Update in Myeloproliferative Neoplasms

2017 Updates in Hematologic Cancers with Proceedings from International Medical Meetings

January 27, 2017

Daria Babushok, MD PhD
Learning Objectives

Philadelphia-chromosome negative MPN
- 2016 Revision of WHO Criteria
- Familial MPN
- Risk-stratification of MPN
- Therapy in ET and PV
- Allo SCT in MF
- Non-transplant therapies for MF

CML
- Treatment milestones
- Caveats of BCR-ABL assay
- TKI sequencing
- TKI symptom burden
Classification of Myeloproliferative Neoplasms

MPN

Philadelphia Chromosome Negative

Philadelphia Chromosome Positive

PV

ET

PMF

Others (rare)

CML

Classical Ph- MPN

Classical Ph- MPN

the cure is within

ABRAMSON CANCER CENTER
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2016 WHO Classification Criteria

**PV**
- **2016 update:** 1) Hgb/Hct threshold, 2) BM biopsy requirement
- • Hgb >16.5 (M)/16.0(F)g/dL or Hct >49%(M)/48%(F) (or increased red cell mass)
- • Characteristic BM pathology
- • JAK2 mutation
- • In the absence of JAK2 mutation, requires subnormal erythropoietin

**ET**
- **2016 update:** 1) Inclusion of CALR, MPL
- • Plt >450k/ul
- • Characteristic BM pathology
- • Exclusion of other disorders
- • Presence of JAK2, CALR or MPL mutation
- • In the absence of JAK2/CALR/MPL mutations, requires a clonal marker or absence of reactive thrombocytosis

**PMF**
- **2016 update:** 1) prefibrotic MF 2) Inclusion of CALR
- • Characteristic BM pathology, with grade 2-3 fibrosis for overt PMF
- • Exclusion of other disorders
- • Presence of JAK2, CALR, MPL, or another clonal marker and exclusion of reactive conditions
- • One more of: elevated LDH, splenomegaly, anemia, leukocytosis, and, in overt PMF, erythroblastosis.
Prognostic Significance of Different MPN Diagnostic Categories

- **Essential Thrombocythemia**
- **Polycythemia Vera**
- **Prefibrotic/Early Primary Myelofibrosis**
- **Overt Primary Myelofibrosis**
- **Overt Primary Myelofibrosis: Collagen Fibrosis**

**Overall Survival**

- **Pre-PMF**
  - Median 14.7 years
- **PMF**
  - Median 7.2 years
  - HR 2.3 (95% CI, 1.8-3.1)
- **ET**
  - Median 31 years

**Graph**

- P < 0.001

Guglielmelli et al. ASH 2016

Prepublished online December 27, 2016; doi:10.1182/blood-2016-10-695957
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Growing Recognition of Familial MPN

- ~7-8% of apparent sporadic MPN have a familial component

- Family history may allow earlier MPN diagnosis

Pontus Lundberg et al. Blood 2014;123:2744-2745
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### Risk Stratification in MPN

<table>
<thead>
<tr>
<th></th>
<th>ET</th>
<th>PV</th>
<th>MF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age ≥60 yrs (1)</strong></td>
<td></td>
<td>Age ≥60 yrs</td>
<td>Age &gt; 65 yrs (1)</td>
</tr>
<tr>
<td><strong>Prior thrombosis (2)</strong></td>
<td></td>
<td>Prior Thrombosis</td>
<td>Constitutional Symptoms (1)</td>
</tr>
<tr>
<td><strong>CV risk factors (1)</strong></td>
<td></td>
<td></td>
<td>Hgb &lt;10g/dl (1-2)</td>
</tr>
<tr>
<td><strong>JAK2 mutation (2)</strong></td>
<td></td>
<td></td>
<td>WBC &gt;25k/ul (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Circulating blasts ≥1% (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*DIPPS-Plus: RBC transfusions, adverse cytogenetics, Plt &lt;100k/ul</td>
</tr>
<tr>
<td><strong>IPSET-Thrombosis</strong></td>
<td>PV Thrombosis Score</td>
<td></td>
<td>MF IPSS/DIPSS/DIPSS-Plus</td>
</tr>
<tr>
<td><strong>Low (0-1; 1.03%/yr)</strong></td>
<td>Low (No risk factors; 2.5%/yr)</td>
<td></td>
<td>Low (0, median survival &gt;20 yrs)</td>
</tr>
<tr>
<td><strong>Intermediate Risk (2, 2.35%/yr)</strong></td>
<td>High (Age OR Thrombosis; 5%/yr)</td>
<td></td>
<td>Intermediate-1 (1-2, median survival 14.2 yrs)</td>
</tr>
<tr>
<td><strong>High Risk (≥3, 3.56%/yr)</strong></td>
<td>High (Age &amp; thrombosis; 10.9%/yr)</td>
<td></td>
<td>Intermediate-2 (3-4, median survival 4.0 yrs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High (5-6, median survival 1.5 yrs)</td>
</tr>
</tbody>
</table>
Prognostic Significance of Somatic Mutations

