Gender and MPNs
Developments and Considerations

Laura C. Michaelis, MD
Medical College of Wisconsin
2015 Joyce Niblack Memorial Conference on Myeloproliferative Neoplasms
Objectives

• Gender
  – Are there differences in these diseases between men and women?

• Select concerns facing female patients
  – Pregnancy
  – Thrombosis, Bleeding risks

• What’s next?
Incidence

• Is the occurrence of these diseases equally frequent in men and women?
## Hematologic diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Male:Female Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>1:1</td>
</tr>
<tr>
<td>ALL</td>
<td>1.3:1.0</td>
</tr>
<tr>
<td>HD</td>
<td>1.3:1.0</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>1.4:1</td>
</tr>
<tr>
<td>CLL</td>
<td>2:1</td>
</tr>
<tr>
<td>CML</td>
<td>3:2</td>
</tr>
<tr>
<td>ET</td>
<td>Female Predominance</td>
</tr>
<tr>
<td>PV</td>
<td>1.2:1.0</td>
</tr>
<tr>
<td>MF</td>
<td>1:1</td>
</tr>
<tr>
<td>N=11668 Insured individuals(^1)</td>
<td>Polycythemia Vera</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Female</td>
<td>35%</td>
</tr>
<tr>
<td>Male</td>
<td>65%</td>
</tr>
<tr>
<td>Average Age</td>
<td>53 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N=1425 MPN SAF(^3)</th>
<th>Polycythemia Vera</th>
<th>Essential Thrombocythemia</th>
<th>Myelofibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>46%</td>
<td>64%</td>
<td>47%</td>
</tr>
<tr>
<td>Male</td>
<td>54%</td>
<td>36%</td>
<td>53%</td>
</tr>
<tr>
<td>Average Age</td>
<td>62.8 years</td>
<td>60.7 years</td>
<td>63.5 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N=272 Johns Hopkins(^2)</th>
<th>Polycythemia Vera</th>
<th>Essential Thrombocythemia</th>
<th>Myelofibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>64%</td>
<td>70%</td>
<td>36%</td>
</tr>
<tr>
<td>Male</td>
<td>36%</td>
<td>30%</td>
<td>64%</td>
</tr>
<tr>
<td>Average Age</td>
<td>50/56 years</td>
<td>50/48 years</td>
<td>59/61 years</td>
</tr>
</tbody>
</table>

\(^1\)Mehta et al., Leuk Lymphoma 2014  
\(^2\)Stein et al., Haematologica 2010  
\(^3\)Emanuel et al., JCO 2012
Incidence of Disease by gender

• Polycythemia Vera
  – Historically studies have shown more frequent in men
  – Women are diagnosed at a younger age compared to men\(^1\)

• Essential thrombocythemia
  – Historically, a female predominance has been cited
  – Large recent study showed incidence the same\(^2\)

• Myelofibrosis
  – Likely a slight male predominance

\(^1\)Stein et al., Haematologica Jul 2010
\(^2\)Titmarsh et al., Am J Hem, March 2014
Cancer and Gender

Why would a disease occur more frequently in one sex vs. the other?
- Biology?
- Diagnostic bias?
- Genetic predisposition?
- Exposure?

Why might the disease behave differently in one sex vs. the other?
- Modulated hormones?
- Gender-based lifestyle differences?
- Stem-cell biology?

Are there different consequences to the disease or treatment that depend on gender?
Figure 1  Age adjusted mesothelioma incidence (cases per 100 000) by gender.
Cancer and Gender

Why would the disease occur more frequently in one sex vs. the other?

- Diagnostic bias?
- Exposure?
- Genetic predisposition?

Why might the disease behave differently in one sex vs. the other?

- Modulated hormones?
- Gender-based lifestyle differences?
- Stem-cell biology?

Are there different consequences to the disease or treatment that depend on gender?
Two Clinical Phenotypes in Polycythemia Vera

Jerry L. Spivak, M.D., Michael Considine, M.S., Donna M. Williams, Ph.D., Conover C. Talbot, Jr., B.A., Ophelia Rogers, A.A., Alison R. Moliterno, M.D., Chunfa Jie, Ph.D., and Michael F. Ochs, Ph.D.

