ITP: Pathophysiology and Treatment in 2008

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Division of Hematology/Oncology
Grand Rounds
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Immune Thrombocytopenic Purpura

- Immune destruction of platelets and impairment of platelet production
  - Usually acute and self limiting in children, rarely in adults
  - Prevalence is around 1/10,000
  - Presentation is often asymptomatic or mucosal bleeding in an otherwise well patient. Life-threatening bleeding occurs, but is rare.
Goals

• Review new ideas concerning the pathophysiology of ITP

• Review new treatment options in ITP
  – Pulse decadron
  – Laparoscopic splenectomy
  – Rituximab
  – H.pylori therapy
  – Refractory disease

• Discuss future novel treatments for ITP
Harrington-Hollingsworth experiment

Harrington. J Lab Clin Med 1951;38: 1-10

Schwartz. NEJM 2007 357(22) 2299-2301
Platelet bound antibody against GP IIB-IIIa

Tomer. Journal of Thrombosis and Haemostasis 2005. 3 (1), 74–78
Autoantibodies in ITP

• Antigenic epitopes:
  – Glycoprotein IIb-IIIa
  – Glycoprotein Ib-IX
  – Other surface antigens

  – Megakaryocytes

Initiating event or trigger is still unclear in most cases
CD34+-rich cells were cultured in media containing rHuMGDF and serially diluted plasma from patient ITP-1. After harvesting the cultures on day 10, the total number of megakaryocytes was determined.
Autoantibodies affect Megakaryocytes in ITP

Houwerzijl Blood 2004; 103(20): 500-506
ITP: Acute Therapy

Emergency or Not?

versus
Non-emergent

- Consider no therapy if non-bleeding and platelet >20-30x10^9 without other bleeding risk factors
- Prednisone 1mg/kg/d vs. pulse dexamethasone 40mg po qd x4 days
- Pulse IVIG in those intolerant to steroids
- Pulse anti-D (WinRho) in those intolerant to steroids
Treatment Protocol and Results in 125 Patients with Newly Diagnosed Immune Thrombocytopenic Purpura

- Decadron 40 mg po QD x 4 days
  - 85% initial response
  - 50% sustained response without further therapy
Figure 2. GIMEMA multicenter pilot study: CR evaluation and quality of initial response.


Dexamethasone 40mg po D 1-4 Q 14 days for four cycles
Acute ITP

• Oral dexamethasone may lead to a more sustained response than prednisone
  – No phase III data

• IVIG and WinRho are options for those intolerant to steroids or when a quicker response is warranted

• For emergent cases combined therapy with platelet transfusion is warranted
What is the current role of splenectomy in ITP?
Splenectomy

• American Society of Hematology (ASH) guidelines
  – Consider if platelet counts remain below $30 \times 10^9$ after 4-6 weeks of medical therapy

• British Committee guidelines
  – Consider as the major second-line therapy
  – No particular timing noted

George Blood 1996; 88:3-40 and Br J Haem 2003; 120:574-96
Splenectomy

• More than 80 articles published since 1995
  – Many with few patients and short follow-up
  – No controlled trials comparing surgery with other treatment modalities or to no treatment

• Retrospective metanalysis, 1966-2004
  – CR 1731/2623 (66%) with follow-up of 1-153 months adult patients

