Myeloproliferative Disorders: Diagnostic Enigmas, Therapeutic Dilemmas

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Case #1

- RM: 62 y.o. retired health-care executive presented in summer of 2008 with fatigue
- PE: splenomegaly
- CBC: H/H 15.3/46; MCV 83; WBC 18.9; 4% eos, 4% basos; platelet count 269,000; smear showed teardrop forms.....
- Following slides graciously supplied by Dr. Stephen Fisher at SNGH
Peripheral blood

- Neutrophilia and Monocytosis
- Basophilia
- Nucleated RBC
- Eosinophilia
- Teardrop
Peripheral blood magnified

teardrops
Bone marrow biopsy

Hypercellular marrow
Megakaryocytic hyperplasia
Increased Reticulin Fibrosis
Focal collagen fibrosis

Collagen = Blue staining Fine strands

Vessels = Internal control
Subsequent Work-Up

• Markedly reduced stainable iron in marrow
  – Recent EGD and colonoscopy negative for source of blood loss
• JAK-2 test +; BCR-ABL translocation -
• Flow cytometry on bone marrow aspirate:
  – Abnormal maturation pattern with CD13, CD10, CD15, and CD64 reflective of abnormal myeloid maturation
• Cytogenetics failed to reveal chromosomal deletion, duplication or translocation
Abdominal CT Scan

- Spleen 18 cm in greatest dimension; no liver abnormalities; no adenopathy
Clinical Follow-Up

- Over the course of the next few months H/H gradually rose to 17/51 and he underwent phlebotomy
- Remained fatigued and became depressed
Original Hematology Conclusion and Recommendation

- Patient told he had agnogenic myeloid metaplasia with myelofibrosis
- Recommendation: Start lenalidomide (Revlimid)
- Patient balked at cost of medication ($7000/mo) and paucity of evidence of efficacy and sought second opinion
Second Opinion

- Presented five weeks ago with above story
- Fatigued out of proportion to objective findings
- H/H back to 15/46 after phlebotomies
- Spleen still moderately enlarged
- Discussed with Dr. Fisher; diagnosis remains uncertain
Second Opinion, continued

• Told him I was uncertain of diagnosis but entire condition fit better with Polycythemia Vera with emerging fibrosis
• Recommended Hydroxyurea in tiny doses to control constitutional symptoms
• No full-blooded siblings to serve as potential bone-marrow (stem-cell) donors
• He is weighing options…felt better after second opinion consult even without starting HU
Case #2

- 66 y.o. lady referred for anemia
- H/H fell from 11.7/35 to 10.4/32 over 18 months
- Platelet count 500-600,000
- 40 pound weight loss
- Serum albumin fell to 2.9
- Serum ferritin elevated at 720
Case #2, continued

• No prior history of note – e.g., drugs or alcoholism
• Physical examination normal
• Concerned about occult malignancy: CT chest, abdomen, pelvis ordered…
Case, continued

- Based on CT findings concern for lymphoma heightened
- Bone Marrow Biopsy performed....
Bone Marrow aspirate
Bone Marrow, continued
Case, continued

- After marrow morphologic findings appreciated second marrow aspiration performed for FISH studies looking for myelodysplastic syndrome; and for complete cytogenetics
- Cytogenetics normal; FISH still pending
- Diagnosis remains in doubt; most compatible with refractory anemia with ringed sideroblasts
- Therapy an open question – few good options
- H/H not very low yet…would defer R-epo for now
Myeloproliferative Disorders

• Wide variety of blood conditions
• Characteristics
  – Disordered growth or maturation of myeloid cell lines
  – Can effect red-cell or platelet lines as well
  – Frequently associated with chromosomal abnormality
Interconnections of MPD’s

Chronic Myelogenous Leukemia

Polycythemia Vera

Myelofibrosis

Essential Thrombocythemia

Myelodysplastic Syndromes
- Refractory Anemia
- Refractory Anemia with Ringed Sideroblasts
- Refractory Anemia with Excess Blasts
- RAEB in transformation
- Chronic Myelomonocytic Leukemia
Interconnections in detail

Chronic Myelogenous Leukemia
-- Obligatory chromosomal translocation
9:22 (Philadelphia Chromosome) creating
BCR/ABL gene sequence

Essential Thrombocythemia
--Can be isolated event without gene
or chromosomal implications
--Can be associated with BCR/ABL
translocation (CML presenting as ↑
plts)
--Can be heralding finding in P.vera
Interconnections, continued

- Polycythemia
- Essential thrombocythemia
- Myelofibrosis
- Acute Myeloblastic Leukemia (as terminal event)
- Acute myelofibrosis
A word on acute myelofibrosis – similar to acute megakaryocytic leukemia

