Diamond-Blackfan Anemia 101

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DBA Camp, July 13, 2015
Diamond-Blackfan Anemia

DBA, not BDA
Questions

1. How many are new to DBA Camp?
2. How many have been here before?
3. How many have DBA and are 18 years of age or older?
4. How many are from Canada?
5. How many are from outside the USA/Canada?
My Tasks

1. DBA101 (advanced DBA) for those who have not heard it.
2. Update on what is new in DBA research.
3. Address specific concerns of those who are new to DBA.

All in 45 minutes…..(including questions)
Diamond and Blackfan

Louis K Diamond, 1902-1999  Kenneth D Blackfan 1883-1941
First DBA Scientific Meeting, Bellagio, Italy
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Hematology</th>
<th>Leukemia</th>
<th>Solid Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanconi Anemia (FA)</td>
<td>Aplastic</td>
<td>AML</td>
<td>SCC</td>
</tr>
<tr>
<td>Dyskeratosis Congenita (DC)</td>
<td>Aplastic</td>
<td>AML</td>
<td>SCC</td>
</tr>
<tr>
<td>Diamond-Blackfan Anemia (DBA)</td>
<td>Pure anemia</td>
<td>AML</td>
<td>Sarcomas</td>
</tr>
<tr>
<td>Shwachman-Diamond Syndrome (SDS)</td>
<td>Neutropenia</td>
<td>AML</td>
<td>-</td>
</tr>
<tr>
<td>Severe Congenital Neutropenia (SCN)</td>
<td>Neutropenia</td>
<td>AML</td>
<td>-</td>
</tr>
<tr>
<td>Amegakaryocytic Thrombocytopenia</td>
<td>Thrombocytopenia</td>
<td>AML</td>
<td>-</td>
</tr>
<tr>
<td>Thrombocytopenia Absent Radii (TAR)</td>
<td>Thrombocytopenia</td>
<td>AML</td>
<td>-</td>
</tr>
</tbody>
</table>

These disorders are the “Inherited Bone Marrow Failure Syndromes” (IBMFS).
IBMFS Pathways

- DNA Repair: FA
- Telomere biology: DC
- Ribosomes: DBA, SDS, DC
- Platelet production: Amega
- Apoptosis: SCN, others
Background

- Diamond-Blackfan anemia (DBA), an Inherited Bone Marrow Failure Syndrome (IBMFS) with varying degrees of pure red cell aplasia
- Heterogeneous disorder
- Patients with an IBMFS have an increased risk of cancer (leukemia and solid tumors)
- Correlation between physical and/or laboratory features and outcomes?
- Birth rate 5-10 per million live births
First Publications

- **Josephs HW**: Anaemia of infancy and early childhood. Medicine, 1936
- **Diamond LK, Blackfan KD**: Hypoplastic anemia. Am J Dis Child, 1938
- Why not “Josephs, Diamond, Blackfan anemia”?
Diamond-Blackfan Anemia

- Normochromic, usually macrocytic anemia, developing in infancy
- Reticulocytopenia
- Marrow erythroblastopenia
- Normal or slightly decreased leukocytes
- 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 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
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

- Evaluation at the NIH Clinical Center
  - IBMFS Team
  - Genetic Counseling
  - Subspecialists
  - Biospecimens

- Questionnaires
- Medical Record Review
- Consultation
DBA Literature 1936-2015

- Case Reports: ~1430; (+ Case Series ~1400)
- Male:Female: 1.08:1
- Died: 149 (10% crude rate)
- Alive: median age 8 yrs (0-60)
- Died: median age 9 yrs (0-65)
- Abnormal physical findings reported 30%
- Remissions reported 10%

*Biased by under-reporting, over-reporting, and missing data.*
DBA Literature: Age at Diagnosis

Median age at diagnosis 2.5 mo; 90% by 2 and 99% by 10 years
More than 95% were reported to be over age 18 in the last decade, compared with 20% in the earlier reports.

Cases according to year of publication.
DBA Literature Physical Abnormalities

Any PE
Short
Thumbs
Cardiac
Eyes
Face
Cleft palate
Skeletal
GU
Hands
Neck
Gonads
Head
Dev
Ears

% of Cases
Comparison of Physical Findings

Note that NCI has higher frequencies – more thorough exams?
Aase Syndrome and other Thumbs
Neck 1
Major Complications in DBA

- Anemia
- Rarely pancytopenia
- Iron overload
- MDS/AML
- Tumors
Treatment of Anemia in DBA

- **Current:**
  - Steroids
  - Transfusions
  - Iron chelation
  - Stem cell transplant

- **Future clinical trials:**
  - Leucine
  - Lenalidomide
  - Sotatercept

- Spontaneous remission, ~10-20%
Steroids for Anemia

- Prednisone, 2mg/kg/day, divided 3 times per day, for 1-4 mo
- If response, taper slowly
  - 2 doses per day x 1 month
  - 1 dose per day x 1 month
  - Double this dose, every other day in am
- If no response, transfuse
- Consider stem cell transplant (SCT)
Transfusions for Anemia

- At diagnosis
- For first year of life – or not?
- Hb drops by ~1 gm/week
- Transfuse every 4 weeks, with 15 mL/kg
- Pre-tx, Hb <8 g/dL
- Post-tx, Hb ≥12 g/dL
Chelation for Iron Overload

- Generally after 15-20 transfusions
- Age >2 years
- Ferritin >1000
- Cardiac and liver iron measured by MRI
- Desferal: subQ or IV, 40-50 mg/kg/day, over 8-12 hrs (overnight)
- Exjade (oral)
Stem Cell Transplant for Anemia

- **Who?**
  - Steroid-refractory, transfusion-dependent
  - Age <10?