Godeau Curr Opin Hematol 2007;14:535-56
Ruggeri AM J Hem. Ahead of print
Kojouri Blood 2004; 104; 2623-2634
# Splenectomy-other studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient accrual (years)</th>
<th>Design</th>
<th>Number of patients</th>
<th>Mean time to splenectomy (months)</th>
<th>Overall immediate response (%)</th>
<th>Mean follow-up after splenectomy (years)</th>
<th>Long-term response (%)</th>
<th>Number of deaths due to ITP during follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balague et al. [12]</td>
<td>1993/2003</td>
<td>Retrospective</td>
<td>103</td>
<td>50</td>
<td>89</td>
<td>3.3</td>
<td>89</td>
<td>1 (bleeding)</td>
</tr>
<tr>
<td>Fabris et al. [42]</td>
<td>not done</td>
<td>Retrospective</td>
<td>54</td>
<td>42</td>
<td>88</td>
<td>7.6</td>
<td>66</td>
<td>0</td>
</tr>
<tr>
<td>Johansson et al. [43]</td>
<td>1969/1993</td>
<td>Retrospective</td>
<td>59</td>
<td>5.5</td>
<td>78</td>
<td>18</td>
<td>49</td>
<td>1 (fatal septicemia)</td>
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<td>Kumar et al. [14]</td>
<td>1985/1998</td>
<td>Retrospective</td>
<td>140</td>
<td>7.5</td>
<td>88</td>
<td>3.1</td>
<td>72</td>
<td>2 (postoperative) 2 (bleeding)</td>
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<tr>
<td>Pace et al. [44]</td>
<td>1992/2000</td>
<td>Retrospective</td>
<td>52</td>
<td>Not done</td>
<td>86</td>
<td>4.2</td>
<td>82</td>
<td>0</td>
</tr>
<tr>
<td>Radaelli et al. [45]</td>
<td>1978/1998</td>
<td>Retrospective</td>
<td>65</td>
<td>37.5</td>
<td>88</td>
<td>10.8</td>
<td>78</td>
<td>0</td>
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<tr>
<td>Schwartz et al. [41]</td>
<td>1988/1993</td>
<td>Retrospective</td>
<td>56</td>
<td>12</td>
<td>77</td>
<td>7.5</td>
<td>57</td>
<td>0</td>
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<tr>
<td>Wang et al. [49]</td>
<td>1990/2003</td>
<td>Retrospective</td>
<td>149</td>
<td>23</td>
<td>82</td>
<td>Not done</td>
<td>63</td>
<td>4 (bleeding)</td>
</tr>
<tr>
<td>Katkhouda et al. [40]</td>
<td>1992/1997</td>
<td>Prospective</td>
<td>67</td>
<td>Not done</td>
<td>83</td>
<td>3.2</td>
<td>77</td>
<td>0</td>
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<tr>
<td>Mazzuccconi et al. [47]</td>
<td>1979/1999</td>
<td>Retrospective</td>
<td>94</td>
<td>13</td>
<td>89</td>
<td>7</td>
<td>72</td>
<td>2 (fulminant meningococcus septicemia)</td>
</tr>
</tbody>
</table>

* Patients with follow-up greater than 60 months.
Splenectomy open vs. laparoscopic
51 series with 2940 patients

<table>
<thead>
<tr>
<th></th>
<th>Open</th>
<th>Paired LS</th>
<th>P value*</th>
<th>Total LS</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating room time (min)</td>
<td>114.1</td>
<td>179.9</td>
<td>&lt;.0001</td>
<td>166.8</td>
<td>&lt;.001</td>
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<tr>
<td>Splenic weight (g)</td>
<td>546.2</td>
<td>342.1</td>
<td>NS</td>
<td>408.7</td>
<td>NS</td>
</tr>
<tr>
<td>Accessory spleens (%)</td>
<td>11</td>
<td>11</td>
<td>NS</td>
<td>10.8</td>
<td>NS</td>
</tr>
<tr>
<td>Estimated blood loss (mL)</td>
<td>254.4</td>
<td>224.9</td>
<td>NS</td>
<td>218.8</td>
<td>NS</td>
</tr>
<tr>
<td>Transfusions (%)</td>
<td>14.0</td>
<td>10.2</td>
<td>&lt;.02</td>
<td>8.3</td>
<td>NS</td>
</tr>
<tr>
<td>Length of stay (d)</td>
<td>7.2</td>
<td>3.6</td>
<td>&lt;.001</td>
<td>3.4</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Open (%)</th>
<th>Paired LS (%)</th>
<th>P value*</th>
<th>Total LS (%)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>9.0</td>
<td>3.8</td>
<td>&lt;.0001</td>
<td>3.1</td>
<td>&lt;.0001</td>
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<tr>
<td>Wound</td>
<td>4.3</td>
<td>1.6</td>
<td>&lt;.001</td>
<td>1.7</td>
<td>.03</td>
</tr>
<tr>
<td>Infectious‡</td>
<td>3.8</td>
<td>1.0</td>
<td>&lt;.0001</td>
<td>1.3</td>
<td>.01</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2.5</td>
<td>1.3</td>
<td>.03</td>
<td>1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Bleeding§</td>
<td>2.4</td>
<td>1.4</td>
<td>NS</td>
<td>1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.5</td>
<td>0.1</td>
<td>NS</td>
<td>0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombotic</td>
<td>1.2</td>
<td>0.8</td>
<td>NS</td>
<td>0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Neurologic</td>
<td>0.3</td>
<td>0.1</td>
<td>NS</td>
<td>0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>1.0</td>
<td>0.5</td>
<td>NS</td>
<td>0.4</td>
<td>NS</td>
</tr>
</tbody>
</table>
Splenectomy: Summary