ABSTRACT

BACKGROUND
Polycythemia vera is the ultimate phenotypic consequence of the V617F mutation in Janus kinase 2 (encoded by JAK2), but the extent to which this mutation influences the behavior of the involved CD34+ hematopoietic stem cells is unknown.

METHODS
We analyzed gene expression in CD34+ peripheral-blood cells from 19 patients with polycythemia vera, using oligonucleotide microarray technology after correcting for potential confounding by sex, since the phenotypic features of the disease differ between men and women.

RESULTS
Men with polycythemia vera had twice as many up-regulated or down-regulated genes as women.
Comparison of DNA gene expression

<table>
<thead>
<tr>
<th></th>
<th>Control Men (n=3)</th>
<th>Men with MPD (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Women (n=3)</td>
<td></td>
<td>Women with MPD (n=11)</td>
</tr>
</tbody>
</table>
What is “gene expression?”

Play Form Often Kitchen Banana Blue-Eyes Extra Blood Clots Dog Loves Hates Very Cats Animals Platelets Salads Sunshine Adores Children Tumble Develop Over Make Fibrosis More Blood Clots Don’t Bleed Too Much Clean Obsessively Have

Grow Tall Often Earlobes Liver Blood Clots Toes Loves Grey Hair Very Webbed Long Toes Innovates Develop Tolerates Rain Depression Red Kalidoscopes Develop Blonde Blood Clots Significant Enjoy Eating Stay Quiet Fight Horror Movies Short Alcoholism

What is “gene expression?”

Play Form Often Kitchen Banana Blue-Eyes Extra Blood Clots Dog Loves Hates Very Cats Animals Platelets Salads Sunshine Adores Children Tumble Develop Over Make Fibrosis More Blood Clots Don’t Bleed Too Much Clean Obsessively Have

Grow Tall Often Earlobes Liver Blood Clots Toes Loves Grey Hair Very Webbed Long Toes Innovates Develop Tolerates Rain Depression Red Kalidoscopes Develop Blonde Blood Clots Significant Enjoy Eating Stay Quiet Fight Horror Movies Short Alcoholism
Genetic Differences: PV

CD34+ PB
Healthy Male Controls

Up-regulated

CD34+ PB
Males with PV

Down-regulated

[Diagram showing cell distribution and regulatory status]
Genetics of the PV clones

Female
235
126 up-regulated
109 down-regulated

Male
571
486 up-regulated
85 down-regulated

102

Spivak et al., NEJM 2015
### Table 2. Clinical Features Segregated with the Use of Unsupervised Hierarchical Clustering.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with Aggressive Disease (N = 7)</th>
<th>Patients with Indolent Disease (N = 12)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex — no.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Median age (range) — yr</td>
<td>66 (48–74)</td>
<td>68 (46–82)</td>
<td>NS</td>
</tr>
<tr>
<td>Median disease duration (range) — yr</td>
<td>14 (7–24)</td>
<td>6 (1–25)</td>
<td>0.05†</td>
</tr>
<tr>
<td>Median JAK2 V617F neutrophil allele burden (range) — %</td>
<td>100 (64–100)</td>
<td>85 (55–100)</td>
<td>NS</td>
</tr>
<tr>
<td>Median hemoglobin level (range) — g/dl</td>
<td>11.1 (8.3–12.9)</td>
<td>13.3 (10.7–15.9)</td>
<td>0.007†</td>
</tr>
<tr>
<td>Median white-cell count per mm³ (range)</td>
<td>17,620 (10,020–171,190)</td>
<td>17,870 (4430–27,270)</td>
<td>NS</td>
</tr>
<tr>
<td>Median platelet count per mm³ (range)</td>
<td>454,000 (171,000–1,017,000)</td>
<td>837,000 (151,000–1,480,000)</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombosis — no. of patients</td>
<td>4</td>
<td>1</td>
<td>0.04‡</td>
</tr>
<tr>
<td>Palpable splenomegaly — no. of patients</td>
<td>7</td>
<td>6</td>
<td>0.03‡</td>
</tr>
<tr>
<td>Median spleen size (range) — cm below costal margin</td>
<td>20 (5–32)</td>
<td>2 (0–14)</td>
<td>0.005‡</td>
</tr>
<tr>
<td>Splenectomy — no. of patients</td>
<td>4</td>
<td>0</td>
<td>0.007‡</td>
</tr>
<tr>
<td>Chemotherapy — no. of patients</td>
<td>5</td>
<td>2</td>
<td>0.03‡</td>
</tr>
<tr>
<td>Transformation to acute leukemia — no. of patients</td>
<td>4</td>
<td>1</td>
<td>0.04‡</td>
</tr>
<tr>
<td>Surviving — no. of patients</td>
<td>1</td>
<td>11</td>
<td>0.001‡</td>
</tr>
</tbody>
</table>

