THE OLD AND THE NEW OF ITP

Alison Street
Malaysia April 2010
Malaysia

PROFILE

OFFICIAL NAME:
Malaysia

Geography
Area: 329,748 sq. km. (127,315 sq. mi.); slightly larger than New Mexico.
Terrain: Coastal plains and interior, jungle-covered mountains. The South China Sea separates peninsular Malaysia from East Malaysia on Borneo.
Climate: Tropical.
The Harrington-Hollingsworth Experiment

Harrington et al.
Demonstration of a thrombocytopenic factor in the blood of patients with thrombocytopenic purpura.
Immune Thrombocytopenic Purpura
The Problem, (dependent on definition and population)

Schoonen et al. BJH. 2009; 145: 235-244
Acute symptomatic thrombocytopenia

- Single episode
- Recurrent acute severe episodes

Chronic asymptomatic thrombocytopenia

- Steroids
- IVIG

Chronic thrombocytopenia

- ‘refractory’ ITP
Therapeutic goal

1. Prevent life-threatening bleeding

2. Avoid bleeding-related symptoms

Absolute count required is unknown
The Bleeding Risk and Natural History of Idiopathic Thrombocytopenic Purpura in Patients With Persistent Low Platelet Counts

- Meta analysis 17 trials
- A serious illness in patients with refractory PLT counts <30x10⁹/l
- Predicted 5 year mortality range 2.2% to 47.8%
- Fatality rate and serious bleeding incidence increases with age
<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Risk of fatal bleed per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>0.4%</td>
</tr>
<tr>
<td>40-60</td>
<td>1.2%</td>
</tr>
<tr>
<td>&gt;60</td>
<td>13%</td>
</tr>
</tbody>
</table>

- Treatment only given if PLT < 30 x 10⁹/l
- 1 death and 8 patients with serious haemorrhage (3%)
- Median PLT count 10 x10⁹/l
- Not such “alarming” data, suggesting it is safe to only treat “very low” counts

Table 1. Patients characteristics.

<table>
<thead>
<tr>
<th>Patients</th>
<th>No.</th>
<th>%</th>
<th>median age</th>
<th>range</th>
<th>median plt*</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>asymptomatic</td>
<td>148</td>
<td>48</td>
<td>39.5</td>
<td>8-86</td>
<td>42.5</td>
<td>1-138</td>
</tr>
<tr>
<td>minor bleeding</td>
<td>137</td>
<td>44</td>
<td>43.0</td>
<td>6-87</td>
<td>20.0</td>
<td>1-147</td>
</tr>
<tr>
<td>major bleeding</td>
<td>25</td>
<td>8</td>
<td>29.0</td>
<td>9-23</td>
<td>10.0</td>
<td>2-47</td>
</tr>
</tbody>
</table>

Follow-up (months), median (range) 121 (7-434)

2 patients with follow-up < 12 months
153 patients with follow-up >120 months
15 patients were lost to follow-up

*platelet count (x10⁹/L)
Definition of Refractory ITP by an International Working Party

“Refractory” thrombocytopenia is persistent & severe (<20 x 10⁹/l)

1. With a continuing requirement for therapy to increase PLT count and
2. Failure to respond to splenectomy, if attempted

What does the literature inform us about the fate of patients with PLT 20 - 50 x $10^9$/l?

- It is rare to die with PLT > 20 x$10^9$/l
- But what is the risk over an entire lifespan?
- How do we best manage acute & unexpected falls in PLT count, counselling life style choices, decisions on anticoagulation etc?
Diagnosis of ITP

Failure to respond to 1st line therapies: glucocorticoids, IVIG, IV Anti-D

Investigations for alternative/exacerbating causes of thrombocytopenia

Therapeutic options for persistent thrombocytopenia requiring treatment

Conventional therapies
- Splenectomy / accessory splenectomy
- Repeated IVIG or IV anti-D infusions
- Chronic low-dose corticosteroids

Emerging therapies
- Danazol
- Immunosuppressive therapy (azathioprine, mycophenolate mofetil, vinca alkaloids, cyclosporin A, dapsone)
- Cytotoxic chemotherapy (cyclophosphamide)
- Multi-agent therapy*
- Rituximab
- TPO-receptor agonists

Infections:
- Hepatitis C
- HIV
- H pylori
- CMV

Immunological disorders:
- SLE
- Evans Syndrome
- ALPS
- CVID

Other alternative diagnoses to consider
Inherited thrombocytopenias e.g. MYH9-RD
- MDS
- CLL
- PNH
- TTP

Advertorial for the “new”

