Chronic Leukemia Review and Update 2013

Todd Kliewer, MD
Optim Oncology
Leukemia

- A myeloproliferative malignancy arising from the bone marrow. Cells exhibit both rapid clonal division and biologic immortality. Can arise from any cell lineage; however, most typically, white cell precursors are considered.
Leukemia

- Classified as “acute” or “chronic”.
  - In acute leukemia, immature defective “blast” cells rapidly proliferate leading to fairly quick demise via multi-organ failure.
  - In chronic leukemia, some “blast” cells are present; however, there is less rapid cell division and cell maturation can occur. Death typically occurred due to the eventual accumulation of genetic abnormalities leading to a drug resistant acute leukemia – “blast” crisis or Richter’s transformation.

- Thereafter, classified as “lymphocytic” or “myelogenous” based upon cell lineage.
  - Lymphocytic – characterized by a progressive accumulation of functionally incompetent monoclonal lymphocytes.
    - Considered identical to the mature B cell small lymphocytic lymphoma.
  - Myelogenous – uncontrolled production of mature and maturing granulocytes, predominately neutrophils, but can include basophils and eosinophils.
Chronic Lymphocytic Leukemia
Chronic myeloid leukemia blood smear

Characteristic peripheral blood smear of chronic myeloid leukemia shows basophilia and granulocytosis with neutrophils and immature granulocytes.

Chronic Leukemia

• Chronic leukemias typically have a “biphasic” or “triphase” course.
  – “Chronic” phase during which patients may have some symptoms and exhibit lymphocytosis/granulocytosis. Majority of patients are within this phase of disease, and, this phase can last years.
  – “Accelerated” phase during which cell differentiation becomes progressively impaired and leukocyte counts are more difficult to control with therapy.
  – Acute leukemic phase with uncontrolled blast proliferation: “blast crisis” or “Richter’s transformation”.

Chronic Leukemia: Clinical Findings

- Vary and depend upon the stage of disease.
  - 20 – 50% are asymptomatic, and, the disease is determined via routine CBC evaluation.
  - Constitutional symptoms include fatigue (~35%) and weight loss (~20%).
  - Abdominal fullness and early satiety can be due to splenomegaly.
  - Arthritis can worsen due to marrow expansion or over production of uric acid.
  - Worsened or more frequent infections can occur due to incompetent leukocytosis.
  - Anemia can worsen fatigue and lead to dyspnea.
  - Thrombocytopenia can lead to bruising or bleeding.
Common symptoms of Leukemia

Systemic
- Weight loss
- Fever
- Frequent infections

Psychological
- Fatigue
- Loss of appetite

Lungs
- Easy shortness of breath

Lymph nodes
- Swelling

Spleen and/or liver
- Enlargement

Muscular
- Weakness

Skin
- Night sweats
- Easy bleeding and bruising
- Purplish patches or spots

Bones or joints
- Pain or tenderness
Chronic Myelogenous Leukemia
NCI SEER Data

• 15% of all adult leukemias.
• Median age is 67 years; however, it occurs in all age groups.
  – 20.5% of individuals diagnosed between 75 and 84 years.
• Lifetime risk is 0.17% or 1 in 572 individuals; and, age-adjusted incidence is 1.6 per 100,000.
• It is a little more common in Caucasian men.
• In 2013, an estimated 5,920 cases will be diagnosed in United States with 610 deaths.
• When one reviews disease mortality over the last 40 years, there was an extremely significant decrease in mortality between 1997-2005 corresponding to the release and widespread usage of Imatinib (GLEEVEC) and other tyrosine kinase inhibitors.
• If untreated, the disease typically progresses to accelerated phase within 3-5 years.
Chronic Myelogenous Leukemia

• Typically associated with the fusion of two genes: \( BCR \) (on chromosome 22, region q11) and \( ABL1 \) (on chromosome 9, region q34) resulting in the \( BCR-ABL1 \) fusion gene (t(9;22) translocation) or the Philadelphia (Ph) chromosome. This gene increases cell proliferation, affects differentiation, and, blocks apoptosis in three ways.
  
  – The ABL protein becomes active as a tyrosine kinase enzyme.
  – The DNA protein binding activity of ABL is attenuated.
  – The binding of ABL to cytoskeletal actin microfilaments is enhanced.