* NS denotes not significant.
† The P value was calculated with the use of Student’s t-test.
‡ The P value was calculated with the use of Fisher’s exact probability test (two-sided).
Cancer and Gender

Does the disease occur more frequently in one sex vs. the other?

Diagnostic bias?
Exposure?
Genetic predisposition?

Does the disease behave differently in one sex vs. the other?

Different clinical consequences or complications?
Different treatment strategies?
<table>
<thead>
<tr>
<th></th>
<th>N evaluable</th>
<th>All patients (N = 1545)</th>
<th>Females, N = 785 (51%)</th>
<th>Males, N = 760 (49%)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>1545</td>
<td>61 (18–95)</td>
<td>62 (18–92)</td>
<td>59 (19–95)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ages below 40/50 years</td>
<td>1545</td>
<td>10/24%</td>
<td>10/23%</td>
<td>10/26%</td>
<td>0.58</td>
</tr>
<tr>
<td>Hemoglobin, median in g/dl (range)</td>
<td>1545</td>
<td>18.4 (15.1–26.5)</td>
<td>17.7 (15.1–24.5)</td>
<td>18.9 (17.1–26.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hematocrit (median and range)</td>
<td>1545</td>
<td>55 (36–78)</td>
<td>54 (36–76)</td>
<td>57 (42–78)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Leukocyte count, median × 10³/l (range)</td>
<td>1545</td>
<td>10.4 (3–171.6)</td>
<td>10.3 (3–125.5)</td>
<td>10.5 (4.2–171.6)</td>
<td>0.85</td>
</tr>
<tr>
<td>Leukocytosis (&gt;10.5 × 10⁹/l), n (%)</td>
<td>1545</td>
<td>751 (49%)</td>
<td>375 (48%)</td>
<td>376 (49.5%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Platelet count, median × 10⁹/l (range)</td>
<td>1545</td>
<td>466 (7–2370)</td>
<td>509 (7–2370)</td>
<td>419 (37–1410)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Thrombocytosis (≥450 × 10⁹/l), n (%)</td>
<td>1545</td>
<td>817 (53%)</td>
<td>472 (60%)</td>
<td>345 (45.4%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Extreme thrombocytosis (≥1000 × 10⁹/l), n (%)</td>
<td>1545</td>
<td>58 (4%)</td>
<td>46 (6%)</td>
<td>12 (1.6%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Palpable spleen, n (%)</td>
<td>1477</td>
<td>534 (36%)</td>
<td>241 (32%)</td>
<td>293 (40.3%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pruritus, n (%)</td>
<td>1349</td>
<td>485 (36%)</td>
<td>240 (35.4%)</td>
<td>245 (36.6%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Vasomotor symptoms, n (%)</td>
<td>1412</td>
<td>403 (28.5%)</td>
<td>213 (30%)</td>
<td>190 (27%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Arterial thrombosis before/at diagnosis, n (%)</td>
<td>1545</td>
<td>246 (16%)</td>
<td>108 (14%)</td>
<td>138 (18%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Venous thrombosis before/at diagnosis, n (%)</td>
<td>1545</td>
<td>114 (7.4%)</td>
<td>73 (9.3%)</td>
<td>41 (5.4%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Major hemorrhage before/at diagnosis, n (%)</td>
<td>572</td>
<td>24 (4.2%)</td>
<td>16 (5.5%)</td>
<td>8 (2.8%)</td>
<td>0.11</td>
</tr>
<tr>
<td>↑ Lactate dehydrogenase, n (%)</td>
<td>732</td>
<td>368 (50%)</td>
<td>203 (54%)</td>
<td>165 (47%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Leukocythoblastic smear, n (%)</td>
<td>1056</td>
<td>63 (6%)</td>
<td>28 (5%)</td>
<td>35 (7%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Abnormal karyotype, n (%)</td>
<td>631</td>
<td>77 (12%)</td>
<td>29 (9%)</td>
<td>48 (15%)</td>
<td>0.02</td>
</tr>
<tr>
<td>JAK2 mutation, n (%)</td>
<td>1268</td>
<td>1239 (98%)</td>
<td>626 (98%)</td>
<td>613 (97.3%)</td>
<td>0.68</td>
</tr>
<tr>
<td>V617F/other JAK2 mutation (%)</td>
<td>1268</td>
<td>95%/3%</td>
<td>95.6%/2.5%</td>
<td>95%/3%</td>
<td>0.68</td>
</tr>
<tr>
<td>Serum Epo ↓/normal/↑ (%)</td>
<td>1058</td>
<td>81%/17%/2%</td>
<td>83%/15%/2%</td>
<td>79%/19%/1%</td>
<td>0.17</td>
</tr>
<tr>
<td>EEC, n (%)</td>
<td>454</td>
<td>331 (73%)</td>
<td>182 (76%)</td>
<td>149 (69.3%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Increased red cell mass, n (%)</td>
<td>306</td>
<td>277 (91%)</td>
<td>149 (87.7%)</td>
<td>128 (94%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hemoglobin &gt;18.5 g/dl (&gt;16.5 ♂) n (%)</td>
<td>1545</td>
<td>1122 (73%)</td>
<td>652 (83%)</td>
<td>470 (62%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>History of tobacco use, n (%)</td>
<td>1301</td>
<td>206 (16%)</td>
<td>74 (11.3%)</td>
<td>132 (20.4%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>1149</td>
<td>97 (8.4%)</td>
<td>41 (7%)</td>
<td>56 (11%)</td>
<td>0.11</td>
</tr>
<tr>
<td>History of hyperlipidemia, n (%)</td>
<td>1073</td>
<td>196 (18.3%)</td>
<td>98 (18%)</td>
<td>98 (18.5%)</td>
<td>0.85</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>1388</td>
<td>638 (46%)</td>
<td>339 (48%)</td>
<td>299 (43.7%)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Abbreviations: EEC, endogenous erythroid colony; Epo, erythropoietin; PV, polycythemia vera. Bold numeral indicate differences that were statistically relevant.
Gender Differences: Clinical