- **What?**
  - Bone marrow
  - Cord blood
  - Peripheral blood (stimulated with G-CSF)

- **Donors?**
  - Matched sibling
  - Unrelated
  - Haploidentical
  - Cord
Stem Cell Transplant Survival

Apparent survival better in recent decade, but small numbers (15 vs 76)
Disease-Associated Mutations

A **mutation** is a change in the normal base pair sequence

Commonly used to define DNA sequence changes that alter protein function
Autosomal Dominant Inheritance
Ribosome Genes
DBA Genes, Autosomal Dominant

![DBA Genes Diagram]

- RPS19: 25
- RPS26: 6
- RPS24: 2
- RPS10: 3
- RPS7: 1
- RPS17: 1
- RPS29: 1
- RPL5: 7
- RPL11: 1
- RPL35A: 1
- RPL26: 1
- RPL15: 1
- Unknown: 1
- GATA-1: 1

X-linked
Exome Sequencing and Filtering
NCI IBMFS, 2002 - 2015

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Families</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanconi Anemia</td>
<td>122</td>
<td>141</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>95</td>
<td>146</td>
</tr>
<tr>
<td><strong>Diamond-Blackfan Anemia</strong></td>
<td><strong>85</strong></td>
<td><strong>104</strong></td>
</tr>
<tr>
<td>Shwachman-Diamond Syndrome</td>
<td>29</td>
<td>26</td>
</tr>
</tbody>
</table>
## Red Cell Adenosine Deaminase (ADA)

<table>
<thead>
<tr>
<th>Source</th>
<th>N</th>
<th>% Elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glader, 1983</td>
<td>12/12</td>
<td>100</td>
</tr>
<tr>
<td>Whitehouse, 1986</td>
<td>9/19</td>
<td>47</td>
</tr>
<tr>
<td>Glader, 1986</td>
<td>23/26</td>
<td>88</td>
</tr>
<tr>
<td>Glader, 1988</td>
<td>26/29</td>
<td>90</td>
</tr>
<tr>
<td>Orfali, 2004</td>
<td>48/50</td>
<td>96</td>
</tr>
<tr>
<td>Willig, 1998</td>
<td>28/34</td>
<td>82</td>
</tr>
<tr>
<td>Fargo, 2012</td>
<td>31/37</td>
<td>84</td>
</tr>
</tbody>
</table>

Fargo *et al*, Br J Haematol 2013
ADA in DBA, non-DBA, and Relatives

ADA is ~85% sensitive, and >90% specific

Fargo et al, BJH 2013
ADA and DBA Gene Mutation

ADA is not always elevated (arrow) in DBA, and elevated ADA does not always track with mutated DBA gene

Fargo et al, BJH 2013
Telomeres <1% of normal are diagnostic of dyskeratosis congenita, and are very RARE in DBA.

Alter et al, Blood 2007
DBA do not have Very Short TL

Alter et al, Haematologica 2015
**Ovarian Reserve in DBA**

- DBA have higher AMH than FA or DC
- DBA AMH are in normal range

Sklavos et al, J Clin Endo and Metab, 2015
# Cancer Reported in Literature

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>11</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Osteogenic sarcoma</td>
<td>6</td>
</tr>
<tr>
<td>Sarcoma soft tissue</td>
<td>1</td>
</tr>
<tr>
<td>Stomach</td>
<td>1</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1</td>
</tr>
<tr>
<td>Myelodysplastic Syndrome (MDS)</td>
<td>6</td>
</tr>
</tbody>
</table>
Cancer Reported in Literature

Median age = 55 years
Cancer in the DBAR, 17/608 Patients

<table>
<thead>
<tr>
<th>Type</th>
<th>Count</th>
<th>Log SIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Gyn</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>MDS</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

Significant types of cancers

Vlachos et al: Blood 2012
### NCI DBA Cancer, 2015

<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>6</td>
<td>3</td>
<td>1.9</td>
</tr>
<tr>
<td>Lung</td>
<td>3</td>
<td>0.31</td>
<td>9.7</td>
</tr>
<tr>
<td>Cervix</td>
<td>1</td>
<td>0.04</td>
<td>24.7</td>
</tr>
<tr>
<td>Colon</td>
<td>2</td>
<td>0.16</td>
<td>12.7</td>
</tr>
<tr>
<td>MDS</td>
<td>3</td>
<td>0.02</td>
<td>142</td>
</tr>
</tbody>
</table>

Bold are significant
Cancer in the IBMFS
Physical anomalies and/or short stature are common.

More frequent than previously reported:
- Head and face, cardiac, skeletal (other than upper limb) and developmental delay.

Transfusions and steroids are associated with long-term morbidity.

Cancer in 6%.
Transition from Pediatric to Adult Care

- When?
  - Age 18
  - Age 21
  - When leave home for work or college

- Who decides?
  - Those with DBA
  - Parents
  - Doctors

- How?
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 have a very high risk of developing cancer (either leukemia or certain solid tumors). However, at the moment, we cannot predict which specific patient with an IBMFS is going to 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: 1-800-518-8474 to speak with the referral nurse
Email: NCIIBMFS@westat.com
Blanche Alter, MD, MPH
Sharon Savage, MD
Neelam Giri, MD
Ann Carr, Genetic Counselor
Lisa Leathwood, Research Nurse
Maureen Risch, Research Nurse
Many thanks

To all the families