Use of TPO-mimetics for Indications Other Than ITP

Mazyar Shadman, MD, MPH

Discussant:

Siobán Keel, MD

Hematology Fellows Conference

June 28, 2013
• Thrombopoietin (TPO) and other c-mpl ligands
• TPO-mimetics in ITP
• Long-term (hematologic) side effects and concerns
• TPO-mimetics in Aplastic Anemia
• TPO-mimetics in Myelodysplastic Syndrome (MDS)
• TPO-mimetics in AML

Outline
• **TPO** is a growth factor made in liver and kidneys that stimulates platelet production through interaction with its receptor, **c-mpl** on megakaryocytes and primitive hematopoietic stem cells (self-renewal and expansion)

![Thrombopoietin Levels Graph]

• **C-MPL ligands:**
  – Recombinant thrombopoietins: rHuTPO, PEG-rHuMGDF
  – **Receptor Agonists:** Peptide (**Romiplostim**) and non-peptide (**Eltrombopag**)

• **Functional** rather than structural TPO-mimetics

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**Kaushansky et al, Best Practice Hematology, 2009**

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**Department of Medicine Grand Rounds**
Feb 16th 2012

**An Update on ITP: A New Treatment Paradigm**

**Dr. Terry Gernsheimer**

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**Thrombopoietin and C-MPL ligands**
TPO-Memtics: Mechanism of Action

Kaushansky, NEJM, 2006
<table>
<thead>
<tr>
<th></th>
<th>Romiplostim</th>
<th>Eltrombopag</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand Name</strong></td>
<td>Nplate</td>
<td>Promacta</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td>Peptide TPO receptor agonist</td>
<td>Non-peptide TPO receptor agonist</td>
</tr>
<tr>
<td><strong>FDA approval</strong></td>
<td>Refractory ITP</td>
<td>Refractory ITP and HepC to support INF therapy</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>SubQ</td>
<td>PO</td>
</tr>
<tr>
<td><strong>Starting Dose</strong></td>
<td>1 mcg/kg once weekly</td>
<td>50 mg (25 mg Asian ethnicity) daily</td>
</tr>
<tr>
<td><strong>Maximum Dose</strong></td>
<td>10 mcg/kg once weekly</td>
<td>75 mg daily</td>
</tr>
</tbody>
</table>

**TPO-memtics: Comparison**
Recommended for adults at risk of bleeding who relapse after splenectomy or who have a contraindication to splenectomy and who have failed at least one other therapy.

These agents may also be considered for adults at risk of bleeding who have failed one line of therapy such as corticosteroids or IVIg and who have not undergone splenectomy...”
Thrombosis
– Mimics an “ulcerated atheroma”
– Increased Platelet activation by peptite TPO mimetics

Bone Marrow Fibrosis
– Mouse models: higher fibrosis after TPO gene transfection (TGF-beta1)
– Reversible fibrosis after thrombopoietin administration

Risk of leukemogenesis
– wild-type MPL overexpression in AML samples with t(8;21)

Pulikkan, Blood, 2012

TPO-mimetics: hematologic concerns and side effects
TPO-mimetics: hematologic concerns and side effects

