ROLE OF ELTROMBOPAG IN APLASTIC ANEMIA

Dra. Blanca Xicoy
ICO-Badalona
Refractory aplastic anemia

Role of TPO agonists in second and first line

Clonal evolution

Real life and practical issues
Refractory aplastic anemia

Role of TPO agonists in second and first line

Clonal evolution

Real life and practical issues
Patient <35–50 years
Persistence of severe cytopenia(s) after one course of IST (ATG+CSA)

Availability of suitably matched donor

Yes
HSCT
Matched sibling (>35–50 years) or unrelated donor

No
Patient <35–50 years
Repeat course of IST
Second ATG + CSA

No response 20%-30%
Relapses 10%-30%

Alternate donor HSCT
• Haploidentical
• Umbilical cord

Alternate therapy
• Alemtuzumab
• Androgens
• Eltrombopag
• Cyclophosphamide

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age/Gender</strong></td>
<td>- Women</td>
</tr>
<tr>
<td></td>
<td>- Adults</td>
</tr>
<tr>
<td><strong>ARC, ANC, ALC</strong></td>
<td>- Controversial</td>
</tr>
<tr>
<td><strong>Cytokines</strong></td>
<td>- IFN-γ - in T cells</td>
</tr>
<tr>
<td></td>
<td>- Higher TPO level</td>
</tr>
<tr>
<td><strong>Chromosome abnormalities and Mutations</strong></td>
<td>- No trisomy 8, del(13q)</td>
</tr>
<tr>
<td></td>
<td>- No BCOR, BCORL1</td>
</tr>
<tr>
<td><strong>Minor PNH clones</strong></td>
<td>- Controversial</td>
</tr>
<tr>
<td><strong>Telomere length</strong></td>
<td>- No</td>
</tr>
</tbody>
</table>

Role of TPO agonists in second and first line
ROLE OF ELTROMBOPAG

Aplastic anemia

Stem Cells

Self-renewal or Differentiation

Progenitors

Proliferation and Differentiation

CLP

HSC

EPO R

G-SCF R

TPO R

Lymphoid

Myeloerythroid

GMP

CMP

MEP
ROLE OF ELTROMBOPAG

One approach to augment the quality of hematologic responses to immunosuppression therapy is to improve underlying stem cell function.

Initial cohort n=25 (11/25, 40% responses)
Expanded cohort n=43

 Primary endpoint: response at 3-4 months

- Median age, ys 44 (17-77)
- Very severe AA 6
- Median prior nº of courses of IST 2 (1-4)
- Median time since last IST, mo 9 (6-117)
- Primary refractory 33 (77%)
- TD Hb 40 (93%), PI 42 (98%)
- PNH clones 26 (60%)

Median follow up 9 months (range 3–47 months)

Desmond R et al, Blood 2014; 123: 1818-25
ELTROMBOPAG IN REFRACTORY SAA

Initial cohort n=25 (11/25, 40% responses)  
Expanded cohort n=43  
Primary endpoint: response at 3-4 months

- 17 responders (40%)  
  - 11 platelet responses  
  - 4 erythroid responses  
    - Additional 7 at >16 w  
  - 8 neutrophil responses  
    - Additional 3 at >16 w

- 26 non-responders  
  - 2 responses >16 w  
  - 1 died of progression  
  - 3 deaths from sepsis  
  - 6 clonal evolution

Absolute reticulocyte count was the only predictor for response  
No pts. responded to doses less than 100 mg per day

Median follow up 9 months  
(range 3-47 months)

HEMATOLOGIC RESPONSES

Desmond R et al, Blood 2014; 123: 1818-25
16 weeks – primary endpoint

Best response at follow-up

Platelets
Neutrophils
Haemoglobin

Desmond R et al, Blood 2014; 123: 1818-25
Patient 1

Baseline 39 months on eltrombopag 6 months off drug

Patient 2

Baseline 33 months on eltrombopag 6 months off drug

Desmond R et al, Blood 2014; 123: 1818-25
**ELTROMBOPAG IN REFRACTORY SAA**

- Decrease dose by 50%

**ROBUST RESPONDERS**

- Platelets >50 ×10⁹/L
- Hemoglobin >10 g/dL
- Neutrophils >1 ×10⁹/L
- >8 weeks

Counts remain above limits for 8 weeks

Discontinue drug

n=5

Desmond R et al, Blood 2014; 123: 1818-25
• No grade 4 adverse events attributable to drug
• No significant increase in marrow reticulin
• 1 SAE, abdominal pain, possibly attributed to drug
• 4 patients had significant transaminitis
  • 1 acute hepatitis B infection
  • 1 sepsis
  • 2 decreased with dose modifications

Desmond R et al, Blood 2014; 123: 1818-25
ELTROMBOPAG ADDED TO IST AS FIRST-LINE

Primary endpoints: CR rate and safety at 6 months
Secondary endpoints: OR, PR, survival, clonal evolution and relapse

