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

AA & MDS International Foundation
Living with Aplastic Anemia, MDS, or PNH Patient and Family Conferences in 2014
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Objectives

- To provide new information on emerging therapies in aplastic anemia (AA)
- To provide updates in the development of biomarkers that impact survival, clonal evolution and relapse in AA
- To provide new developments on molecular genetics in AA

Emerging Therapies (Iron Chelators)

Deferasirox

- Rationale:
  - Too much iron can lead to suppressive effects on immature RBC precursors
  - Evaluation of Patient’s Chelation with Exjade (EPIC) Trial
  - Phase IIb, one-year, open-label, single-arm study in patients diagnosed with transfusion-dependent iron overload

- How does the drug work?

W. Lee et al. Haematologica. April 2013
Hartmann J et al. Leuk Res. Mar 2013

Emerging Therapies (Iron Chelators)

Definition of Response

- T1: at least a one 8-week period without transfusions

JW Lee et al. Haematologica. April 2013
Hartmann J et al. Leuk Res. Mar 2013
Emerging Therapies (Iron Chelators)

Clinical Responses

- Total AA Patients in the study: 116
- No Complete Responders
- Median time to response: 85 days (range 1-277)
- One patient had a platelet response

Emerging Therapies (Iron Chelators)

Deferasirox

<table>
<thead>
<tr>
<th>Baseline Ferritin (ng/ml)</th>
<th>Change in ferritin level post-Tx (ng/ml)</th>
<th>% Change from baseline</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Responder N=11</td>
<td>6693 ± 7014</td>
<td>-3948 ± 4998</td>
<td>-45.7%</td>
</tr>
<tr>
<td>No Response N=13</td>
<td>4365 ± 3063</td>
<td>-2021 ± 3242</td>
<td>-27.6%</td>
</tr>
</tbody>
</table>

Emerging Therapies (Novel T cell Therapies)

Alefacept

- **Rationale:**
  - Novel immunosuppressive therapies with less toxicities are needed for AA patients

- **How does the drug work?**
  - **Alefacept**
    - Humanized recombinant dimeric fusion protein composed of LFA3 and Fc portion of human IgG
    - FDA approved for the treatment of chronic plaque psoriasis
    - Have been found to be of use in GVHD

Mechanism of Action of Alefacept
Emerging Therapies (Novel T cell Therapies)

Clinical Response

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose</th>
<th>Response</th>
<th>Type of Hematologic Response†</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.5 mg/week for 12 weeks</td>
<td>PR</td>
<td>N</td>
<td>cough, sore throat, and nasal congestion</td>
</tr>
<tr>
<td>2</td>
<td>7.5 mg/week for 12 weeks</td>
<td>NR</td>
<td>-</td>
<td>Mild muscle aches</td>
</tr>
<tr>
<td>3</td>
<td>7.5 mg/week for 12 weeks</td>
<td>PR</td>
<td>H/ N/ P</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>10 mg/week for 12 weeks</td>
<td>PR</td>
<td>H/ N/ P</td>
<td>None</td>
</tr>
</tbody>
</table>

†: H- Hemoglobin;  N: Neutrophils;  P: Platelets

RV Tiu. AA and MDS International YIA Grant Report. 2012

Unfortunately:

In December 2011, Astellas Pharma US announced that the company has voluntarily discontinued the promotion, manufacturing, distribution and sales of alefacept because of business needs but not related to safety issues.

Emerging Therapies (Combination Therapies)

Cyclosporine plus Levamisole

- Rationale:
  - Developing novel therapies for patients with moderate AA

- Patient Cohort
  - 118 patients with mAA
    - 42 newly diagnosed
    - 76 chronic

- Regimen
  - CsA 3 mg/kg per day in adults plus Levamisole 150 mg per day in adults
  - CsA 5 mg/kg per day in children plus or 2.5 mg/kg per day in children,

  Either regimen will be continued for 12 more months after achieving maximal hematologic response, followed by a slow taper.