• Determination of the Philadelphia chromosome
  
  – Cytogenetics or karyotyping – actual chromosome evaluation
  – Fluorescent in situ hybridization (FISH)
  – Quantitative RT-PCR
The Philadelphia chromosome in chronic myeloid leukemia

G-band ideograms (left) and partial karyotype (right) of the CML-associated chromosome translocation t(9;22)(q34;q11.2). Breakpoints are indicated with arrows on the normal chromosome homologs. Translocated segments are framed on the der(9) and Ph ideograms. The translocation results in a slightly longer chromosome 9 [der(9)] and a shorter chromosome 22 [der(22)], which is termed the Philadelphia (Ph) chromosome.

Courtesy of Athena Cherry, PhD.
t(9;22)(q34;q11) Translocation
# Prognostic scoring systems for newly diagnosed chronic myeloid leukemia*

<table>
<thead>
<tr>
<th>Scoring system</th>
<th>Variables</th>
<th>Equation for relative risk of progression</th>
<th>Calculator</th>
<th>Risk groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUTOS score[1]</td>
<td>Percentage basophils*</td>
<td>Relative risk calculated as $7 \times (\text{basophils}) + 4 \times (\text{spleen size})$</td>
<td>A EUTOS score calculator is available online at: <a href="http://www.leukemia-net.org/content/leukemias/cml/eutos_score/">http://www.leukemia-net.org/content/leukemias/cml/eutos_score/</a></td>
<td>Low risk: sum ≤ 87; High risk: &gt; 87</td>
</tr>
<tr>
<td>Euro (Hasford) score[2]</td>
<td>Spleen size*: 0.012(spleen in cm below costal margin) Percentage blasts*: 0.0684 (myeloblasts) Age: 0.666 when age ≥ 50 years Platelet count: 1.0956 when ≥ 1500 x 10^9/L Percentage eosinophils*: 0.0413 (eosinophils) Percentage basophils*: 0.20399 when basophils ≥ 3 percent</td>
<td>Relative risk calculated as the total obtained from the variables adjusted by weight and then multiplied by 1000.</td>
<td>A Euro score calculator is available online at: <a href="http://www.leukemia-net.org/content/leukemias/cml/cml_score/">http://www.leukemia-net.org/content/leukemias/cml/cml_score/</a></td>
<td>Low risk: score ≤ 780; Intermediate risk: score &gt; 780 and ≤ 1480; High risk: score &gt; 1480</td>
</tr>
<tr>
<td>Sokal score[3]</td>
<td>Spleen size*: 0.0345(spleen - 7.51 cm) Percentage blasts*: 0.087 (myeloblasts - 2.10) Age: 0.110(age - 43.4 years) Platelet count: 0.116 ([platelets/700]^2 - 0.563)</td>
<td>Relative risk calculated as the exponential of the total obtained from the variables adjusted by weight. $\Lambda(r) = \exp(0.0115(\text{age} - 43.4) + 0.0345(\text{spleen} - 7.51) + 0.087([\text{platelets}/700]^2 - 0.563) + 0.0287(\text{blasts} - 2.10))$</td>
<td></td>
<td>Low risk: relative risk &lt; 0.8; Intermediate risk: relative risk 0.8 to 1.2; High risk: relative risk &gt; 1.2</td>
</tr>
</tbody>
</table>

* These scoring systems were designed for patients with newly diagnosed CML who have not yet received any treatment, including hydroxyurea. In addition, the EUTOS score was specifically designed to predict outcomes among patients undergoing initial treatment with imatinib.*

* Percentage blasts, basophils, and eosinophils are measured from peripheral blood.

* Spleen size as assessed by physical examination.