CR = ANC ≥1 x10⁹/L, Hb ≥10 g/dL, PL ≥100 x10⁹/L
PR = Blood counts no longer meeting criteria for SAA or CR

Townsley DM, Blood 2015; 126: LBA2
### ELTROMBOPAG ADDED TO IST AS FIRST-LINE

<table>
<thead>
<tr>
<th>Cohort 1 (n=30)</th>
<th>Cohort 2 (n=31)</th>
<th>Cohort 3 (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3 months</strong></td>
<td></td>
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</tr>
<tr>
<td>OR</td>
<td>23 (77)</td>
<td>24 (77)</td>
</tr>
<tr>
<td>CR</td>
<td>5 (17)</td>
<td>8 (26)</td>
</tr>
</tbody>
</table>

| **6 months**    |                 |                 |
| OR              | 24 (80)         | 27 (87)         | 19/20 (95)     |
| CR              | 10 (33)         | 8 (26)          | 12/20 (60)     |

**Historic IST response rates (%)**

<table>
<thead>
<tr>
<th></th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>57–62</td>
<td>62–68</td>
</tr>
<tr>
<td>CR</td>
<td>7–10</td>
<td>10–15</td>
</tr>
</tbody>
</table>

- Median time to ANC >0.5 x10⁹/L was 47 days for all cohorts, 35 days for cohort 3
- Time to transfusion independence: PL 32 days, RBC 42 days
- 80% improved cellularity on trephine biopsy with no fibrosis
- Telomere length, reticulocyte count, lymphocyte count, PNH clones NOT predictive for response
- Combination well tolerated; 2 patients discontinued eltrombopag (cutaneous reactions)
- Six withdrawals before 6-month time point (4 refractory patients; 2 patients experienced clonal evolution)
Phase II, open label, single-arm trial to assess efficacy and safety of eltrombopag with CsA as first-line therapy in patients with SAA

**Primary endpoints:** OR rate at 6 months

**Secondary endpoints:** OR rate at 3 and 12 months, survival and safety
Refractory aplastic anemia

Role of TPO agonists in second and first line

Clonal evolution

Real life and practical issues
Patients with aplastic anemia have a rate of clonal evolution of about 15\% over 10 years.
**CLONAL EVOLUTION IN SECOND AND FIRST LINE**

**SECOND LINE n=8/43**
- Monosomy 7 (n= 5)
- Dysplasia (n= 2)
- 6 non-responders/2 responders
- del13q at 9 and 13 months in 2 responders
- No predictive factors identified

**FIRST LINE n=7/92**
- Monosomy /partial deletion of Chr 7 (n=4)
- Complex (t(3;3)(q21;q26), -7) (n=1)
- Trisomy 6 and trisomy 1 (in 2 metaphases) (n=1)
- del 13q (later normalized) (n=1)
- Similar to historic Standard IST

Desmond R et al, Blood 2014; 123: 1818-25

## CLONAL EVOLUTION IN SECOND AND FIRST LINE

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- Monosomy 7 (n=5)
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- Similar to historic Standard IST

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Desmond R et al, Blood 2014; 123: 1818-25

<table>
<thead>
<tr>
<th>Recruiting</th>
<th>hATG+CsA vs hATG+CsA+Eltrombopag for SAA</th>
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</thead>
<tbody>
<tr>
<td><strong>Condition:</strong></td>
<td>Severe Aplastic Anemia</td>
</tr>
<tr>
<td><strong>Interventions:</strong></td>
<td>Drug: hATG; Drug: CsA; Drug: Eltrombopag</td>
</tr>
</tbody>
</table>
Eltrombopag Modulates Reactive Oxygen Species and Decreases Acute Myeloid Leukemia Cell Survival

Anna Kalota¹, Mary A. Selak², Laura A. Garcia-Cid³, Martin Carroll¹ *

Eltrombopag inhibits the proliferation of leukemia cells via reduction of intracellular iron and induction of differentiation

Michael Roth, Britta Willi, Guillermo Simkin, Swathi Narayananagi, Laura Barreyro, Boris Bartholdy, Roni Tamari, Constantine S. Mitsiades, Amit Verma and Ulrich Steidl

PLoS One. 2015 Apr 27;10: e0126691
Refractory aplastic anemia

Role of TPO agonists in second and first line

Clonal evolution

Real life and practical issues
### BASELINE CHARACTERISTICS (n=46)*

<table>
<thead>
<tr>
<th>Courses CsA + ATG (relapse/refractory n=35)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 (49)</td>
</tr>
<tr>
<td>2</td>
<td>2 (29)</td>
</tr>
<tr>
<td>3</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>61 [40-70]</td>
</tr>
<tr>
<td>Idiopathic SAA</td>
<td>44 (96)</td>
</tr>
<tr>
<td>PNH clone</td>
<td>17 (37)</td>
</tr>
<tr>
<td>Months after diagnosis of SAA, median [range]</td>
<td>17 [8-50]</td>
</tr>
<tr>
<td>Months after IST, median [range]</td>
<td>6 [3-14]</td>
</tr>
<tr>
<td>Maximal dose, median [range]</td>
<td>150 [100-150]</td>
</tr>
<tr>
<td>Transfusions/month</td>
<td></td>
</tr>
<tr>
<td>RBC packs</td>
<td>4 [2-4]</td>
</tr>
<tr>
<td>Platelets apheresis units</td>
<td>3 [2-4]</td>
</tr>
</tbody>
</table>