Professor Gregory Cheng from Chinese University in Hong Kong is speaking this evening about

Meeting the challenges in the management of ITP
‘The thrombocytopenic factor’

- Cluster of IgG auto antibodies
- Directed to platelet-specific receptors such as CD41a (GPIIb/IIIa) and CD42b (GPIb) & other platelet antigens
- Antibodies arise from clonal B cells arising from specific antigenic stimulus
- Sensitized platelets rapidly cleared by the monocyte-macrophage cell system
Approaches to the Treatment of ITP
Approaches to treating ITP

- Several drugs used in the treatment of ITP impair the clearance of autoantibody-coated platelets by Fc(\(\gamma\)) receptors expressed on tissue macrophages. Splenectomy works partly by this mechanism but may also impair the interactions between T cells and B cells that are involved in the synthesis of antibody in some patients (1).
- Corticosteroids may also increase platelet production by impairing the ability of macrophages within the bone marrow to destroy platelets, and thrombopoietin and thrombopoietic agents stimulate megakaryocyte progenitors (2).
- Many non-specific immunosuppressive agents, such as azathioprine and cyclosporine, act at the level of the T cell (3).
- A monoclonal antibody against CD154 that is under clinical investigation targets a co stimulatory molecule needed for the optimization of T-cell-macrophage and T-cell-B-cell interactions involved in antibody production (4).
- Intravenous immune globulin may contain antiidiotypic antibodies that decrease autoantibody production. A monoclonal antibody that recognizes CD20 expressed on B cells causes their depletion (5).
- Plasmapheresis transiently removes autoantibody from the plasma (6)
- Platelet transfusions may be required (7)
- Adapted from Cines and Blanchette.2
An evolving story of germs, antibodies and peptides

1. ‘germs’
   • H. pylori
   • CMV

2. ‘antibodies’
   • anti CD20 moAb rituximab
   • anti CD154 (CD40 ligand)

3. ‘peptides’ - thrombopoietin analogues
Regression of autoimmune thrombocytopenia after eradication of *Helicobacter pylori*

Gasbarrini et. al. Lancet 1998; 352:878

18 pts with ITP (PLT autoAbs + thrombocytopenia)

11 pts $^{13}$C urea breath test positive

Eradication successful in 8/11

6/8 autoAbs disappeared

Treatment with steroids when PLT < 100 x 10^9/l

Platelet count in patients with autoimmune thrombocytopenia

Data are mean (SD). *p<0.05 compared with initial count.
Effects of eradication of *Helicobacter pylori* infection in patients with immune thrombocytopenic purpura: a systematic review

Stasi et al, Blood 2009. 113(6), 1231-40.
Table 1. Design of studies included in the systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Type of data reported for <em>H. pylori</em>-positive patients</th>
<th>No. of ITP patients</th>
<th>Diagnostic tests for <em>H. pylori</em> infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gasbarrini et al (1998)</td>
<td>Italy</td>
<td>Observational, case series, single center</td>
<td>Group</td>
<td>18</td>
<td>UBT</td>
</tr>
<tr>
<td>Jarque et al (2001)</td>
<td>Spain</td>
<td>Observational, case series, single center</td>
<td>Group</td>
<td>56</td>
<td>UBT</td>
</tr>
<tr>
<td>Kohda et al (2002)</td>
<td>Japan</td>
<td>Observational, case series, single center</td>
<td>Group</td>
<td>40</td>
<td>UBT/RUT/His/Ab</td>
</tr>
<tr>
<td>Hino et al (2003)</td>
<td>Japan</td>
<td>Observational, case series, single center</td>
<td>Individual</td>
<td>30</td>
<td>UBT/Ab</td>
</tr>
<tr>
<td>Venori et al (2005)</td>
<td>Italy</td>
<td>Observational, case series, single center</td>
<td>Group</td>
<td>52</td>
<td>UBT</td>
</tr>
<tr>
<td>Inaba et al (2005)</td>
<td>Japan</td>
<td>Observational, case series, multicenter</td>
<td>Group</td>
<td>35</td>
<td>UBT/Ab</td>
</tr>
<tr>
<td>Stasi et al (2005)</td>
<td>Italy-United Kingdom</td>
<td>Observational, case series, multicenter</td>
<td>Group and individual</td>
<td>137</td>
<td>UBT</td>
</tr>
<tr>
<td>Fujimura et al (2005)</td>
<td>Japan</td>
<td>Retrospective, case series, multicenter</td>
<td>Group</td>
<td>435</td>
<td>UBT</td>
</tr>
<tr>
<td>Suzuki et al (2005)</td>
<td>Japan</td>
<td>Randomized, phase 3, single center</td>
<td>Group</td>
<td>36</td>
<td>UBT/His</td>
</tr>
<tr>
<td>Suvajdić et al (2006)</td>
<td>Serbia</td>
<td>Observational, case series, single center</td>
<td>Group</td>
<td>54</td>
<td>UBT</td>
</tr>
<tr>
<td>Sayan et al (2006)</td>
<td>Turkey</td>
<td>Observational, case series, single center</td>
<td>Individual</td>
<td>34</td>
<td>UBT</td>
</tr>
<tr>
<td>Campuzano-Mayo (2007)</td>
<td>Colombia</td>
<td>Retrospective, case series, single center</td>
<td>Group</td>
<td>32</td>
<td>UBT</td>
</tr>
<tr>
<td>Satake et al (2007)</td>
<td>Japan</td>
<td>Observational, case series, single center</td>
<td>Group</td>
<td>38</td>
<td>UBT or RUT</td>
</tr>
<tr>
<td>Emilia et al (2007)</td>
<td>Italy</td>
<td>Observational, case series, single center</td>
<td>Individual</td>
<td>75</td>
<td>UBT ± His</td>
</tr>
</tbody>
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1555 patients, 25 studies
Response rates to H. pylori eradication