- Despite higher response rates than any other therapy and a chance for cure splenectomy is increasingly viewed as a treatment of last resort

- Initial responses > 80%, long-term >60%
- No great predictors of response
- Platelets should be increased to greater than $20 \times 10^9$ prior to surgery
- Laparoscopic approaches are increasingly performed
- Immunizations are critical
What is the role of Rituximab in the treatment of ITP?
Rituximab

• No comparative trials either randomized or nonrandomized have been published in patients with ITP

• Despite this rituximab has been increasingly used in the early and late management of ITP
Rituximab- Arnold study

- Systematic review of published reports
  - 1997-2004
  - Age >15
  - 19 eligible reports with 313 patients on efficacy
  - 29 reports with 306 patients on safety
  - Heterogeneous dosing and entry criteria

- Significant toxicities including death in 2.9% of cases

**Rituximab-systematic review**

**Table 2.** Overall, Complete, and Partial Platelet Count Response after Treatment with Rituximab in Adults with Idiopathic Thrombocytopenic Purpura according to Studies Enrolling at Least 5 Patients Each*

<table>
<thead>
<tr>
<th>Platelet Count Response, ( \times 10^9 ) cells/L</th>
<th>Pooled Estimate (95% CI), %</th>
<th>Contributing Reports (Patients), ( n (n) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response (( \geq 50 ))</td>
<td>62.5 (52.6–72.5)</td>
<td>19 (313)</td>
</tr>
<tr>
<td>Complete response (( \geq 150 ))</td>
<td>46.3 (29.5–57.7)</td>
<td>13 (191)</td>
</tr>
<tr>
<td>Partial response (50–150)</td>
<td>24.0 (15.2–32.7)</td>
<td>16 (284)</td>
</tr>
</tbody>
</table>

* Platelet count response criteria were based on the most common criteria used in primary reports.

**Table 3.** Time to Response, Response Duration, and Follow-up of Patients with Idiopathic Thrombocytopenic Purpura Treated with Rituximab*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median</th>
<th>Interquartile Range</th>
<th>Range</th>
<th>Contributing Reports (Patients), ( n (n) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to response, wk</td>
<td>5.5</td>
<td>3.0–6.6</td>
<td>2.0–18.0</td>
<td>6 (123)</td>
</tr>
<tr>
<td>Response duration, mo</td>
<td>10.5</td>
<td>6.3–17.8</td>
<td>3.0–20.0</td>
<td>16 (252)</td>
</tr>
<tr>
<td>Follow-up, mo</td>
<td>9.5</td>
<td>6.0–21.3</td>
<td>2.0–25.0</td>
<td>10 (187)</td>
</tr>
</tbody>
</table>