Women with PV
- Diagnosed earlier than men
- Higher likelihood of splenomegaly
- Lower JAK2 allele burden
- More risk for a blood clot in the liver system
- “Occult” disease
- More likely to evolve from ET → PV than men

Women with ET
- Less likely than men to have CAL-R mutations
- More likely then men to have “Triple-Negative disease”

Stein et al., Thrombosis 2011
MF Risk Factors

- Monosomal karyotype
- inv (3)/i(17q) abnormalities
- Any two of the following: >9% circulating blasts, Leukocytes >40x10⁹/L, unfavorable karyotype
- Absence of CALR, JAK2 and MPL mutation
- High-molecular risk category
  - ASXL1, EZH2, SRSF2, IDH1/2
  - CALR-/ASX1+
<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60</td>
<td>1.5</td>
<td>“Triple Neg” for JAK2, MPL, CALR</td>
<td>1.5</td>
</tr>
<tr>
<td>Symptoms</td>
<td>0.5</td>
<td>JAK2 + or MPL +</td>
<td>0.5</td>
</tr>
<tr>
<td>Hgn &lt;10g/dL</td>
<td>0.5</td>
<td>ASKL1</td>
<td>0.5</td>
</tr>
<tr>
<td>Platelets &lt;200</td>
<td>1.0</td>
<td>SRSF2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Vannuchi et al. ASH 2014 Abstract 405
Gender and Blood Clots

• Both genders get blood clots
• In one study, women were
  – less likely to have high cholesterol
  – less likely to smoke
  – but more likely to get blood clots (odds 1.9:1)
• Men – more likely to have heart attacks or blood clots in the legs
• Women – more likely to have blood clots in the large blood vessels of the abdominal cavity
  – “Budd-Chiari Syndrome”
  – Portal Hypertension
Abdominal vessels
Symptom differences? ET

Predominantly female (61.7%) and had intermediate risk (54.9%).
Symptom differences? PV