Ahn et al (2006) - USA
Jarque et al. (2001) - Spain
Estrada-Gomez (2007) - Mexico
Suvajdzic et al. (2006) - Serbia
Suzuki et al (2005) - Japan
Michel et al. (2004) - USA
Stasi et al. (2005) - Italy/UK
Inaba et al (2005) - Japan
Hino et al. (2003) - Japan
Takahashi et al. (2004) - Japan
Fujimura et al. (2005) - Japan
Sato et al. (2004) - Japan
Yeneri et al. (2005) - Italy
Satake (2007) - Japan
Ando et al. (2003) - Japan
Sayan et al. (2006) - Turkey
Kodama et al (2007) - Japan
Asahi et al (2006) - Japan
Kohda et al. (2002) - Japan
Ando et al. (2004) - Japan
Hashino et al. (2003) - Japan
Emilia et al. (2007) - Italy
Campuzeno-Mayo (2007) - Colombia
Nomura et al. (2004) - Japan

Pooled Response Rate = 50.3% (41.6% to 59.0%)
Platelet response to therapy  
\( n=696 \)

<table>
<thead>
<tr>
<th></th>
<th>Complete response &gt;100</th>
<th>Overall response &gt; 30 and “doubled”</th>
</tr>
</thead>
<tbody>
<tr>
<td>All comers</td>
<td>42.7%</td>
<td>50.3%</td>
</tr>
<tr>
<td>PLT &lt;30</td>
<td>20.1%</td>
<td>35.2%</td>
</tr>
<tr>
<td>Japanese studies</td>
<td>43.5%</td>
<td>57.9%</td>
</tr>
<tr>
<td>Other countries</td>
<td>27.3%</td>
<td>38.3%</td>
</tr>
</tbody>
</table>
Limitations of study

• Studies nearly all retrospective and observational
• Durability of responses not studied
• Many patients had concomitant therapies
• Background incidence of H. pylori varies between populations and role in pathogenesis of ITP not well established
• Should we screen and treat??
The role of routine H.pylori testing and eradication?

**COST**

- Cost of $^{13}$C breath test <US$100-200
- Cost of 2 weeks course for antibiotics (plus Bismuth)

**BENEFIT**

- Save on expensive drugs
  - IVIG US$2500 -70g
  - Rituximab US$12000
  - ?splenectomy
- Low toxicity of therapy
Response to B-cell depleting therapy with rituximab reverts the abnormalities of T-cell subsets in patients with idiopathic thrombocytopenic purpura

Patients with active ITP showed:

- significantly higher Th1/Th2 and Tc1/Tc2 ratios
- increased expression of FasL
- higher $Bcl-2/Bax$ ratio
- oligoclonal expansion of T cells

...compared with both healthy controls and ITP patients in remission
Systematic Review: Efficacy and Safety of Rituximab for Adults with Idiopathic Thrombocytopenic Purpura

• 19 studies enrolled >5 patients with reported efficacy (n=313)
• 29 studies analysed for toxicity (n=306)
• Inconsistent definitions and duration of ITP
• Many other patients treated out of a clinical trial

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, x 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 (&gt;50)</td>
<td>62.5 (52.6–72.5)</td>
<td>19 (313)</td>
</tr>
<tr>
<td>Complete response (&gt;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>
A heterogeneous group

- 10 patients (3.7%) experienced severe or life-threatening events (grade 3 to 4)
- 9 patients died (2.9%)
- 4 x weekly infusions of 375 mg/m$^2$ “usual”
- nearly all patients had received corticosteroids..(current approach is to combine with dexamethasone ASH 2009)
- half had failed splenectomy
- most were refractory to multiple treatments before receiving rituximab
Conclusions

“The efficacy of rituximab compared with standard treatments for ITP cannot be determined.”

