New Directions in Aplastic Anemia: What’s on the Horizon?

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Baltimore, MD

Objectives

- To provide information on new concepts emerging in AA in somatic molecular testing
- To review updates on markers of response to therapy in AA
- To review newer data on emerging therapies in aplastic anemia (AA)

Better way to evaluate clonal evolution?

- As survival is improving, we may see more late development of MDS/AML in ≥15% of patients → clonal evolution
- Extrapolation from MDS field → somatic mutational testing
- Goal: to use this testing to ID group of AA pts more likely to get MDS (treatment would be modified)

The Dawn of the Molecular Era of the Myelodysplastic Syndromes

- 51% of patients ≥1 mutation (including ~50% with normal karyotype)
- FIVE genes (in ~30% of pts) → independent prognostic significance and predicted poor overall survival
  - EZH2  ETV6  RUNX1  ASXL1  P53

Genes Recurrently Mutated in MDS

<table>
<thead>
<tr>
<th>Tyrosine Kinase Pathway</th>
<th>Transcription Factors</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2  IRB2  RAF  BRAF</td>
<td>RUNX2  GATA2  ETV6</td>
<td>TP53  RBP4  NOTCH  MAML  SF1  SF3  SRFP</td>
</tr>
<tr>
<td>PTPN11  KRAS  NRAS  BRAF</td>
<td>JAK2  GATA2  ETV6</td>
<td>TP53  RBP4  NOTCH  MAML  SF1  SF3  SRFP</td>
</tr>
<tr>
<td>SF3B1  SF1  SF3  SF3A  SRSF2  DNM 3A  TET2  ASXL1  SETBP1  U2AF1  ZRSF2  SETBP1  U2AF2  PRPF8  SRSF2  U2AF2  PRPF8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Epigenetic Dysregulation

- Dekker et al. Blood 2014
- Yoshizato et al. NEJM 2015

Courtesy of Bejar R.
Retrospective from the UK

- From UK: looked at 150 pts with no evidence (by microscope) of MDS
- Screen for mutations
  - ASXL1, DNMT3A, BCOR, TET2, MPL at least
  - 19% AA pts had mutations
  - Pts with mutations had a longer disease duration (37 vs. 8 months, p<0.04)
  - AA patients with disease duration of > 6 mos AND mutation→40% risk of transformation to MDS (p <0.0002)

Candidate gene mutations in acquired aplastic anemia - correlation with survival and clonal evolution to myelodysplastic syndrome

courtesy of Dr. Dumitriu

Yoshizato et al. NEJM 2015

NIH SAA cohort

“Stable AA” – responders or non-responders to immunosuppressive therapy
≈ 15% clonal evolution to MDS/AML

De novo
MDS/AML

Time

Clonal evolution

N = 256 patients (3 institutions)

Yoshizato et al. NEJM 2015

ACQUIRED MUTATIONS IN SAA – NIH COHORT (n=256)

Number mutations per SAA patient

Targeted gene panel

ACQUIRED MUTATIONS IN SAA – STRONG AGE BIAS

All mutations  P < 0.001
PIGA & BCOR/BCORL1  P = 0.88
Non.PIGA/BCOR/BCORL1 mutations  P < 0.001
ACQUIRED MUTATIONS DO NOT CORRELATE WITH CYTOPENIAS, PRESENCE OF PNH CLONE, OR RESPONSE TO IST

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARC&lt;25k/uL</td>
<td>1.09 (0.59, 2.07)</td>
<td>0.885</td>
</tr>
<tr>
<td>ANC&lt;200/uL</td>
<td>1.46 (0.79, 2.68)</td>
<td>0.185</td>
</tr>
<tr>
<td>PNH+</td>
<td>1.46 (0.80, 2.64)</td>
<td>0.202</td>
</tr>
<tr>
<td>Response to IST</td>
<td>1.42 (0.78, 2.62)</td>
<td>0.256</td>
</tr>
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ACQUIRED MUTATIONS DO NOT CORRELATE WITH REFRAC TORY DISEASE

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<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
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<tr>
<td>Refractory to 2 rounds of IST</td>
<td>1.45 (0.49, 4.31)</td>
<td>0.498</td>
</tr>
<tr>
<td>Refractory to 2nd IST given for relapse</td>
<td>0.85 (0.22, 3.15)</td>
<td>0.805</td>
</tr>
<tr>
<td>HSCT (for relapse/refractory/clonal evolution)</td>
<td>0.51 (0.23, 1.10)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

MUTATIONS IN BCOR/BCOL1 CORRELATE WITH BETTER RESPONSE TO IST

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<tr>
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<th>Odds ratio (95% CI)</th>
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<tr>
<td>BCOR/BCORL1</td>
<td>2.73 (1.05, 7.11)</td>
<td>0.038</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>0.89 (0.31, 2.55)</td>
<td>0.835</td>
</tr>
<tr>
<td>ASXL1</td>
<td>0.68 (0.25, 1.83)</td>
<td>0.447</td>
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ACQUIRED MUTATIONS CORRELATE WITH PROGRESSION TO MDS

