Should Mutational Status in Primary Myelofibrosis (PMF) Guide Therapy.....YES!!!

Lindsay Anne Magura Rein, MD

Division of Hematologic Malignancies and Cellular Therapy/BMT
A Little Bit of History…..

- 1665 – Advanced microscopes
- 1668 – Jan Swammerdam describes red blood cells
- 1749 – Joseph Lietaud describes white blood cells
- 1842 – Alfred Donne describes platelets
- 1845 – John Hughes Bennett publishes first report of chronic myeloid leukemia (CML)
  - Discovery of the Philadelphia chromosome, 1960
  - 9;22 translocation described, 1973
  - Molecular and oncogenic characterization of BCR-ABL, 1982-1990
  - Imatinib discovered, 1996
- 1879 – Gustav Heuck first describes primary myelofibrosis
  - Splenic medullary leukemia, pure splenic leukemic

Tefferi, Leukemia, 2007
PMF: A Complex Disease With Multiple Pseudonyms

- Osteosclerotic anemia, agnogenic myeloid metaplasia, chronic idiopathic myelofibrosis, myelofibrosis with myeloid metaplasia

Mughal et al., Int J Gen Med 2013
?? So How Do I Treat My Patient ??
How Do We Stratify Risk?

DIPSS-PLUS

**PROGNOSTIC VARIABLE** | **POINTS**
--- | ---
DIPSS low-risk | 0
DIPSS intermediate-risk (INT-1) | 1
DIPSS intermediate-risk (INT-2) | 2
DIPSS high-risk | 3
Platelets <100 x 10⁹/L | 1
Transfusion need | 1
Unfavorable karyotype* | 1

**RISK GROUP** | **POINTS**
--- | ---
Low | 0
Intermediate-1 (INT-1) | 1 or 2
Intermediate-2 (INT-2) | 3 or 4
High | 5 or 6

*Unfavorable karyotype: complex karyotype or sole or two abnormalities that include trisomy 8, 7/7q-, i(17q), 5/5q-, 12p-, inv(3), or 11q23 rearrangement.

5-7% of patients
Suggested Treatment, NCCN

**TREATMENT FOR LOW-RISK MYELOFIBROSIS**

- **Asymptomatic**
  - Observation or Clinical trial
  - Monitor for signs and symptoms of disease progression every 3–6 months

- **Symptomatic**
  - Assess symptom burden using MPN-SAF TSS-10 items if not done previously
  - Ruxolitinib or Interferons (Interferon alfa-2b, pegylated interferon alfa-2a, and pegylated interferon alfa-2b) or Clinical trial
  - Monitor response and signs/symptoms of disease progression every 3–6 months

**See Evidence Blocks on MPN-4A**

**TREATMENT FOR INTERMEDIATE-RISK 1 (INT-1) MYELOFIBROSIS**

- **Intermediate-risk 1 (INT-1)**
  - Risk score: IPSS=1, DIPSS-Plus = 1, DIPSS = 1 or 2
  - Assess symptom burden using MPN-SAF TSS-10 items if not done previously
  - Observation or Ruxolitinib if symptomatic or Clinical trial or Allogeneic HCT
  - Monitor response and signs/symptoms of disease progression every 3–6 months

**Response**
- Continue prior treatment
- No Response or Loss of response
- Disease progression

**See Evidence Blocks on MPN-4A**
Suggested Treatment, NCCN

TREATMENT FOR INTERMEDIATE-RISK 2 (INT-2) OR HIGH-RISK MYELOFIBROSIS

Intermediate-risk 2 (INT-2) Risk score:
(IPSS = 2, DIPSS-Plus = 2 or 3
DIPSS = 3 or 4)k
Or High-risk
Risk score:
(IPSS ≥ 3, DIPSS-Plus = 4 to 6
DIPSS = 5 or 6)k

Transplant candidate$ → Allogeneic
HCT,e,s
Not a transplant candidate
Assess symptom
burden using
MPN-SAF TSS-10
itemsi if not done
previously
Not a transplant candidate and symptomaticin
anemia only

Platelets ≤50K
→ Ruxolitinibn
or Clinical
trial
See Evidence
Blocks on
MPN-4A
See Management of
MF-Associated
Anemia (MPN-5)

Platelets >50K
→ Monitor
responsep and
signs/symptoms
of disease progression
every 3–6 monthsl,o,t
Response
No Response or
Loss of response
Disease progression

Consider Clinical trial
Continue prior treatmentn,r
→ See MPN-6
But What About Mutations? Do They Matter?
Driver Mutations Versus Other Somatic Mutations