X Li et al. Ann Hematol. April 2013
**Clinical Response**

<table>
<thead>
<tr>
<th></th>
<th>Newly dx mAA</th>
<th>Chronic mAA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>100 %</td>
<td>86.8 %</td>
<td></td>
</tr>
<tr>
<td>24 month PFS</td>
<td>95.2 %</td>
<td>93.6 %</td>
<td>0.50</td>
</tr>
<tr>
<td>(95% CI: 85.9-100)</td>
<td>(95% CI: 86.9-100 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 year EFS</td>
<td>86.8 %</td>
<td>57.9 %</td>
<td>.001</td>
</tr>
<tr>
<td>(95% CI: 70.4-100)</td>
<td>(95% CI: 43.5-70.4 %)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

X Li et al. Ann Hematol. April 2013

**Biomarkers**

**Predictive/Prognostic Biomarkers (ARC and ALC)**

- NIH Study of 316 SAA patients (1989-2005)
- Defining important predictors of response to hATG + CsA therapy at 6 mos of therapy
- Factors looked at includes age, PNH clone, hematological factors like ANC, platelet count, Absolute reticulocyte count (ARC), Absolute lymphocyte count (ALC), severity of disease, etiology
- Presence of PNH clone is defined as presence of positive Ham test for samples until 2000 and subsequently GPI-(neg) Neutrophils or red cells >1%
- ARC and ALC are predictive

Scheinberg P et al. BJH . 2008

**Predictive/Prognostic Biomarkers (ANC and ARC)**

- Defining important predictors/prognostic markers
- Patient got rATG + CsA or hATG + CsA
- Factors looked at includes age, type of ATG clone, hematological factors like ANC, platelet count, Absolute reticulocyte count (ARC), severity of disease, etiology
- Only predictive factor is ANC >0.3 x10^9/L
- Prognostic Factors: ARC >10 x10^9/L and response status

Chang M et al. EJH . 2009
Importance of Telomeres in Aplastic Anemia

Telomeres

Importance of Telomeres in Aplastic Anemia

Telomerase Complex

Importance of Telomeres in Aplastic Anemia

Telomere Length and Disease Relapse

Importance of Telomeres in Aplastic Anemia

Telomeres and Clonal Evolution

Scheinberg P et al. JAMA. 2010
Importance of Telomeres in Aplastic Anemia

Telomere Length as a predictor for clonal evolution in AA

Calado RT et al. Leukemia. April 2012

Importance of Telomeres in Aplastic Anemia

More Monosomy 7 and chromosomal instability in patients with short telomeres

Calado RT et al. Leukemia. April 2012

Importance of Telomeres in Aplastic Anemia

Telomeres and Survival

Scheinberg P et al. JAMA. 2010

Importance of Telomeres in Aplastic Anemia

Differentiating AA vs hypocellular MDS using SNP-A Karyotyping

Afable M et al. Blood. 2011
Differentiating AA vs hypocellular MDS using SNP-A Karyotyping

More chromosomal defects detected by SNP-Array Karyotyping compared to metaphase cytogenetics in AA and hypocellular MDS

Afable M et al. Blood. 2011

SNP-A Karyotyping

Early Detection of Clonal Evolution by SNP-Array Karyotyping

Genetic Causes of Inherited AA

Presence of MPL mutations in Inherited cases of AA

Walne A J et al. Haematologica 2012;97:524-528

Cytogenetic Defects and Molecular Mutations in Fanconi Anemia

Rare NRAS, RUNX1, Flt-3 and MLL mutations in FA that transformed to AML

STAT3 mutations in Aplastic Anemia And MDS

Impact of STAT3 mutations on survival outcomes in AA and MDS

Conclusions

- Some patients with AA treated with iron chelator, deferasirox achieved transfusion independence but the results will need to be clarified in bigger studies
- Targeting the CD2-LFA3 pathway is a viable treatment option in AA
- ARC and ALC are important in predicting immunosuppressive response in AA
- Shorter Telomeres have adverse impact on survival, clonal evolution and relapse in AA
- SNP-A karyotyping can improve cytogenetic detection in AA
- Molecular genetics can unravel new information on the pathophysiology of AA.