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Platelet Count (× 10^9/uL)</th>
<th>Days After TPO</th>
<th>Hyperplasia</th>
<th>Megakaryocyte Morphologic Features</th>
<th>Reticulin</th>
<th>Bone Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Overall</td>
<td>Myeloid</td>
<td>Erythroid</td>
<td>MHPF</td>
</tr>
<tr>
<td>With TPO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>52</td>
<td>6</td>
<td>++</td>
<td>+++</td>
<td></td>
<td>10.8</td>
</tr>
<tr>
<td>2</td>
<td>209</td>
<td>31</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>3.6</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>0</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>511</td>
<td>4</td>
<td>+++</td>
<td>+</td>
<td>+/-</td>
<td>37.9</td>
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<tr>
<td>5</td>
<td>450</td>
<td>0</td>
<td>+++</td>
<td>+</td>
<td>–</td>
<td>58.4</td>
</tr>
<tr>
<td>6</td>
<td>348</td>
<td>16</td>
<td>+++</td>
<td>++</td>
<td>–</td>
<td>9.9</td>
</tr>
<tr>
<td>7</td>
<td>159</td>
<td>36</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>3.6</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>23</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3.8</td>
</tr>
<tr>
<td>9</td>
<td>1,275</td>
<td>11</td>
<td>+++</td>
<td>++</td>
<td>–</td>
<td>8.8</td>
</tr>
<tr>
<td>Without TPO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NA</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>++</td>
<td>0.6</td>
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<tr>
<td>2</td>
<td>214</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>3.2</td>
</tr>
<tr>
<td>3</td>
<td>168</td>
<td>–</td>
<td>+++</td>
<td>++</td>
<td>–</td>
<td>4.8</td>
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<td>4</td>
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<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>2.0</td>
</tr>
<tr>
<td>5</td>
<td>NA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2.1</td>
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<tr>
<td>6</td>
<td>19</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>0.4</td>
</tr>
<tr>
<td>7</td>
<td>NA</td>
<td>–</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>11.2</td>
</tr>
<tr>
<td>8</td>
<td>587</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>5.6</td>
</tr>
</tbody>
</table>

MHPF: megakaryocytes per high-power field; NA, not available; +, slight; ++, moderate; ++++, marked; –, none.

* Values are given as conventional units; to convert to Système International units (× 10^9/L), multiply by 1.0.

Thrombosis
- Mimics an “ulcerated atheroma”
- Increased Platelet activation by peptite TPO mimetics

Bone Marrow Fibrosis
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Risk of leukemia
- wild-type MPL overexpression in AML samples with t(8;21)

Pulikkan, Blood, 2012

TPO-mimetics: Hematologic concerns and side effects
292 patients – up to 5 years follow-up
US, Europe, Australia, Canada
25 thrombotic events (19 patients) – 6 events were Romiplostim related
– MI (10), CVA (6), VTE (9)
– Duration–adjusted rate of thrombosis was 4.1/100 patient–years

No routine bone marrow evaluations
39 patients had bone marrow biopsy because of poor response
– 11 patients showed increased reticulin
– Resolved in 4 months in 1 patient
– Present in 8 patients by “end of follow-up”
No positive type I collagen when staining was done
“Myelofibrosis” in 1 patient based on Reticulin and not trichrome

No Leukemia

ROMIPLOSTIM: Long-term (hematologic) effects

Kuter, BJH, 2013
• 299 patients – up to 3 years follow-up
• EXTEND study
• Thromboembolic events (20)
  – MI (4), CVA (5), VTE (11)
  – IR of 3.17 of 100 patient-years (stable since a 2009, 1.7-fold increase in exposure)

• Bone Marrow:
  – 147 BM biopsies on 135 patients who received EP for median of 12 months (range, 1-32)
    • Grade 0: 88
    • Grade 1: 48 (1 with collagen)
    • Grade 2: 11 (2 with collagen)
  – 11 patients had a second biopsy after being treated for 2 years:
    • No change: 8 of 11 patients
    • Grade 1 to grade 2: 1 patient
    • Grade 2 to grade 0 and grade 1 to grade 0: 2 of 11
  – 2-year longitudinal study ongoing (NCT01098487)

• Hematologic Malignancies
  – DLBCL: 1 patient (64 days)
  – Hodgkin’s Lymphoma (3 years)
  – No Leukemia

Salesh, Blood, 2012

ELTROMBOPEG: Long-term (hematologic) effects:
Kaushansky, NEJM, 2006

TPO : More than megakaryocytes
• Hematopoietic stem cells and progenitor cells also express c-MPL

• Addition of recombinant TPO expands the pool of hematopoietic stem cells in culture

• Knockout mice that are deficient in expression of the TPO or its receptor have reduced numbers of hematopoietic stem and progenitor cells