* Summary variables and interquartile ranges were calculated on the basis of the assumption that the data were normally distributed. Only studies that enrolled 5 or more patients each were analyzed.
Selected individual studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Number of patients (number of splenectomized patients)</th>
<th>Overall immediate response (%)</th>
<th>Overall sustained response (%)</th>
<th>Follow up with sustained response (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braendstrup et al. [124]</td>
<td>Retrospective</td>
<td>35 (16)</td>
<td>44</td>
<td>Not done</td>
<td>47</td>
</tr>
<tr>
<td>Cooper et al. [119**]</td>
<td>Retrospective</td>
<td>57 (31)</td>
<td>54</td>
<td>30</td>
<td>72</td>
</tr>
<tr>
<td>Penalver et al. [120]</td>
<td>Retrospective</td>
<td>89 (47)</td>
<td>55</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>Zaja et al. [121]</td>
<td>Retrospective</td>
<td>16 (2)</td>
<td>50</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>Shanafelt et al. [126]</td>
<td>Retrospective</td>
<td>12 (10)</td>
<td>42(^a)</td>
<td>25</td>
<td>36</td>
</tr>
<tr>
<td>Giagounidis et al. [87]</td>
<td>Pilot study</td>
<td>12 (11)</td>
<td>59</td>
<td>33</td>
<td>229</td>
</tr>
<tr>
<td>Saleh et al. [88]</td>
<td>Pilot study (^b)</td>
<td>12 (7)</td>
<td>25</td>
<td>25</td>
<td>12–24</td>
</tr>
<tr>
<td>Narat et al. [123]</td>
<td>Retrospective</td>
<td>6 (3)</td>
<td>83</td>
<td>50</td>
<td>46</td>
</tr>
<tr>
<td>Delgado et al. [127]</td>
<td>Retrospective</td>
<td>4 (3)</td>
<td>25</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>Aggarwal et al. [141]</td>
<td>Case report</td>
<td>3 (1)</td>
<td>100</td>
<td>100</td>
<td>8, 12 and 24</td>
</tr>
<tr>
<td>Faurshou et al. [142]</td>
<td>Case report</td>
<td>2 (0)</td>
<td>100</td>
<td>100</td>
<td>41 and 51</td>
</tr>
<tr>
<td>Koulpa et al. [140]</td>
<td>Case report</td>
<td>1 (0)</td>
<td>100</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>D'Arena et al. [143]</td>
<td>Case report</td>
<td>1 (1)</td>
<td>100</td>
<td>100</td>
<td>36</td>
</tr>
</tbody>
</table>

\(^a\) In the retrospective study of Shanafelt et al. [126], three responders were simultaneously receiving other drugs for ITP during rituximab therapy.

\(^b\) In the pilot study of Saleh et al. [88] only seven patients received rituximab at a dosage of 375 mg/m\(^2\) × 4.
Rituximab conclusions

• Appears promising, BUT
  – Heterogeneous pretreatment status
  – Poor follow-up data
  – Publication bias
  – Lack of comparative or randomized studies
  – Potential toxicity
  – Appropriate dosing never established

Difficult to draw definitive conclusions
What is the role of H. pylori testing and treatment?
H. pylori

• Seroprevalence in healthy individuals
  – Adults in developed countries 50-60%
  – Adults in developing countries up to 80%