Predominantly male (65.8%). Variable risk PV

Geyer et al., Blood 2014
Symptom Differences

• Females
  – Lower rates of thrombocytopenia
  – Higher rates of fatigue
  – Higher rates of microvascular symptoms
    • Migraines
    • Erythromelalgia
Objectives

• Gender differences
  – Risks of acquiring disease
  – Risks for symptoms
  – Risks for complications

• What are special concerns facing female patients
  – Fertility
  – Bleeding, Clotting risks

• Newest research on this issue
Challenges: Fertility

- **Contraception**
  - Combination hormones > progesterone only OCPs
  - General population have a 3–6-fold increased risk of venous thrombosis with OCPs

- **One retrospective study of >300 ET patients. Subset on OCPs**
  - ET + OCPs = 23% VTE
  - ET no OCPs = 7% VTE

- **Recommendation:** Avoid combination OCPs, Discuss carefully the use of hormones of any kind
Challenges: Pregnancy
Challenges: Pregnancy

• Pregnancy outcomes impacted by MPNs
  – Live birth rate 50-70%
  – First trimester loss 10-20%
  – Late pregnancy loss 10%
  – Increased rates of placental abruption, intrauterine growth restriction

• Can we change those outcomes?
Preconception Counseling

• Risk Assessment
  – Prior VTE or arterial clot
  – Prior hemorrhage
  – Prior pregnancy complication
  – Diabetes or Hypertension requiring treatment
  – Platelet count of $>1500 \times 10^9$ before or during pregnancy
Preconception Counseling

• Multidisciplinary approach
• Discussion of teratogenic drugs
• Therapeutic options
  – Aspirin
  – LMWH
  – Cytoreductive therapy
• Delivery and post-partum plan
• Breastfeeding information
Pregnancy: Low-Risk Patients

- Generally
  - Continue low-dose aspirin
  - Monitor platelet or Hct
    - Keep HCT under 45%
    - Consider venesection if necessary
  - Increased plasma volume of pregnancy means no set targets

Antiplatelet agents → reduce risk of VTE in ET patients

Pregnancy is thrombotic

Aspirin is likely safe in pregnancy (APLA pts)
Pregnancy: High-risk patients

- Remove possible teratogenic drugs
  - Taper off hydrea or anagrilide 3-6 months prior to conception
  - Hydrea likely contraindicated, men and women
  - Anagrilide crosses the placenta
- Cytoreduction
  - Interferon-alpha -- Case reports indicating likely safe
- Prevent Clotting
  - LMWH
  - Prophylactic or, in some cases, therapeutic doses
Challenges: Clotting

• Be aware of additive risks
  – Hospitalization, surgery, immobility, smoking, obesity

• Surgical risk
  – Ask about anticoagulation post-operatively
  – Discuss all surgeries with your hematologist

• Duration of anticoagulation
  – Depends on clot, other factors influencing risk
Challenges: Bleeding

- More common when platelets are elevated
  - 1,000-1,500 X $10^9$ -- Often related to acquired Von Willebrand's Disease
Objectives

• Gender differences
  – Risks of acquiring disease
  – Risks for symptoms
  – Risks for complications

• Select concerns facing female patients
  – Contraception
  – Pregnancy
  – Clotting
  – Bleeding risks
Outcomes:
Venous, Arterial Events like stroke, heart attack, VTE, bleeding
What’s next?
What if?

• We could link genetic characteristics (clone DNA, gender, somatic DNA) to future disease behavior?

• We could deliver *just enough* treatment to mitigate those risks?

We understood these diseases well enough to eradicate them?
What's next?

Clinical Trials

Translational Research

Peer Education

Fund Raising

Patient Advocacy

Public Policy Advocacy
“The kind of hope I often think about…I understand, above all, as a state of mind… it is a dimension of the soul…”

“Hope is not the same thing as optimism… but the certainty that something makes sense, regardless of how it turns out…”

Vaclav Havel
Thanks

• To all of you for your continued engagement in this journey of research and development

• Ruben Mesa, John Camoriano and conference organizers for the kind invitation to join you this year

• My colleagues, mentors, advisors and friends
  • Ruben Mesa        Mary Horowitz
  • Vikas Gupta       Linda Brubaker
  • P. Hari           Jason Gotlib
  • Serge Verstovsek  Ehab Atallah
  • Brady Stein