**References**
CML Treatment Objectives and Options

• Potential cure with allogeneic hematopoietic cell transplantation
• Disease control with tyrosine kinase inhibitors (TKI’s)
• Palliative therapy with cytotoxic agents
CML Treatment

- Allogeneic Hematopoietic Stem Cell Transplant
  - Potentially curative; however, therapeutic use has diminished over time.
    - Excellent responses to TKI’s.
    - Limited donor availability.
    - Toxicity of therapy in patients over 65 years.
  - Improvement in outcomes with unrelated, fully matched donors due to improvements in HLA typing.
  - Investigations into non-myeloablative reduced-intensity conditioning to produce graft-versus-leukemia effect without the toxicity of myeloablative regimens.
CML Treatment: Tyrosine Kinase Inhibitors (TKIs)

- Prevents tyrosine kinase, in this case BCR-ABL, from phosphorylating proteins necessary for unrestricted cell division and for aversion of apoptosis.
- Imatinib introduced in May 2001 followed by dasatinib, nilotinib, bosutinib (Bosulif), and ponatinib (Iclusig).
  - 8 year IRIS trial follow up: Continuous treatment with imatinib induces high durable responses with decreased rates of relapse.
  - Data from randomized trials demonstrate superior cytogenetic and molecular response rates and lower rates of disease progression with dasatinib and nilotinib.
- Bosutinib approved September 2011.
- Ponatinib approved December 2012 for resistant or intolerant CML and Ph+ ALL.
CML Treatment

• First-Line Therapy
  – NCCN guidelines recommend imatinib (Gleevec), nilotinib (Tasigna), or dasatinib (Sprycel).
  – Choice often determined by side effect profile and reported improved efficacy of newer agents.
  – At least for now, molecular sub-typing of BCR-ABL is not recommended.
CML Treatment

• TKI goals of therapy:
  – Complete hematological response by 3 to 6 months
    • Normalization of peripheral blood counts
  – Any cytogenetic response by 6 months
    • Decrease in RT-PCR detectable Ph-positive metaphases
  – Major cytogenetic response by 12 months
    • 0-35% Ph-positive metaphases
  – Complete cytogenetic response by 18 months
    • No Ph-positive metaphases detected
Sub-typing of BCR-ABL mutation

– Determination of the BCR-ABL mutation status
  • In patients in accelerated phase or blast crisis
  • In cases of first-line failure
  • In cases of increased BCR-ABL transcript leading to loss of major molecular response (>= 3-log reduction in BCR-ABL mRNA)
  • In any other case of suboptimal response
  • Failure of second-line therapy
Flow chart summarizing when mutation analysis is recommended in CML patients treated with imatinib first-line.

Soverini S et al. Blood 2011;118:1208-1215
NCCN Guidelines Version 4.2013 Chronic Myelogenous Leukemia

TREATMENT OPTIONS BASED ON BCR-ABL KD MUTATION STATUS1,2,3

- Mutation T315L
  - Treatment Options ponatinib, or omacetaxine, HSCT, or clinical trial
  - V299L T315A
  - Consider ponatinib or nilotinib or omacetaxine4
  - F317L/V/I/C
    - Consider ponatinib, nilotinib, or bosutinib, or omacetaxine 4
    - Y253H, E255K/V, F359V/C/I
    - Consider ponatinib, dasatinib, or bosutinib, or omacetaxine 4
  - Any other mutation
  - Consider ponatinib, high dose imatinib,6 dasatinib, nilotinib, bosutinib, or omacetaxine4

4 Omacetaxine is a treatment option for patients with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKIs).
5 If mutation detected following dasatinib.
6 There are not sufficient data on dose escalation available to indicate if mutations with lower IC50 values are sensitive to high dose imatinib.

Note: All recommendations are category 2A unless otherwise indicated.
Determination of Response

• Assess medication compliance and toxicities
• 3 month interval QPCR evaluation of bone marrow or blood
  – NCCN: Strong correlation between the results from the peripheral blood and bone marrow, allowing molecular monitoring without the necessity of bone marrow aspirations.

• Achievement of a major molecular response is associated with durable long-term remission and lower rates of disease progression.
  – 5 year IRIS data showed no patient with CCyR or MMR at 12 months progressing to accelerated or blast phase.
Main TKI Toxicities

- Fluid retention
- Rash
- GI upset including diarrhea and nausea
- Hepatotoxicity
- Pancytopenia
- Headache
• Imatinib
  – Arthralgias and muscle cramps
    • Hypophosphatemia

• Nilotinib
  – Prolongation of the QT interval
    • Avoid with hypokalemia, hypomagnesemia, or long QT syndrome
    • Avoid other medications that prolong QT interval and CYP3A4 inhibitors
    • Serial ECGs should be monitored
  – Rare peripheral arterial occlusive disease
TKI Toxicities

