS26
- RPS27
- RPS28
- RPS29
- TSR2
- GATA1
- UNKNOWN

Unknown
Blood Production (Hematopoiesis)

Pluripotent Stem Cell

Myeloid Stem Cell

Lymphoid Stem Cell

Neutrophils
Monocytes
Eosinophils
Basophils

Red Cells
Platelets

T
B

Lymphocytes
Blood Production in DBA

**Myeloid Stem Cell**

- Neutrophils
- Monocytes
- Eosinophils
- Basophils
- Red Cells
- Platelets

**Pluripotent Stem Cell**

- Lymphoid Stem Cell
  - T Lymphocytes
  - B Lymphocytes

**Lymphoid Stem Cell**
Cytopenias: Signs and Symptoms

- **Anemia** (Hb)
  - Fatigue, lassitude, dyspnea
- **Thrombocytopenia** (platelets)
  - Bruises, petechiae
- **Neutropenia** (white cells)
  - Infections
Complications

- Aplastic Anemia (AA)
  - Pancytopenia
  - Hypocellular bone marrow
- Myelodysplastic Syndrome (MDS)
  - Cytopenias with hypo/hypercellular bone marrow
- Acute Leukemia (AL)
  - Malignant proliferation of immature cells
- Solid tumors
When to Treat Bone Marrow

- **Cytopenias**
  - Hb <8 g/dL or symptoms
  - Platelets <30,000/mm³
  - ANC (absolute neutrophils) <500/mm³

- **MDS**
  - Morphologic + cytopenias
  - Not for clone alone

- **Leukemia**
  - Blasts in blood
  - >20% blasts in marrow
What about MDS?

- Definition: dyspoieses (specific types of abnormal cellular appearances) in $\geq 10\%$ of one or more bone marrow cell lines, or $\geq 5\%$ in two or three lines. Cell lineages are precursors of red cells, neutrophils, or platelets.

- Clones: Abnormal numbers or appearance of chromosomes, in at least 3 cells among 20.

- Significance: Possible prediction of leukemia. Cellular morphology (appearance), or clones, or decreasing blood counts?
Treatment for Bone Marrow in DBA

- Steroids
- Transplant
- Hematopoietic growth factors?
- Gene therapy?
Supportive Care

- RBCs: for Hb <8 g/dl or symptoms
- Platelets: for platelets <10,000/mm³ or symptoms
- Blood products:
  - No family member donors
  - Leukopoor, possibly irradiated
- Antibiotics:
  - As needed for infections
Treatment with Transplant

- **Stem cell source:**
  - Bone marrow, cord blood, or peripheral blood

- **Donor:**
  - HLA-related donor: when meet treatment criteria
  - Alternate donor (mismatched unrelated [MUD], partial match family member): Leukemia or clinical MDS (not clone alone); refractory aplastic anemia

- **Preparative regimens:**
  - MAC, myeloablative conditioning
  - RIC, reduced intensity conditioning
Cancer in DBA, NCI Cohort

- 135 patients
- 125 not transplanted
  - 7 patients with 9 cancers
    - 3 lung, 1 colon, 1 cervix, 1 cervix + lung, 1 colon + liver
    - 5 patients with 8 skin cancers (SCC, BCC)
- 10 transplanted
  - 1 cancer
    - Non-Hodgkin lymphoma
## NCI DBA Cancer, 2002-2016

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Observed</th>
<th>Expected</th>
<th>O/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (not MDS)</td>
<td>9</td>
<td>3.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Lung</td>
<td>4</td>
<td>0.3</td>
<td>12</td>
</tr>
<tr>
<td>Cervix</td>
<td>2</td>
<td>0.05</td>
<td>37</td>
</tr>
<tr>
<td>Colon</td>
<td>2</td>
<td>0.2</td>
<td>11</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
<td>0.04</td>
<td>27</td>
</tr>
<tr>
<td>MDS</td>
<td>1</td>
<td>0.02</td>
<td>42</td>
</tr>
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Bold are significant with O/E >1, 95% CI >1.
First Event, Competing Risk

NCI Cohort, 2017
First Event, Competing Risk

NCI Cohort, 2017
IBMFS Survival
Surveillance/Management

- Every 4-6 months (or more as needed): CBC
- Annual:
  - BM aspirate/biopsy/chromosomes
  - Liver enzymes, chemistries, lipids, thyroid
  - Liver ultrasound
  - Dental
  - Do not smoke or drink
  - Gyn exam
  - Skin exam
  - MRI liver and heart if transfused
- HPV vaccine
Endocrine Surveillance/Management

- **Annual:**
  - Growth, weight
  - Fasting glucose, Hb A1c, lipids
  - TSH, FT4
  - Tanner staging, menstrual history
  - Bones: Ca, Vitamin D; dexascan for density
Transition Pediatric to Adult Care

- **When?**
  - Age 18
  - Age 21
  - When leave home for work or college
- **Who decides?**
  - Those with FA
  - Parents
  - Doctors
- **How?**
Shared Decision Making

- Benefits vs risks
- Decision by family
- Advice by doctors
- Needs data

NY Times Oct 20, 2013
Inherited Bone Marrow Failure Syndromes (IBMFS)

Inherited bone marrow failure syndromes (IBMFS) are rare disorders; usually these patients have some form of aplastic anemia (failure of the bone marrow to produce blood), and may have a family history of the disorder. There are several well-described syndromes that can be recognized by healthcare experts either by physical characteristics in the patients or from laboratory findings. There are also patients who are harder to classify.

Patients with these syndromes are of interest to the NCI because they have a very high risk of developing cancer (either leukemia or certain solid tumors). At the moment, we cannot predict which specific patient with an IBMFS is going to develop cancer, and we want to study all patients with an IBMFS to learn more about those without and those who may develop cancer.

The NCI IBMFS Cohort Study enrolls families from North America that have at least one member with an IBMFS. The study includes individuals known to have an IBMFS as well as their first degree relatives (brothers, sisters, parents, and children) as well as other relatives where appropriate.

Our overall goal is to reach a better understanding of how cancers develop in persons with IBMFS, so that we may improve the health care that can be offered to persons with these disorders.

How can I join?

Individuals with one of the inherited bone marrow failure syndromes and their family members are encouraged to participate.

Phone: 1-800-660-9449 to speak with the referral nurse
Email: NCIBMFS@westat.com
NCI IBMFS Study Team, 2017

Blanche Alter, MD; Sharon Savage, MD; Neelam Giri, MD; Lisa Leathwood, RN, BSN; Ann Carr, MS, CGC; Kristen Davis, BA; Maureen Risch, RN, BSN; Gloria Chu, BS.