• Multilineage marrow failure eventually develops in patients with congenital amegakaryocytic thrombocytopenia who have MPL mutations

Becker, The Hematologist, 2013

TPO-mimetics: Aplastic Anemia – rationale
• Single arm

**Inclusion:** refractory AA, ATG+CSP ≥ 6 months, Platelet < 30,000/ul, Age ≥ 18

**Exclusion:** Fanconi, PNH clone (≥ 50%), HIV, Renal/Hepatic/Cardiac abnormalities

**Response Criteria:**
- **Platelet:** ↑ 20,000 or Transfusion Independence
- **Erythroid:** ↑ 1.5 g/dl w/o transfusion or ↓ pRBC units (4 units in 8 weeks)
- **Neutrophil:** ↑ 500 or 100% increase

Aplastic Anemia – NHLBI study - Design
Aplastic Anemia – NHLBI study - Response

Total 25 patients

Response Criteria:
- **Platelet**: \( \uparrow \) 20,000 or Transfusion Independence
- **Erythroid**: \( \uparrow \) 1.5 g/dl w/o transfusion or \( \downarrow \) pRBC units (4 units in 8 weeks)
- **Neutrophil**: \( \uparrow \) 500 or 100% increase

- **44%** of patients had positive responses in at least one lineage at 12 weeks, with significantly reduced transfusion requirements (9 platelet and 3 pRBC)

Olnes, NEJM, 2012
Fibrosis:
• Bone marrow in 23 patients (3 months and every 6 months)
• No increase in fibrosis or reticulin (all 0 or +1)

Clonal evolution:
• Monosomy 7 in 2 patients
• Both with poor response
• 1 had a very short telomere
• Difficult to monitor

Predictors of poor response:
– Lower reticulocyte count
– Lower immature platelet count

High TPO level

Longer response (months vs. weeks)
– ? Longer duration for non-responders

Olnes, NEJM, 2012

Aplastic Anemia – NHLBI study – Hematologic effects
Eltrombopag Added to Standard immunosuppression in Treatment-Naive Severe Aplastic Anemia (NCT01623167)
Single arm phase I/II study

- 44 low risk patients
- 300-1500 mcg SQ weekly ×3 => if no DLT => 1 year (93%)

Response (IWG 2006):
- 8 consecutive weeks independent of platelet transfusions (46%)

Adverse effects:
- Thromboembolism: 1 line-related DVT (1500 µg; Plt 250 k)
- Bone marrow in 24 patients (pre and post) => reticulin grade (↑ in 7 and ↓ in 7)
- No antibodies
- No change in the Cytogenetics category (only 11 patients checked)
- Blast increased in 4 patients and normalized after stopping the treatment
- 2 AML progressions:
  - #1: IPSS 0.5 (4% blast) => 300 µg => Chloroma => 2 weeks after stopping (1%)
  - #2: IPSS 0 (4% blast) => 1000 µg => 24%

Kantarjian, JCO, 2010
40 pts with low-int MDS => AZA x 4 cycles
Randomization to Romiplostim 500 mcg, 750 mcg, or placebo SQ weekly

Romiplostim resulted in ↑ PLTs, ↓ PLT Tx (67% vs. 38% vs. 21%), ↓ bleeding

3 cases of AML progression:
- 1 in the placebo
- 2 in the romiplostim 500-mcg group.
  RAEB-I (IPSS 1.0) (baseline 5-10%) => 500 µg => (60%)
  RAEB-I (IPSS 2.0) (baseline 5-10%) => 500 µg => (20%)

Bone marrow in 27 patients (Pre- and Post-)
- ↑ reticulin grade in 13 (3 in placebo, 10 in treatment)
- No grade 4 reticulin
- Negative trichrome stainings

Kantarjian, Blood, 2010

MDS : AZA ± Romiplostim
MDS: Romiplostim – Phase III Randomized study

26-Week Treatment Period

- Romiplostim 750 mcg weekly ($N = 160$)
- Placebo weekly ($N = 80$)