“We would caution against the indiscriminate use of this treatment.”

Thrombopoietin treatment in ITP

• ITP associated with suboptimal platelet production and reduced TPO levels NOT JUST increased destruction

• There was clear demonstration of efficacy in refractory ITP (PEG-rHuMGDF) (Nomura et al. Blood. 2002, 100; 728-730)

• BUT treatment was complicated by severe thrombocytopenia
Leading to the development of thrombopoietin receptor agonists

1. TPO peptide thrombopoietic agonists
   • romiplostim (Nplate, AMG-531)

2. Non-peptide TPO-R agonists
   • eltrombopag
Romiplostim

- Registered for treatment of chronic ITP
- The peptide has 4 binding sites to the MPL receptor
- It is given by weekly sc injection in a dose of 1-10 μg/kg titrated to PLT count
- Long-term therapy is required
Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP


142 US patients chronic ITP treated for mean 69 weeks

Ongoing, open-label, single arm study
Platelet responses (platelet count >50 x 10^9/L and double baseline) 87% of all patients.
Eltrombopag

- Oral agent taken daily
- Ongoing therapy required
Eltrombopag for the treatment of idiopathic thrombocytopenic purpura. Bussel et. al. NEJM 2007, 357; 2237-2247

- 118 patients
- Randomised 1:1:1:1:1 (placebo, 30mg, 50mg, 75mg)
- 6 weeks of therapy only
Splenicectomy – “out of fashion”

- Previous decades rate 50-60%
- Now only 20-25% in UK, Europe
- Physician reluctance
- Continuing risks of procedural (and post) mortality & morbidity, even with laparoscopic techniques
- Enthusiasm among physicians for ‘medical’ therapies with perceived less risk
Splenectomy - the ‘gold standard’

- Review of 135 case series, 1966-2004
- Complete response: 1731 (66%) of 2623 adult patients
- Follow-up: 1-153 months
- None of 12 preoperative characteristics that have been reported consistently predicted response to splenectomy

Points to ponder, perhaps provocative

<table>
<thead>
<tr>
<th></th>
<th>complete response</th>
<th>response duration</th>
<th>mortality</th>
<th>morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>62.5%</td>
<td>Median response 10.5 mths</td>
<td>(2.9%)</td>
<td>3.7%</td>
</tr>
<tr>
<td>laparoscopic splenectomy</td>
<td>66%</td>
<td>5yr 64%</td>
<td>0.2%</td>
<td>9.6%</td>
</tr>
</tbody>
</table>
New Options

An appetiser to tonight’s talk!
In the adult presenting with ITP in 2010, we can offer **steroids**, followed by

- Splenectomy or
- Rituximab/dexamethasone or
- TPO mimetics
And many new references

A series of web based monographs on ITP produced as a CPD program through HematologyTimes.com

Most recent (5th) release is about Thrombopoietin receptor agonists for ITP

Supported by grants from GSK
Please attend Professor Cheng’s much more comprehensive talk tonight

Grateful acknowledgements to Dr Susan Morgan who is developing our Unit protocols for testing and managing ITP

THANK YOU
CMV, is it a treatable cause of ITP?

- 16 of 19 patients with positive results responded to ganciclovir
- 4 of 27 non-infected CFU-MK responded…..
CMV, further reports?

Levy & Bussel

Subsequent report of 4 patients responding to CMV therapy (abstract only)
“Indefinite but interesting”

- 108 pts presenting with ITP to New York Presbyterian Hospital
- Urine shell-vial testing for CMV
- 11% of 28 pediatric pts +ve
- 3% of 80 adult pts +ve
- No definitive link
- No therapy given
Rationale for anti CD 154 treatment

- PLT derived CD154 increased in ITP patients
- Ongoing interaction between T cells and B cells through CD40-CD40L (CD154) is necessary to maintain active platelet autoimmunity. It has been recently reported that platelets themselves express CD154 and may thus play a more active role in the autoimmune process than simply bearing antigens and accepting a fate of destruction.
Anti CD154