Hypercellular marrow with many atypical megakaryocytes
Primary Myelofibrosis: Also known as “Agnogenic Myeloid Metaplasia with Myelofibrosis”

H&E Stain

Trichrome stain
Primary Myelofibrosis

• Can occur *de novo* (Agnogenic Myeloid Metaplasia with Myelofibrosis)

• Can arise from
  – P. Vera
  – Essential thrombocythemia
  – All the myelodysplastic syndromes
Myelodysplastic Syndromes

- Refractory Anemia
- Refractory Anemia with Ringed Sideroblasts
- Refractory Anemia with Excess Blasts
- RAEB in Transformation
- Chronic Myelomonocytic Leukemia
MDS – Predictors of Outcome

• Cytogenetics
  – If normal, no transformation to acute leukemia
  – Progression to AML and short survival associated with cytogenetic abnormalities – the higher number of mutations the shorter the survival
### MDS – Other Predictors of Survival

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>RARS</th>
<th>RAEB</th>
<th>RAEB-T</th>
<th>CMML</th>
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<tbody>
<tr>
<td><strong>Proportion of Patients</strong></td>
<td>25</td>
<td>15</td>
<td>35</td>
<td>15</td>
<td>10</td>
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<tr>
<td>with MDS, %</td>
<td></td>
<td></td>
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<tr>
<td><strong>Median Survival,</strong></td>
<td>43</td>
<td>73</td>
<td>12</td>
<td>5</td>
<td>20</td>
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<tr>
<td>months</td>
<td></td>
<td></td>
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<tr>
<td><strong>Transformation to</strong></td>
<td>15</td>
<td>5</td>
<td>40</td>
<td>50</td>
<td>35</td>
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<tr>
<td>AML, %</td>
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## Risk Assessment

<table>
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<th>Variable</th>
<th>Score</th>
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<tr>
<td>B M Blasts (%)</td>
<td>0, 0.5, 1, 1.5, 2</td>
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<tr>
<td>Karyotype</td>
<td>Good, Intermed, Poor</td>
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<tr>
<td>Cytopenias</td>
<td>0/1, 2/3</td>
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### IPSS* Score

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<th>Risk Assessment</th>
<th>IPSS* Score</th>
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<tr>
<td>Low</td>
<td>0</td>
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<tr>
<td>Intermediate-1</td>
<td>0.5 - 1</td>
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<tr>
<td>Intermediate-2</td>
<td>1.5 - 2</td>
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<tr>
<td>High</td>
<td>2.5 - 3.5</td>
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*International Prognosis Scoring System*
IPSS Predicts Outcome in MDS
Complications of Diseases

- Transformation to Acute Leukemia
- Morbidity/Mortality from Bone-Marrow Failure (infection, bleeding, anemia)
- Constitutional Failure (?from hypometabolic effects of diseases)
Concepts of Therapy – Agreement Among Authorities

• Classic CML should be treated with targeted Tyrosine Kinase Inhibitor (Gleevec as first-line therapy)
• Red-cell and platelet elevations are associated with excess mortality from thrombotic complications – both should be lowered
• For diseases with high anticipated mortality allogeneic stem-cell transplantation may be considered if co-morbidities allow
Other Aspects of Treatment

• Hydroxyurea often successful in reducing platelet count and hypermetabolic effects of disease burden – can be used in very low doses in some circumstances

• Erythropoietic Stimulating Factors controversial – FDA approved for MDS but may increase likelihood of thrombosis; theoretical ↑mortality from epo receptors on malignant myeloid cells
Other Drugs in MDS

- Hypomethylating agents – azacytidine and decitabine
- Lenalidomide (Revlimid) for 5q- mutation
- Supportive Care – transfusions with leukopenic RBC’s if long-term support contemplated
- Iron chelation if long-term transfusions contemplated
- WBC stimulating agent in acute infectious crisis
Therapy, continued

• Disputed role: medium-high-dose chemotherapy (e.g., remission-induction therapy for AML) used if IPSS is high and patient can tolerate
  – Not universally agreed upon
  – More frequently used for RAEB or RAEB-T
  – Risk of short-term toxicity and death may be higher than that for AML itself treated with same drugs

• As with other aspects of MPD and MDS much difference of opinion exists
Summary

- Group of diseases diverse and overlapping syndromes exist
- Increased understanding of relation of genetic mutations to behavior and outcome
- Relative paucity of effective therapy except for classic CML
- Supportive care a challenge in patients with cytopenias and hypermetabolic state
- Ultimate survival multifactorial
- Still in search of magic bullet
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