24-Week Treatment Continuation

- Romiplostim 750 mcg weekly + standard of care ($N = 160$)
- Placebo weekly + standard of care ($N = 80$)

- IPSS low/int-1 MDS on supportive care only, Plt $<20$ or $<50$ with bleeding
- 250 patients (July 2008 – March 2011)
- After completing Rx, pts moved to long-term follow-up (LTFU) for 5 years
- Primary end point: Significant Bleeding
- Secondary: Transfusion, Plt response, Survival, Safety, Progression to AML, Antibodies

Kantarj, ASH, 2011

Courtesy of Dr. Kantarj
Romiplostim in MDS. Interim Results (58 weeks) (June 2011) presented at ASH 2011

Efficacy:
- Reduced clinically significant bleeding events (HR 0.83, 95% CI: 0.66, 1.05, P = 0.13)
- Reduced PLT transfusions (RR 0.77, 95% CI: 0.66, 0.88)
- Increased Platelet counts (per IWG) (OR 15.6, 95% CI: 4.7, 51.8)

Safety concerns:
- Increases in peripheral blast to >10% more with romiplostim (15% vs. 3.6%)
- AML diagnosed in 10 pts on romiplostim and 2 pts on PBO (HR 2.51, 95% CI: 0.55, 11.47)
- 58-week overall survival (OS) and AML-free survival not statistically different

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 83)</th>
<th>Romiplostim (N = 167)</th>
<th>Total (N = 250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed study</td>
<td>20 (24)</td>
<td>36 (22)</td>
<td>56 (22)</td>
</tr>
<tr>
<td>Discontinued study</td>
<td>63 (76)</td>
<td>131 (78)</td>
<td>194 (78)</td>
</tr>
<tr>
<td>Study-defined AML</td>
<td>2 (2)</td>
<td>10 (6)</td>
<td>12 (5)</td>
</tr>
</tbody>
</table>

MDS : Romiplostim – Randomized study  Courtesy of Dr. Kantarjian
Study-independent safety DMC recommendation in February 2011 to **discontinue investigational product** based on concerns that:

- Potential benefit in reduction of bleeding did not outweigh potential risk for disease progression to AML

- Transient increases in blast cell counts in Romiplostim arm put patients at risk for diagnosis and treatment of AML

MDS : Romiplostim – Randomized study
### Romiplostim in MDS. 58-week Updated Data:

<table>
<thead>
<tr>
<th></th>
<th>Romiplostim</th>
<th>Placebo</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>17.9% (30)</td>
<td>20.7% (17)</td>
<td>0.86</td>
<td>0.47, 1.56</td>
</tr>
<tr>
<td>AML</td>
<td>6.0% (10)</td>
<td>4.9% (4)</td>
<td>1.20</td>
<td>0.38, 3.84</td>
</tr>
<tr>
<td>AML-free survival</td>
<td>19.6% (33)</td>
<td>23.2% (19)</td>
<td>0.85</td>
<td>0.48, 1.50</td>
</tr>
</tbody>
</table>

### Through July 2012:

<table>
<thead>
<tr>
<th></th>
<th>Romiplostim</th>
<th>Placebo</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>38.1% (64)</td>
<td>37.8% (31)</td>
<td>1.08</td>
<td>0.70, 1.67</td>
</tr>
<tr>
<td>AML</td>
<td>8.9% (15)</td>
<td>8.5% (7)</td>
<td>1.15</td>
<td>0.47, 2.85</td>
</tr>
<tr>
<td>AML-free survival</td>
<td>39.3% (66)</td>
<td>39.0% (32)</td>
<td>1.09</td>
<td>0.71, 1.68</td>
</tr>
</tbody>
</table>