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ACQUIRED MUTATIONS CORRELATE WITH OVERALL SURVIVAL

CONCLUSIONS

- Somatic mutations in 35% of cases
- PIGA, DNMT3A, ASXL1, and BCOR/BCORL1 were most frequently mutated genes
- Presence and number of mutations correlated with age only
- BCOR/BCORL1 mutated clones associated with a better chance of responding to IST
- Response to IST, clonal evolution and overall survival are associated with acquired mutations
- Mutations remain independent predictors of clinical outcomes in multivariate analysis
Telomeres

- Telomeres: regions of repetitive nucleotides at the ends of chromosomes that are there to protect the chromosomes from damage and breakdown.
- Telomere length testing very helpful in inherited AA DKC (very short)
- Reports suggest that telomeres are shorter (not very short) in up to one-third of patients with acquired SAA
- At NIH, telomere lengths measured in the white blood cells of 183 patients treated with IST
- Shorter telomeres not found to predict who would have improved blood counts at 6 months after IST
- Shorter lengths may be associated with late effects such as relapse or clonal evolution to MDS

PNH clones and telomeres predict response to IST in Pediatric AA

- Prospective study of 113 children (Ages 0-16)
- All had PNH clones and telomeres done in CLIA certified way before IST
- Response assessed based on PNH clone presence and telomere length
  - If PNH clone + and telomeres “long” ~70% response
  - If PNH clone - and telomeres “short” ~19% response
- Suggestion for upfront HSCT if in this group

Severe Aplastic Anemia 2015 Treatment Paradigm

- Diagnosis of Severe Aplastic Anemia
- Treatment based upon age and donor availability
  - Age < 40 years with HLA matched sibling
  - Age > 40 years OR No HLA matched sib
  - Bone Marrow Transplantation
  - Immunosuppressive Therapy
  - Response Rate ~70%
  - ~40% Relapse or Clonal Evolution
  - Clinical follow up
  - No Response ~30%
  - TRANSPLANT

Alternative Donor transplants in SAA

- Reserve for relapsed or refractory SAA
  - After failing ATG
- Should be done in a “specialist center with major experience in hematopoietic SCT procedures”
- Perform in setting of clinic trial “designed specifically to address the prevention of graft rejection and GVHD”
**Unrelated Donor or Alternative donor BMT**

- The sooner, the better after relapse/ refractoriness noted
- Bone marrow still the best source
- Similar conditioning regimens
- Often in setting of clinical trial
  - Unrelated donor (NMDP- “MUDs”)
  - Haplo-identical donor (half match)
  - Umbilical cord donor

**New Trial**

**Optimizing Cord Blood and Haploidentical Aplastic Anemia Transplantation (CHAMP)**

(Presented on clinicaltrials.gov as CHAMP)

BMT CTN PROTOCOL 1502

**Hopkins Haplo BMT for Acquired and inherited SAA**

<table>
<thead>
<tr>
<th>Age/ Sex</th>
<th>Pre-BMT Therapy</th>
<th>Degree of HLA match</th>
<th>Day of engraftment (ANC &gt;1000)</th>
<th>Donor chimerism at day 100</th>
<th>cGVHD</th>
<th>cGHVD</th>
<th>Response</th>
<th>Follow-Up (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35M</td>
<td>ATG CsA</td>
<td>5/10</td>
<td>30</td>
<td>100</td>
<td>none</td>
<td>none</td>
<td>CR</td>
<td>56</td>
</tr>
<tr>
<td>52M</td>
<td>ATG CsA</td>
<td>5/10</td>
<td>24</td>
<td>100</td>
<td>none</td>
<td>none</td>
<td>CR</td>
<td>27</td>
</tr>
<tr>
<td>45F</td>
<td>ATG CsA</td>
<td>5/10</td>
<td>27</td>
<td>100</td>
<td>Gr 2 skin</td>
<td>Gr 2 skin</td>
<td>CR</td>
<td>22</td>
</tr>
<tr>
<td>27F</td>
<td>ATG</td>
<td>5/10</td>
<td>24</td>
<td>100</td>
<td>none</td>
<td>none</td>
<td>CR</td>
<td>22</td>
</tr>
<tr>
<td>33M</td>
<td>HCY</td>
<td>5/10</td>
<td>16</td>
<td>100</td>
<td>none</td>
<td>none</td>
<td>CR</td>
<td>17</td>
</tr>
<tr>
<td>17M</td>
<td>HCY</td>
<td>5/10</td>
<td>17</td>
<td>100</td>
<td>none</td>
<td>none</td>
<td>CR</td>
<td>17</td>
</tr>
<tr>
<td>54M</td>
<td>ATG CsA</td>
<td>5/10</td>
<td>15</td>
<td>100</td>
<td>None</td>
<td>CR</td>
<td>CR</td>
<td>9</td>
</tr>
<tr>
<td>26F</td>
<td>CsATPO</td>
<td>5/10</td>
<td>17</td>
<td>100</td>
<td>None</td>
<td>None</td>
<td>CR</td>
<td>6</td>
</tr>
<tr>
<td>59</td>
<td>CsATPO</td>
<td>5/10</td>
<td>24</td>
<td>100 (Day 100)</td>
<td>none</td>
<td>None</td>
<td>CR</td>
<td>10</td>
</tr>
<tr>
<td>21</td>
<td>Steroids</td>
<td>5/10</td>
<td>10</td>
<td>100</td>
<td>none</td>
<td>none</td>
<td>CR</td>
<td>10</td>
</tr>
<tr>
<td>38</td>
<td>Danazol</td>
<td>9/10</td>
<td>17</td>
<td>100</td>
<td>Gr 2 skin</td>
<td>None</td>
<td>CR</td>
<td>20</td>
</tr>
</tbody>
</table>