• Recent data suggest high rates of platelet responses in ITP patients who underwent bacterial eradication
  – Especially in Japan and Italy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Bacterial eradication (%)</th>
<th>Platelet response (%)</th>
<th>Median follow up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective phase II studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gasbarrini et al. (1998) [37]</td>
<td>8/11 (73)</td>
<td>8 (100)</td>
<td>4</td>
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<tr>
<td>Emilia et al. (2001) [39]</td>
<td>12/13 (92)</td>
<td>6 (50)</td>
<td>8.3</td>
</tr>
<tr>
<td>Jarque et al. (2001) [40]</td>
<td>23/32 (72)</td>
<td>3 (13)</td>
<td>24</td>
</tr>
<tr>
<td>Veneri et al. (2002) [41]</td>
<td>15/16 (94)</td>
<td>11 (73)</td>
<td>11.7</td>
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<tr>
<td>Kohda et al. (2002) [42]</td>
<td>19/19 (100)</td>
<td>12 (63)</td>
<td>14.8</td>
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<td>Hino et al. (2003) [43]</td>
<td>18/21 (86)</td>
<td>10 (56)</td>
<td>15</td>
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<td>Hashino et al. (2003) [44]</td>
<td>13/14 (93)</td>
<td>5 (39)</td>
<td>15</td>
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<tr>
<td>Ando et al. (2003) [45]</td>
<td>27/29 (93)</td>
<td>16 (59)</td>
<td>11</td>
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<td>Michel et al. (2004) [46]</td>
<td>14/16 (93)</td>
<td>0 (0)</td>
<td>11.5</td>
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<tr>
<td>Takahashi et al. (2004) [47]</td>
<td>13/15 (87)</td>
<td>7 (54)</td>
<td>4</td>
</tr>
<tr>
<td>Sato et al. (2004) [48]</td>
<td>27/32 (84)</td>
<td>15 (56)</td>
<td>6</td>
</tr>
<tr>
<td>Ando et al. (2004) [49]</td>
<td>15/17 (88)</td>
<td>10 (67)</td>
<td>24</td>
</tr>
<tr>
<td>Nomura et al. (2004) [50]</td>
<td>12/28 (43)</td>
<td>15 (54)</td>
<td>NR</td>
</tr>
<tr>
<td>Veneri et al. (2005) [54]</td>
<td>41/43 (95)</td>
<td>21 (51)</td>
<td>31.2</td>
</tr>
<tr>
<td>Inaba et al. (2005) [52]</td>
<td>25/25 (100)</td>
<td>11 (44)</td>
<td>6(^d)</td>
</tr>
<tr>
<td>Stasi et al. (2005) [53]</td>
<td>52/52 (100)</td>
<td>11 (21)</td>
<td>25</td>
</tr>
<tr>
<td>Suvađzic et al. (2006) [55]</td>
<td>23/30 (77)</td>
<td>6 (26)</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>357/413 (86)</td>
<td>164 (46)</td>
<td></td>
</tr>
<tr>
<td><strong>Retrospective studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fujimura et al. (2005) [56]</td>
<td>161/207 (78)</td>
<td>101 (63)</td>
<td>12(^e)</td>
</tr>
<tr>
<td><strong>Phase III trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suzuki et al. (2005) [38]</td>
<td>11/13 (85)</td>
<td>6 (55)</td>
<td>6</td>
</tr>
</tbody>
</table>

H. pylori

- 75 patients with ITP form a single center
  - 60 month follow-up
  - December 1999-2004
  - H. pylori diagnosed by $^{13}$C urea breath test or histological examination if available
  - Eradication consisted of Amoxicillin 1000mg BID, Clarithromycin 250mg TID, proton pump inhibitor 20-40mg BID for 1 week

### $H$ pylori infection and ITP:

<table>
<thead>
<tr>
<th>Time</th>
<th>No. of patients</th>
<th>Eradicated, no. (%)</th>
<th>Responders, no. (%)</th>
<th>CR/PR/NR, no.</th>
<th>Median follow-up, mo (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>30</td>
<td>12 (92)</td>
<td>*</td>
<td>4/2/6</td>
<td>81</td>
</tr>
<tr>
<td>2002</td>
<td>7</td>
<td>3 (100)</td>
<td>2 (66)</td>
<td>2/0/1</td>
<td>67</td>
</tr>
<tr>
<td>2004</td>
<td>38</td>
<td>19 (86)</td>
<td>15 (79)</td>
<td>10/5/5</td>
<td>32 (18-46)</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>34 (89)</td>
<td>23 (68)</td>
<td>16/7/12</td>
<td>60 (18-90)</td>
</tr>
</tbody>
</table>

Of those with platelet counts less than $30 \times 10^9$ response rate was 71%

Responses usually occurred within two weeks

H. pylori - Conclusions

• Response rates to eradication is high in Japan and Italy and lower in other countries
  – Likely due to variability in H. pylori strains

