Perplexing Platelets: Highs, Lows and New Targets
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UNECEM ‘94
Disclosures
Objectives

- Workup for High Platelets
- Diagnoses for High Platelets
- Treatments
- Workup for Low Platelets
- Diagnoses
- Treatments and new targets
Platelet Maturation
The "Highs"
Thrombocytosis

• Most commonly reactive
  – Infection, inflammation, malignancy.
• Iron deficiency
• Primary Myeloproliferative Disorder
  – ET, PV, MF
• Medications
  – Epinephrine, Tretinoin, Vincristine
Case 1 HL

- 63y/o retired air traffic controller
- Regular Blood Donor
- CBC 8.8–15/56–659k
- Spleen enlarged but not painful
- Otherwise ROS neg
Work-up

• Iron, TIBC, Ferritin.
• Treat underlying disorder and follow platelet count.
• If suspect a Chronic Myeloproliferative Disorder- Send for JAK-2 and BCR-ABL
JAK-2

Who is JAK2 V617F positive?

People with PV 98%
People with ET 50%
People with MF 50%
CASE 1 HL

Jak 2 V617F = Positive
Ferritin borderline low
EPO level = wnl
Smear Elev platelets some large and giant
Dx: Essential Thrombocytopenia (ET)
Treatments

• Treat Underlying Infection/inflammation
• Replete Fe
• Low dose ASA
• Hydroxyurea or Anegrelide
NEJM 2005

- Hydroxyurea Compared with Anagrelide in High-Risk Essential Thrombocythemia
Case 2 DC

- 78y/o Hispanic Female CC: Fatigue, DOE
- MCV=77, MCHC=31.9
- Ferritin =6
- Trans Sat=3.8%
DX: IDA
Case 3 AG

- 73y/o male Jak-2 pos ET for 10yrs treated with Anagrelide then Hydrea
- Develops significant fatigue, dyspnea, abdominal discomfort, weight loss.
- Exam Splenomegaly
- CBC WBC 2.0--- 7.4/18 --- 35k
- Hydrea stopped
- No improvement
Case 3 AG

• Bone Marrow- Dry tap. Bx-Dense fibrosis
Dx: Post-ET Myelofibrosis
Treatment

• COMFORT-1 AND COMFORT-2
  About 300pts Comparing Ruxolitinib(Jakafi) to placebo
  - Published NEJM March 2012
Case 3 AG

- Started Ruxolitinib 15mg BID
- After 2 weeks- “I feel great, doc!”
- Continues on tx now
The “low’s” Thrombocytopenias

- Thrombocytopenia → a platelet count of less than 150,000/mm³ (<150,000/mm³)

- N.B. *With normal platelet function*, thrombocytopenia is rarely the cause of bleeding unless the count is less than 50,000/mm³.

- Thrombocytopenia should always be confirmed by examination of a peripheral smear.

- It can be caused by:
  - decreased platelet production
  - increased destruction
  - Sequestration (DISORDERS OF DISTRIBUTION of platelets)
  - or a combination of these causes.
Thrombocytopenia

- Alcohol, virus
- Antiviral and immunosuppressive therapies
- Bone marrow suppression
- Abnormal thrombopoietin metabolism
- Hypersplenism and portal hypertension
- Secondary to platelet activation

Decreased platelet production

Decreased platelet survival

Thrombocytopenia
Case 4 IP

- 53y/o otherwise healthy male
- Routine annual physical shows Plts=85k
- WBC and H&H wnl
- Repeat gives similar result
Peripheral Smear

- Repeat in Sodium Citrate (blue top)
  = 156k
Dx: Pseudothrombocytopenia

• Due to EDTA antibodies
• Time also plays a role
• Platelet clumps cannot be counted
• Clinically meaningless
Case 5 FA

• 57y/o male construction worker admitted with upper GI bleed
  – Hematemesis
• Admits to 2-3 six-packs/day, more when it is hot.
• EGD (+) varices
• CBC  11.2– 8.4/24 – 72k
• PT/PTT wnl
Peripheral Smear
Nuclear Medicine L/S scan

Anterior  Posterior  Rt. Lateral
Dx: Hypersplenism/splenic sequestration

- Platelets Usually 50-100k
- ETOH is also directly toxic to marrow
- Bleeding **NOT** due to low platelets
Final Case, MP

- 51y/o Ukrainian female cc of abdominal pain
- Gastroenterologist EGD/EUS fatty liver and did a CBC Plts=10k
- Pt admits to epistaxis.
- PE significant for petechiae
Peripheral Smear
Bone Marrow Biopsy
Dx: ITP

- Pt placed on prednisone 1mg/kg x 2 weeks
- CBC 17–13.5/40 ---249K
- Taper prednisone
- 4 months later 5.4–12.7/38 ---41k
  - Rituximab chimeric anti-CD20 monoclonal antibody treatment for adult refractory idiopathic thrombocytopenic purpura.
  - Rituxan- 151k→60k→36k
Thrombopoietin

[Diagram showing the interaction of Thrombopoietin with JAK2 and STAT5, leading to increased megakaryocyte proliferation and differentiation, and subsequent platelet production.]
New Target 2 New Agents

- Romiplostim (Nplate)
- Lancet, Feb 2008, Pivitol trial
# Nplate™ - Romiplostim

## Common Adverse Effects:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Romiplostim</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>35%</td>
<td>32%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>26%</td>
<td>20%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>16%</td>
<td>7%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14%</td>
<td>2%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>Shoulder pain</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>6%</td>
<td>0%</td>
</tr>
</tbody>
</table>
New Target 2 New Agents

- Eltrombopag (Promacta)
- Oral Agent
- Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial.
  - Lancet. 2009;373(9664):641
Mechanism of Action
<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Eltrombopag (n = 106)</th>
<th>Placebo (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Cataract</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase, AST = aspartate aminotransferase.
Back to our patient

- Started on Eltrombopag 50mg daily on an empty stomach
- Some early GI side effects but these resolved spontaneously
- Week 4 plts = 333k
- Rx written 8/09.
- Now on 50mg Once weekly, maintaining normal platelets
References

• Kitchens, Craig, Consultative Hemostasis and Thrombosis. 3rd Ed, 2013
• UptoDate Online: Chapter on ITP
• Srdan Verstovsek, M.D., A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis, NEJM March 1, 2012
• Bussel JB, Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial
• Kuter, et al: Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial
Questions?