*SAA in patients unfit for ATG (n=11)

### TRANSFUSION INDEPENDENCE n(%)

<table>
<thead>
<tr>
<th>Time Point</th>
<th>3 months</th>
<th>6 month</th>
<th>Last Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still on treatment</td>
<td>33%</td>
<td>46%</td>
<td>46%</td>
</tr>
<tr>
<td>Treatment stopped</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good hematologic response</td>
<td></td>
<td></td>
<td>4 (9)</td>
</tr>
<tr>
<td>Limited toxicity</td>
<td></td>
<td></td>
<td>1 (2)</td>
</tr>
<tr>
<td>Failure to improve hematologic status</td>
<td></td>
<td></td>
<td>15 (33)</td>
</tr>
</tbody>
</table>

### TOXICITY

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>11 (grade 3 in 1)</th>
<th>2 (grade 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver (cytolisis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CYTOGENETICS AFTER TREATMENT, n=12

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>10</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trisomy 8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Single-Center Experience of Immunosuppressive Therapy with or without Eltrombopag in Patients with Aplastic Anemia

Tapan Kadia, Farhad Ravandi, Naval Daver, Gautam Borthakur, Jorge E. Cortes, Elias Jabbour, Steven M. Kornblau, Srdan Verstovsek, William Wierda, Jan A Burger, Zeev Estrov, Courtney DiNardo, Xiao Qin Dong, Naveen Pemmaraju, Maro Ohanian, Koichi Takahashi, Stephany Hendrickson, Hagop Kantarjian and Guillermo Garcia-Manero

Blood 2015 126:4779;

- hATG Day 1 to 4
- G-CSF for 3 months
- CSA for 6 months
After the results of Eltrombopag in refractory AA, the protocol was amended to study the addition of Eltrombopag to IST.

<table>
<thead>
<tr>
<th></th>
<th>n=31</th>
<th>N (%)</th>
<th>Responders 68% (CR 23%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IST</td>
<td>17</td>
<td>(55)</td>
<td>59%</td>
</tr>
<tr>
<td>IST + Eltrombopag</td>
<td>14</td>
<td>(45)</td>
<td>79%</td>
</tr>
</tbody>
</table>

Grade 3 non hematologic toxicity: infection (3), chest pain (1), headache (1)
Optimal dose?
Initial dose 50 mg once daily; hematologic response may need 150 mg and >16 w

Monitoring crucial
Blood tests monthly after stable dose achieved and 6 monthly bone marrow

Drug interactions
Rosuvastatin, anti-acids, high fat/high calcium diet

When to stop?
Discontinue treatment if robust response attained
PLATELET COUNT | DOSE ADJUSTMENT
--- | ---
<50 x10⁹/L following at least 2 weeks | Increase daily dose by 50 mg to a maximum of 150 mg/day
| For patients taking 25 mg once daily (East Asian, hepatic impairment), increase the dose to 50 mg daily before increasing the dose amount by 50 mg
>200 x10⁹/L to ≤400 x10⁹/L at any time | Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments
>400 x10⁹/L | Stop eltrombopag for 1 week
| Once the platelet count is <150 x10⁹/L, reinitiate therapy at a dose reduced by 50 mg
>400 x10⁹/L after 2 weeks off therapy at lowest dose | Discontinue eltrombopag

Target platelet count greater than or equal to 50 x10⁹/L as necessary
ROLE OF ROMIPLOSTIM

- Patients with IST refractory thrombocytopenia
- Efficacy and safety
- Recommended initial dose
- Pharmacokinetics
- Efficacy and safety during the extension period beyond one year

- Efficacy Yes
- Patients with thrombocytopenia refractory to or ineligible for IST therapy
- Safety (yes) and pharmacokinetics after repeated administration
- Recommended initial dose (10 μg/Kg SC) (Lee JW et al, ASH 2016: 3010a)
Conclusions

- Eltrombopag acts on c-Mpl receptors, present in more primitive progenitor HSCs
- Eltrombopag restores trilineal hematopoiesis
- Useful as a salvage therapy for patients who are refractory to IST/relapse after IST
- Preliminary very good responses added to IST in first line
- It may reduce IST treatment complications in monotherapy
- Good tolerability
- Results from ongoing trials will provide robust data on its use in AA with an optimal strategy