• Dasatinib
  – Rare pulmonary arterial hypertension

• Bosutinib
  – Liver toxicity and severe diarrhea

• Ponatinib
  – Pancreatitis
  – Arterial thrombosis including MI and stroke
  – Venous thromboembolism
  – Left ventricular dysfunction and arrhythmias
  – Hemorrhage
  – Tumor lysis syndrome
Discontinuation of TKI Therapy

• STIM study
  – Patients with at least 2 yrs MMR on imatinib
    • At median of 2 yrs, 39% remained in CMR and 61% relapsed, most within 6 months.
    • Overall probability of maintaining CMR at 3 yrs was 39%, esp. for low risk patients.

• Australian CML8 trial with similar results
• No real data regarding dasatinib or nilotinib
• Recommendation: Only stop with clinical trial
Ponatinib

- Approved December 2012 for patients with resistant or intolerant CML and Ph+ ALL.
- Approved under FDA’s accelerated approval program therefore additional studies are required.
- Intended to target all mutations of BCR-ABL
- Has activity against the T315I mutation
Omacetaxine/homoharringtonine (Synribo)

- Approved October 2012 for patients with resistant or intolerant CML after 2 or more TKI’s.
- Alkaloid from *Cephalotaxus harringtonia*, the Japanese Plum Yew.
- Protein translation inhibitor that prevents ribosomes and amino acids from interacting.
- Subcutaneous injection – currently FDA mandates that it cannot be self-administered.
- Initially discovered over 40 years ago.
- Most common side effects are myelosuppression and diarrhea.
AND EVERYONE WILL HAVE HEALTH CARE AND IT WON'T REALLY COST ANYONE ANYTHING AND...

D.C. DISNEY WORLD...THE HAPPIEST PLACE ON EARTH
Cost of Therapy

• Doctors Denounce Cancer Drug Prices of $100,000 a year by Andrew Pollack, New York Times, April 25, 2013
  – “Gleevec entered the market in 2001 at a price of about $30,000 a year....Since then, the price has tripled”.
  – “Gleevec’s sales were $4.7 billion in 2012, making it Novartis’s best-selling drug.”
  – “Manufacturers of the drugs....say the prices reflect the value of the drug.”
  – The price of ponatinib is $115,000-$138,000/year
  – “In many developing nations,...experts were advocating risky bone marrow transplants because that is a one-time procedure that is cheaper”.
  – In the U.S., survival rates are less than expected because “costs are forcing patients to not take their medicine”.
  – Dr. Hagop Kantarjian, MDA – “Pharmaceutical companies have lost their moral sense. Prices are getting to the point where it is becoming unsustainable”.
Chronic Lymphocytic Leukemia

• 7% of newly diagnosed NHL and the most common adult leukemia in Western countries.
• In the U.S., 15680 new cases and 4580 deaths in 2013.
• Course extremely variable with survival times of 2 to 20 years.
• Most frequent causes of death include systemic infection, bleeding, and inanition with cachexia.
CLL Diagnosis

• Requires at least 5000 clonal B-cells/mcL in the peripheral blood.

• Flow cytometry of the peripheral blood.
  – Typical immunophenotype includes CD5+, CD10-, CD19+, CD20 dim, CD23+, and cyclin D1-.
    • CD23 and cyclin D1 essential to differentiate from mantle cell lymphoma.

• “Smudge” cells on peripheral smear
### Modified Rai clinical staging system for chronic lymphocytic leukemia

<table>
<thead>
<tr>
<th>Risk</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>Lymphocytosis in blood or bone marrow</td>
</tr>
<tr>
<td>Intermediate</td>
<td>I</td>
<td>Lymphocytosis + enlarged lymph nodes</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Lymphocytosis + enlarged liver or spleen with or without lymphadenopathy</td>
</tr>
<tr>
<td>High</td>
<td>III</td>
<td>Lymphocytosis + anemia (Hgb &lt;11 g/dL) with or without enlarged liver, spleen, or lymph inodes</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Lymphocytosis + thrombocytopenia (platelet count &lt;100,000/µL) with or without anemia or enlarged liver, spleen, or lymph nodes</td>
</tr>
</tbody>
</table>
Binet Staging System For Chronic Lymphocytic Leukemia