Kantarjian, ASH, 2012

MDS: Romiplostim – Randomized study

Courtesy of Dr. Kantarjian
### MDS: Romiplostim – Randomized study

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 43)</th>
<th>Romiplostim (N = 87)</th>
<th>Placebo (N = 40)</th>
<th>Romiplostim (N = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Significant bleeding</strong> (rate/100 pt-yr)</td>
<td>501.2</td>
<td>514.9</td>
<td>226.4</td>
<td>79.5</td>
</tr>
<tr>
<td>RR</td>
<td>1.03, p = 0.83</td>
<td>0.35, p&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Platelet transfusion</strong> (rate/100 pt-yr)</td>
<td>1778.6</td>
<td>1250.5</td>
<td>179.8</td>
<td>251.8</td>
</tr>
<tr>
<td>RR</td>
<td>0.71, p&lt;0.0001</td>
<td>1.38, p = 0.15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**<20x10⁹/L**

**20-50 x10⁹/L**

MDS: Romiplostim – Randomized study

Courtesy of Dr. Kantarjian
Development and Validation of a Model to Predict Response to Romiplostim in Patients with Lower-Risk Myelodysplastic Syndromes (MDS)

Sekeres, ASH, 2012

MDS: Prediction models to identify responders to Romiplostim
• Eltrombopag leads to:
  – ↓cell division rate
  – Block in G1 phase of cell cycle
  – ↑differentiation in human and murine leukemia cells

• Eltrombopag only bind TPO-R in human and primate cells => antileukemic effect is independent of TPO-R

• Antileukemic effects are mediated through modulation of intracellular iron content

• Eltrombopag’s anti-leukemic activity in vivo demonstrated its ability to prolong survival in 2 mouse models of leukemia

Roth, Blood, 2012

AML : Rationale for therapeutic use
- Patients ≥ 60 years old Plt ≤75,000/ul
- 4 sequential cohorts of 50mg, 100mg, 200mg and 300mg of Eltrombopag daily

- **23 patients** (June 2010 to February 2012), 21 of 23 patients were *relapsed or refractory* after prior therapy
- 19 were plt transfusion dependent

- Reasons for drug cessation:
  - Possible DLT=1 (Grade 4 hepatic lab abnormalities)
  - Progressive disease=5
  - Death due to sepsis=5
  - Lack of response=6
  - Loss of response=1
  - Hospice or alternative therapy=4

- 4 patients (200mg and 300mg dose) achieved a platelet response and became transfusion independent.

- 1 patient (primary refractory, monosomy 7) => CR (morphologic and CG) by 3 months of therapy at the 300mg dose level. This response was sustained at most recent bone marrow biopsy at 6 months of therapy and the patient remains on study drug. + reticulin fibrosis

- 6 patients had stable disease (SD) at one month, which was maintained at 3 months for 4 patients

Frey, ASH,2012

**AML: phase I study of Eltrombopag for Elderly AML**
• Phase II - Eltrombopag in Elderly Acute Myelogenous Leukemia (AML)
  – (University of Pennsylvania - NCT01113502)

• Eltrombopag in Patients With Relapsed/Refractory Acute Myeloid Leukemia
  – (Roswell Park-NCT01550185)

AML: Current Trials
• Chemotherapy of solid tumors (PEG-rHuMGDF)
• Thrombocytopenia of HIV
• Harvesting peripheral blood progenitor cells
• Platelet apheresis
• Liver diseases (Hep C and ESLD)
• Multiple thrombocytopenia syndromes

Other indications:
• AML

• After Cord Transplant

Potential Research Projects:  

Courtesy of Dr. DeLaney
• Despite the concerns based on the pre-clinical studies, the clinical follow-up studies have not proven increased risk of marrow fibrosis...yet

• Effect of TPO-mimetics on patients with abnormal clones needs to be investigated

• Eltrombopag is a promising agent in treatment of refractory Aplastic Anemia and the frontline study is ongoing

• Romiplostim is effective in treatment of MDS but its safety is still being evaluated

• Possible benefit in elderly AML patients

• Potential role after Cord transplants

Summary
Thanks to:

- Dr. Siobán Keel
- Dr. Terry Gernsheimer
- Dr. Collen DeLaney
- Dr. Hagop Kantarjian