**Mini-BMT for Refractory SAA**

**Treatment schema**

- Survival now >75%
- Similar conditioning regimens- may add TBI

**Primary Objective**

Assess overall survival in 2 cohorts (unrelated cord blood and haplo-identical) at 1 year post-hematopoietic stem cell transplantation in patients with severe aplastic anemia

Hypothesis—both cohorts >75% 1yr OS

**Adult URD**
### Kaplan-Meier survival rate estimates (and 95% confidence intervals) for recipients of an HLA-matched sibling or unrelated donor HCT for SAA registered with CIBMTR from 1990 through 2011, by donor type, age group, and graft source

<table>
<thead>
<tr>
<th>Survival rate (95% CI), Graft Source: BM and PB</th>
<th>HLA-Matched Sibling Donor</th>
<th>Unrelated Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 40y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>84 (82–85)</td>
<td>68 (64–72)</td>
</tr>
<tr>
<td>3 years</td>
<td>80 (78–82)</td>
<td>61 (57–66)</td>
</tr>
<tr>
<td>5 years</td>
<td>77 (73–81)</td>
<td>57 (52–62)</td>
</tr>
<tr>
<td>10 years</td>
<td>77 (73–81)</td>
<td>50 (45–56)</td>
</tr>
<tr>
<td>Survival rate (95% CI), Graft Source: CB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>79 (59–94)</td>
<td>–</td>
</tr>
<tr>
<td>3 years</td>
<td>72 (48–96)</td>
<td>–</td>
</tr>
<tr>
<td>5 years</td>
<td>72 (48–96)</td>
<td>–</td>
</tr>
</tbody>
</table>

* CIBMTR requires a sample size of at least 20 for KM survival-rate estimations.

### Umbilicord Transplants

- Survival is still lower ~40%
- Conditioning regimens more varied
  - CY/Flu/TBI
  - Melphalan/Flu/TBI
- Japanese study
  - 12 adult patients, 11/12 engrafted, survival 10/12 median 36 mos

Yamamoto et al, Blood 2011
Peffault et al, BMT 2013
Yoshimi et al, BBMT 2008

### URD in children

- 44 children in UK (40 s/p IST)
- Fludarabine, CY, Alemtuzumab

### 2nd HSCT in AA

- Retrospective of 162 European pts
  - 1998-2009: 1° or 2° in 14% of pts with 1 txp for AA
  - Used same donor 81% of time
  - Changed from BM to PBSC in 56%
  - Excluded 2nd txp using cord blood
  - Graft failure still occurred 26% of 2nd txp
  - Follow up 3.5 years (median) 60% OS

Cassar et al, BMT 2015

### ASH 2014: Transplants

- Abstract 256 Dufour et al
- Similar Outcome of Upfront Unrelated and Matched Sibling Donor Hematopoietic Stem Cell Transplantation in Idiopathic Aplastic Anemia of Childhood and Adolescence
- 29 SAA children had unrelated donor HSCT without prior IST in UK
- Compares each with 3 matched controls from the database of the SAAWP of the EBMT with MSD HSCT

### Androgens: Danazol

- Suggestion in literature that androgens may slow telomere shortening in some pts
- Phase I/II at NIH in 27 pts (20 with mod AA) to take danazol daily for 2 years
- Increased telomere lengths and hematologic improvement seen
- No significant liver toxicity
- At publication 9 pts stopped drug prior to 2 years

Dumitriu et al, Blood 2014
Iron Overload

- Iron burden increased in patients with AA at presentation and over time with transfusions
  - Follow ferritin (lab measure of body’s iron stores)
- Iron overload in other marrow failure (MDS) studied and problematic
  - Deposition in liver and heart

Iron Chelation

- Deferasirox (Exjade oral) or Desferoxamine (IV)
  - To discuss with doctor as meds have liver and kidney side effects and can lower platelets
- Recent study of 53 AA pts showed deferasirox improves ferritin and liver iron overload when taken daily

THANK YOU!