JAK, MPL, CALR

LNK, CBL, TET2, ASXL1, IDH, IKZF1, EZH2, DNMT3A, TP53, SF3B1, SRSF2, U2AF1
JAK2 Mutations

• 2005 – 4 independent labs observed a JAK2 gain-of-function mutation (JAK2V617F) in BCR-ABL negative MPNs
  – 50% PMF patients

• 2007 – Green et al. describe 4 exon 12 JAK2 mutant alleles (PV)
MPL Mutations

- 2006 – Discovery of a gain-of-function mutation of the thrombopoietin receptor, MPLW515L
- MPLW515K incidentally found
- 5% PMF patients
CALR Mutations

- 2013 - 2 separate groups describe exon 9 mutations
  - Type 1
  - Type 2

- 25% PMF patients
Prognostic Significance of Driver Mutations

Cumulative Incidence Leukemic Transformation

Overall Survival According to Driver Mutation Status

A Historical Perspective

Not All CALR Mutations Are Created Equal

JAK2V617F vs type 1/type 1-like, p<0.0001; HR 2.7, 95% CI 1.9-3.7
JAK2V617F vs type 2/type 2-like, p=0.84; HR 1.1, 95% CI 0.6-1.8
Type 2/type 2-like vs type 1/type 1-like, p=0.003; HR 2.5, 95% CI 1.4-4.5
Driver Mutations Versus Other Somatic Mutations

JAK, MPL, CALR

LNK, CBL, TET2, ASXL1, IDH, IKZF1, EZH2, DNMT3A, TP53, SF3B1, SRSF2, U2AF1
“Other Mutations” Are Important Too!

- Genes involved in intracellular signaling
  - LNK, CBL, SOCS
- Genes involved in spliceosome machinery
  - SF3B1, SRSF2
- Genes involved in leukemic progression
  - IDH1/2, IKZF, TP53, RUNX1
- Mutations in epigenetic regulator genes
  - EZH1/2, ASXL, TET2, DNMT3A
  - Pre-JAK events?
## Prognostic Significance of Mutations in MPN

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>Primary Myelofibrosis (PMF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2V617F</td>
<td>Intermediate prognosis and higher risk of thrombosis compared to patient with CALR mutation&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>MPLW515L/K</td>
<td>Intermediate prognosis and higher risk of thrombosis compared to patient with CALR mutation&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>CALR</td>
<td>Improved survival compared to JAK2 mutation and &quot;triple-negative&quot; PMF&lt;sup&gt;1-4&lt;/sup&gt; Lower risk of thrombosis compared to JAK2 mutation&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>CALR Type 1/Type 1-like</td>
<td>Improved overall survival compared to CALR type 2/type 2-like and JAK2 V617F mutation&lt;sup&gt;5-8&lt;/sup&gt;</td>
</tr>
<tr>
<td>&quot;Triple Negative&quot; (non-mutated JAK2, MPL, and CALR)</td>
<td>Inferior leukemia-free survival compared to patients with JAK2- and/or CALR-mutated PMF&lt;sup&gt;1-3&lt;/sup&gt; Inferior overall survival compared to patients with CALR-mutated PMF&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>ASXL1</td>
<td>Independently associated with inferior overall survival&lt;sup&gt;*&lt;/sup&gt; and leukemia-free survival&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>EZH2</td>
<td>Independently associated with inferior overall survival&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>IDH1/2</td>
<td>Independently associated with inferior leukemia-free survival&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>SRSF2</td>
<td>Independently associated with inferior overall survival and leukemia-free survival&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Combined CALR and ASXL1 status</td>
<td>Survival longest for CALR(+)-ASXL1(-) patients (median 10.4 years) and shortest in CALR(-)-ASXL1(+) patients (median 2.3 years)&lt;sup&gt;**10&lt;/sup&gt; Intermediate survival (median 5.8 years) for CALR(+)-ASXL1(+) or CALR(-)-ASXL1(-) patients&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>TP53</td>
<td>Associated with leukemic transformation&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Driver + Other Somatic Mutations

- CALR-ASXL1-
  - $N=46$
  - Median 10.4 years

- CALR-ASXL1+
  - $N=62$
  - Median 2.3 years

- CALR+ASXL1-
  - $N=169$
  - Median 5.8 years

P < 0.0001
Number of Mutations Matters

- 797 PMF patients
  - ASXL1, EZH2, SRSF2, IDH1/2 mutations
- High versus low molecular risk patients
Treatment Considerations…..
Should We Consider Mutation Status???