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Two or less lymphoid bearing areas enlarged*</td>
</tr>
<tr>
<td>B</td>
<td>Three or more lymphoid bearing areas enlarged*</td>
</tr>
<tr>
<td>C</td>
<td>Presence of anemia (Hgb &lt;10.0 g/dL) or thrombocytopenia (platelet count &lt;100,000/microL)</td>
</tr>
</tbody>
</table>

Staging and Prognosis

• Stage 0 - 25% of patients, median survival 150 months
• Stage I and II - 50% of patients, median survival 101 and 71 months respectively
• Stage III and IV - 25% of patients, median survival 19 months
Prognostic Factors

- IgVH (immunoglobulin variable heavy gene) mutation status
  - Unmutated status has shorter survival and higher risk of relapse

- ZAP-70 (zeta chain associated protein)
  - A tyrosine kinase typically found on T cells that, if found on CLL B cells, denotes poor prognosis

- CD38
  - Denotes adverse prognosis and may portend fludarabine resistance
Genetic Abnormalities

• Unfavorable
  – Del(17p) – strongest predictor of poor survival.
  – Del(11q) – extensive adenopathy, progressive disease, and shorter survival, particularly under age of 55.

• Neutral – Normal

• Favorable – del(13q) as a sole abnormality
### Prognostic features in chronic lymphocytic leukemia

<table>
<thead>
<tr>
<th>Good prognostic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Rai or Binet clinical stage</td>
</tr>
<tr>
<td>Interstitial or nodular pattern of lymphocyte infiltration in marrow</td>
</tr>
<tr>
<td>Lymphocyte doubling time &gt;12 months</td>
</tr>
<tr>
<td>CD 38 negativity</td>
</tr>
<tr>
<td>Mutated immunoglobulin Vh genes</td>
</tr>
<tr>
<td>ZAP-70 negativity (low levels)</td>
</tr>
<tr>
<td>Chromosome 13q14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Poor prognostic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Rai or Binet stages</td>
</tr>
<tr>
<td>Diffuse pattern of lymphocyte marrow infiltration</td>
</tr>
<tr>
<td>Lymphocyte doubling time &lt;12 months</td>
</tr>
<tr>
<td>CD 38 positivity</td>
</tr>
<tr>
<td>Unmutated immunoglobulin Vh genes</td>
</tr>
<tr>
<td>ZAP-70 positivity (high levels)</td>
</tr>
<tr>
<td>Del 11q23</td>
</tr>
<tr>
<td>17p-/p 53 abnormalities</td>
</tr>
<tr>
<td>p 53 dysfunction or increased expression</td>
</tr>
<tr>
<td>Increased levels of TNF-alpha, beta-2 microglobulin, IL-6, IL-8, IL-10, LDH, VEGFR-2, CD20, and CD52</td>
</tr>
</tbody>
</table>
CLL Therapy Indications

- Weakness, night sweats, weight loss, painful adenopathy, or fever
- Symptomatic anemia and/or thrombocytopenia
- Autoimmune hemolytic anemia and/or thrombocytopenia
- Progressive disease, typically manifesting as lymphocytosis with rapid doubling time and/or rapidly enlarging lymph nodes, spleen, or liver.
- Repeated bouts of infection due to hypogammaglobulinemia.
CLL Therapy

- Observation for early stage, low risk disease.
- Current debate regarding observation vs. therapy for early stage, high risk disease.
  - Clinical trials recommended
- No agreed upon “standard of care” regimen
CLL Therapy: Pretreatment

• Age and comorbid conditions should be considered.
• Remember HIV, hepatitis B and C testing especially if using monoclonal antibodies.
• Appropriate radiology if adenopathy suspected.
• Tumor lysis precautions in patients with renal disease, elevated uric acid, or high wbc.
CLL Therapy