• Diagnosis should be made by breath test or stool antigen test

• Due to noninvasive work-up and treatment the detection and eradication of H. pylori should be considered in the initial work-up of ITP

What is the role of the thrombopoietin agonists in trial?
ITP: production

• Mid 1990’s
  – rHuMGDF - recombinant human megakaryocyte growth and development factor
  
  – rhTPO - full-length recombinant human thrombopoietin
  
  – Effective in post chemotherapy induced thrombocytopenia
ITP production

Development halted secondary to severe thrombocytopenia due to the presence of neutralizing antibodies cross-reacting with native thrombopoietin
Novel molecules

- Thrombopoietin receptor (c-mpl) agonists
  - Same avidity as native thrombopoietin
  - Share no sequence homology with native thrombopoietin

- AMG-531-peptibody administered once weekly SQ

- Eltrombopag - small molecule taken orally
Shown are three classes of pharmaceuticals that share little homology to thrombopoietin (TPO), yet still activate the TPO-receptor (TPO-R).

AMG 531
Eltrombopag
Inclusion required a mean platelet count (the mean value of two counts) of less than $30 \times 10^9$ (with no count $>35 \times 10^9$) for patients not receiving corticosteroids or a mean count of less than $50 \times 10^9$ (with no count $>55 \times 10^9$) for patients receiving corticosteroids. Patients were eligible for enrollment regardless of whether they had undergone splenectomy.
Peak Platelet Counts in Phase 2

No major AE (mild – moderate HA)
Target platelet count in 10/16 patients

Other AMG 531 studies American Society of Hematology Meeting 2007

- Splenectomized patients, Phase III, randomized double blind
  - Overall response 79% vs. 0%
  - 38% vs. 0% achieved a durable platelet response

- Non-splenectomized patients Phase III, randomized double blind
  - 88% vs. 14% overall response
  - 61% vs. 4% durable platelet response

- Long term dosing
  - 82% achieved a platelet count $>50 \times 10^9$ and a doubling of the prior count
  - Median 2 weeks to first response

Eltrombopag

- Multicenter Randomized placebo controlled trial comparing various doses to placebo
  - platelet counts $<30 \times 10^9$
  - At least one prior therapy
Analyses of Platelet Counts Responses and Bleeding

A Platelet Count ≥ 50,000/mm³

D Eltrombopag, 75 mg

EXTENDED Eltrombopag

- Ongoing open label extension trial
- Titrated to minimally effective dose
- Baseline 44% with platelet $<15 \times 10^9$
- 46% were splenectomized

- 73% RR in those with entering platelet count less than $30 \times 10^9$
Conclusions

• New ideas about the pathophysiology of ITP
  – Destruction and production

• Additional treatment approaches
  – No treatment
  – Pulse dexamethasone
  – H.pylori
  – Rituximab
  – Laparoscopic approaches to splenectomy

• Novel treatment approaches soon on the horizon
  – Thrombopoietin analogues
  – ?? New ASH guidelines
How should I treat refractory disease?
Refractory Disease

• Definitions
  – Failure to sustain a response to steroids or splenectomy in a patient still requiring therapy
    • Either due to bleeding
    • Severe thrombocytopenia
      – $<10^{-20}\times10^9$
  • Represents fewer than 10% of patients diagnosed with ITP

Godeau Curr Opin Hematol 2007;14:535-56
Problems

• Lack of data
  – No randomized trials
  – No studies comparing one treatment to another
  – No studies comparing treatment to no treatment
  – Very heterogeneous patient populations
  – The majority of reports are not in the most severe thrombocytopenic patients
    • i.e. <10x10⁹
  – Data on an individual drug often comes from the same institution or group of authors
  – Most meaningful endpoints (i.e. bleeding) often not reported

Refractory Disease-Conclusions

• Strongly consider risk benefit ratio of any treatment

• Rituximab probably has the best benefit/toxicity ratio of any drug in the refractory setting

• No data to choose one cytotoxic or immunosuppressive agent over another
  – I prefer danazol, immuran as initial drugs

• Thrombopoietin agonists will be available in the near future