YES!!!
Transplant is the only curative option

<table>
<thead>
<tr>
<th>Reference</th>
<th>Timeline of HCT</th>
<th>N</th>
<th>Median age (range), years</th>
<th>Conditioning regimen</th>
<th>% of patients with RIC</th>
<th>NRM</th>
<th>PFS</th>
<th>OS</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rondelli [34]</td>
<td>NR</td>
<td>21</td>
<td>54 (27–68)</td>
<td>Multiple</td>
<td>100</td>
<td>10% at 1 y</td>
<td>81% at 2 y</td>
<td>85% at 2.7 y</td>
<td>Intensive cGVHD in 44%; 2 patients needed DLI for 100% donor chimerism; resolution of fibrosis and splenomegaly in majority.</td>
</tr>
<tr>
<td>Kerbany [35]</td>
<td>NR</td>
<td>104</td>
<td>49 (18–70)</td>
<td>Multiple, Bu/Cy (62%)</td>
<td>9</td>
<td>35% at 5 y</td>
<td>NR</td>
<td>61% at 5 y</td>
<td>HLA, syngeneic donors, 54 of the patients overlapped with a prior report; targeted Bu improved OS; comorbidity score had impact on survival.</td>
</tr>
<tr>
<td>Patriarca [36]</td>
<td>1986–2006</td>
<td>100</td>
<td>49 (21–68)</td>
<td>Multiple, Bu/Cy 50% of full intensity; Thiotepa + Cy in 46% of RIC</td>
<td>52</td>
<td>43% at 3 y</td>
<td>35% at 5 y</td>
<td>42% at 3 y</td>
<td>Bilateral MFE, cGVHD in 43%; 12% NRM for fully matched donor AHT; age &gt;50 y and HLA mismatch adversely affected OS; JAK2-positive recipients had better EFS and OS; splenectomy increased risk of relapse.</td>
</tr>
<tr>
<td>Kroger [9]</td>
<td>2002–2007</td>
<td>103</td>
<td>55 (32–68)</td>
<td>Flu-Bu (100%)</td>
<td>100</td>
<td>16% at 1 y</td>
<td>51% at 5 y</td>
<td>67% at 5 y</td>
<td>HCT before 1995; unrelated donor and longer interval from diagnosis predicted worse outcome; age, conditioning intensity, relapse at 2 y &gt;41%, progressive decline in NRM over 20 y studied.</td>
</tr>
<tr>
<td>Ballen [10]</td>
<td>1989–2002</td>
<td>289</td>
<td>47 (18–73)</td>
<td>Multiple, Bu/Cy (43%)</td>
<td>21</td>
<td>35% siblings</td>
<td>33% siblings</td>
<td>37% siblings</td>
<td>Bilateral MFE, cGVHD in 43%; 12% NRM for fully matched donor AHT; age &gt;50 y and HLA mismatch adversely affected OS; JAK2-positive recipients had better EFS and OS; splenectomy increased risk of relapse.</td>
</tr>
<tr>
<td>Alchalby [31]</td>
<td>1999–2010</td>
<td>162</td>
<td>56 (32–73)</td>
<td>Flu-Bu in 96%</td>
<td>100</td>
<td>22% at 1 y</td>
<td>46% at 5 y</td>
<td>62% at 5 y</td>
<td>2 patients reported previously54; age and HLA mismatch impacted NRM; 23% relapse at 3 y; clearance of mutated JAK2 at median of 96 days, and this reduced relapse risk.</td>
</tr>
<tr>
<td>Bacigalupo [37]</td>
<td>1994–2007</td>
<td>46</td>
<td>51 (24–67)</td>
<td>Thiotepa-Cy + melphalan</td>
<td>100</td>
<td>24% at 5 y</td>
<td>NR</td>
<td>45% at 5 y</td>
<td>Risk score based on transfusion history, spleen &gt;22 cm and alternative donor use predicted lower OS; no benefit for splenectomy.</td>
</tr>
<tr>
<td>Robin [38]</td>
<td>1997–2008</td>
<td>147</td>
<td>53 (20–68)</td>
<td>Multiple</td>
<td>69</td>
<td>39% at 4 y</td>
<td>32% at 4 y</td>
<td>39% at 4 y</td>
<td>19% patients had LT; poor outcome with mismatched donor.</td>
</tr>
<tr>
<td>Samuelson [20]</td>
<td>1999–2007</td>
<td>30</td>
<td>65 (60–78)</td>
<td>Multiple</td>
<td>63</td>
<td>13% at day 100</td>
<td>40% at 5 y</td>
<td>45% at 3 y</td>
<td>Studied outcomes in patients ≥60 y, 7 patients had preceding LT.</td>
</tr>
<tr>
<td>Ditschkowski [13]</td>
<td>1994–2010</td>
<td>76</td>
<td>50.5 (22–67)</td>
<td>Multiple</td>
<td>NR</td>
<td>36% at 5 y</td>
<td>50% at 5 y</td>
<td>53% at 5 y</td>
<td>Significant high risk of relapse in patients without cGVHD; DIPSS was predictive of survival.</td>
</tr>
<tr>
<td>Scott [16]</td>
<td>1990–2009</td>
<td>170</td>
<td>51.5 (12–78)</td>
<td>Multiple</td>
<td>NR</td>
<td>34% at 5 y</td>
<td>57% at 5 y</td>
<td>57% at 5 y</td>
<td>Post-HCT success was dependent on pre-HCT DIPSS scores.</td>
</tr>
</tbody>
</table>
Ruxolitinib – FDA Approved Therapy