- Patients over 70 years or younger patients with comorbidities
  - Chlorambucil, an oral mustard alklylating agent, and prednisone comparable to CHOP type regimens.
  - Fludarabine produced superior ORR, CR, and median time to treatment failure rates to chlorambucil; however, OS similar; and, it is more toxic.
  - Single agent rituximab has superior activity to chlorambucil; 51% ORR and 4% CR
  - ASCO 2013: Adding rituximab to chlorambucil significantly improved OR and CR with minimal increase in adverse event rate with rituximab.
CLL Therapy

- Age less than 70 without comorbidities
  - Fludarabine superior to chlorambucil. CR rates better than CHOP and felt to be better tolerated.
  - Fludarabine and cyclophosphamide superior to fludarabine regarding ORR, CR, and PFS; however, OS not different.
  - Fludarabine and rituximab prolongs PFS and OS; however, increased neutropenia and infusion-related events.
  - FCR with superior ORR, CR, and OS rates compared to FC; however, significantly higher neutropenia.
CLL Therapy

• Alemtuzumab (Campath)
  – First-line option in elderly patients; second-line in younger healthy patients
  – Recombinant humanized monoclonal antibody against CD52.
  – Aug/Sept 2012 withdrawn from market to prepare for relaunch under the name Lemtrada with a different dose for multiple sclerosis treatment.
  – Lancet, 10/31/12 – “the move would the company to adjust the price”. A full course of Campath costs about $60,000 when given 3x/wk for up to 12 weeks.
CLL Therapy

• Fludarabine (Fludara)
  – Purine analog that inhibits DNA synthesis
  – Significant toxicities
    • Severe bone marrow suppression that can last a long time.
    • MDS and secondary AML can occur.
    • Associated with autoimmune cytopenias including AIHA.
    • Can cause neurotoxicity and rarely progressive multifocal leukoencephalopathy.
    • Increased risk of infection
CLL Therapy

- **Bendamustine (Treanda)**
  - Alkylating agent synthesized in East Germany in 1963.
  - Lancet. 2013;381(9873);1203
  - Bendamustine plus rituximab compared to R-CHOP for newly diagnosed follicular lymphoma
    - Superior median progression-free survival and equivalent overall survival with less toxicity.
CLL Therapy

• Ibrutinib
  – Oral inhibitor of the enzyme Bruton tyrosine kinase
    • Thought to block cell signaling driving cells into apoptosis and/or disrupts cell migration and adherence to protective tumor microenvironments.
  – Well tolerated
    • Diarrhea, fatigue, and upper respiratory infections
  – May be beneficial in the aggressive del(17p) subset
  – Dramatic reduction in size of bulky lymph nodes and enlarged spleens with a simultaneous lymphocytosis that subsequently declined.
CLL Therapy

• Lenalidomide (Revlimid)
  – Use complicated by tumor flare and increased risk of opportunistic infections.
  – Recent phase III trial comparing lenalidomide to chlorambucil halted in July after an excess number of deaths in the lenalidomide arm. Cause of excess deaths has not been determined.
  – If used, prophylaxis for thromboembolism strongly considered.
CLL Therapy

• Splenectomy or splenic irradiation in patients with splenomegaly and cytopenias refractory to treatment.

• Leukapheresis if wbc exceeds 400,000 or there are hyperviscosity symptoms.

• Hematopoietic cell transplantation rare due to typical age of patient and relatively benign course of disease in most.
  
  – Investigational in young healthy patients with high-risk disease.
Supportive Care Measures

• Monitor for recurrent upper respiratory infections
  – Antibiotics and IVIG
• Anti-infective prophylaxis for patients receiving purine-analog and/or alemtuzumab
  – Herpes virus, CMV, HBV, and PCP
• Autoimmune Cytopenias
  – Fludarabine induced, ITP, and pure red cell aplasia
• Vaccinations
  – Annual influenza
  – Pneumococcal every 5 years
  – Avoid all live vaccines, including Zostavax
Supportive Care Measures

- Transfuse according to established standards
  - Irradiate all blood products to avoid transfusion-associated GVHD
- Tumor lysis precautions
- Tumor flare reactions in patients receiving lenalidomide
  - Painful adenopathy, splenomegaly, fever, or rash
- Thromboprophylaxis in patients receiving lenalidomide
  - Aspirin 81 mg daily if platelets above 50,000.
Then:

Doggone it, if it's good enough for the American people, then it's good enough for us!

Now:

It's not good enough for us!