• COMFORT-1 and COMFORT-II
  – Ruxolitinib versus placebo or best available therapy (BAT)
  – Decreased spleen size and MF-related symptoms
  – *** Survival benefit
  – No significant differences in efficacy measures when comparing WT to JAK2-mutated patients

• Other somatic mutations in COMFORT-II
  – Post-hoc analysis
  – Benefits of ruxolitinib were independent of mutational status.

• High risk mutations ASXL1, EZH2, SRSF2, and IDH1-2.

But this is all of the data we have... for one drug... and it’s retrospective.....
Mutations Inform Clinical Trial Enrollment

- JAK1/2 inhibitors
  - Ruxolitinib, fedratinib, momelotinib, pacritinib, NS-018
- PI3Kinase inhibitors – BKM120
- Hedgehog inhibitors – Glasdegib, vismodegib
- Telomerase inhibitors – Imetelstat
- HDAC inhibitors – Panobinostat
- Anti-fibrosis agents – PRM-151
- Anti-apoptosis agents – LCL161
- Hypomethylating agents – Azacitadine, decitabine
- Monoclonal antibodies
  - Durvalumab, nivolumab
# The Future of PMF?

## Clinical and molecular risk stratification and risk-adapted therapy in primary myelofibrosis

<table>
<thead>
<tr>
<th>Molecular risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
</tr>
</tbody>
</table>

### Integration of Mutations and Karyotype Towards a Genetics-Based Prognostic Scoring System (GPSS) for Primary Myelofibrosis

Ayalew Tefferi, Paola Guglielmelli, Christy Finke, Terra L Lasho, Naseema Gangat, Rhett Ketterling, Curtis A. Hanson, Animesh Pardhanani, Alessandro M. Vannucchi

*Blood* 2014 124:406;

- **High**
  - Stem cell transplant
  - Stem cell transplant or
  - Observation

- **Intermediate**
  - Stem cell transplant
  - Stem cell transplant or
  - Observation

- **Low**
  - Stem cell transplant
  - Stem cell transplant or
  - Investigational drug therapy

### Mutation-Enhanced International Prognostic Scoring System (MIPSS) for Primary Myelofibrosis: An AGIMM & IWG-MRT Project

Alessandro Maria Vannucchi, Paola Guglielmelli, Giada Rotunno, Cristina Pascutto, Animesh Pardhanani, Virginia Ferretti, Annalisa Pacilli, Alessandro Pancrazzi, Terra Lasho, Curtis A Hanson, Rhett Ketterling, Naseema Gangat, Enrico Tagliafico, Rossella Manfredini, Valentina Artusi, Isabella Bernardis, Daniela Pietra, Elisa Rumi, Margherita Maffioli, Vittorio Rosti, Silvia Salmoiraghi, Federica Delaini, Alberto Bosi, Daniela Cillonzi, Francisco Cervantes, Francesco Passamonti, Giovanni Barosi, Alessandro Rambaldi, Tiziano Barbui, Mario Cazzola, Ayalew Tefferi

*Blood* 2014 124:405;
Conclusions

- PMF is a complex disease with a complex mutational landscape. Not the next success story like BCR-ABL in CML.
- Mutations affect disease biology. Should also inform therapy.
- Current strategies for risk stratification DO NOT include mutational status although we know (based on the published literature) that mutational status makes a difference.
  - MIPSS and GPSS scoring systems proposed although not validated
- Effective, disease modifying therapies for PMF are lacking.
- We need randomized, prospective data. Clinical trials are key.
Thank you!