Impact of Driver Mutation

A. Patients stratified according to their driver mutation

- CALR mutant
- JAK2 or MPL mutant
- Triple negative

Clinical-molecular prognostic model

B. Patients stratified according to a clinical-molecular prognostic model

- Very high risk
- High risk
- Intermediate risk
- Low risk
- Very low risk

Rumi and Cazzola
Prepublished online December 27, 2016; doi:10.1182/blood-2016-10-695957
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Penn Medicine
Treatment Approach to Low Risk ET and PV

Low Risk

PV
- Aspirin
- Phlebotomy

ET
- Aspirin*

* Low risk CALR-mutant ET may not benefit from aspirin, have higher bleeding risk

Lanfoldi et al. ECLAP NEJM 2004;350(2):114-124
Marchioli et al. NEJM 2013;368(1):22-33
Treatment Approach to High Risk ET and PV

**High Risk**

- Aspirin
- Phlebotomy
- Hydroxyurea
- Interferon
- Ruxolitinib

**PV**
- Hydroxyurea
- Interferon
- Ruxolitinib

**ET**
- Hydroxyurea
- Anagrelide*
- Interferon

**Hydroxyurea-resistant & intolerant PV**

- PT-1. NEJM. 2005

2016: Ongoing studies comparing hydroxyurea to interferon

References:
- Mesa EJH 2016;97:192.
- Pieri Blood 2015;125:3352.
Interferon versus Hydroxyurea in ET and PV

Gisslinger et al. ASH 2016

Final Results from PROUD-PV a Randomized Controlled Phase 3 Trial Comparing Ropeginterferon Alfa-2b to Hydroxyurea in Polycythemia Vera Patients
- Population: PV population in need of cytoreduction (HU pre-treatment allowed).
- Study outcomes: non-inferiority at 12 months in CHR.
- Final analysis: Non-inferior at 12 months.

Mascarenhas et al. ASH 2016

Interim Analysis of the Myeloproliferative Disorders Research Consortium (MPD-RC) 112 Global Phase III Trial of Front Line Pegylated Interferon Alpha-2a Vs. Hydroxyurea in High Risk Polycythemia Vera and Essential Thrombocythemia
- Population: High-risk ET and PV; randomized 1:1
- Study outcomes: CHR.
- Interim analysis (75 patients, 12 months): no difference.

Conclusions: No significant differences in CHR at 12 months. Longer studies including endpoints such as survival, thrombosis and disease transformation will be important in comparing these agents.
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Approach to Treatment of MF in 2017

Selection of upfront therapy for patients with MF: HCT vs nontransplant therapies

**Benefits**
- Curative potential

**Risks**
- Risk of early mortality
- ↓QOL
  - GVHD
  - Recurrent infections

**Benefits**
- Usually well-tolerated
- ↑QOL

**JAK inhibitor therapy/clinical trial**

**Risks**
- Non-curative
- Unknown duration of response
  - 50% of patients discontinue by 3 years

Devlin and Gupta Hematology 2016:543-551
Worse outcomes with non-transplant therapies
- Severe thrombocytopenia (<50k/ul)
- Heavily transfusion-dependent anemia
- 3 or more mutations
- High risk cytogenetics
- Increased circulating blasts

Worse outcomes with transplant
- Poor performance status
- Multiple comorbidities
- Increased age
- Severe portal hypertension
- Poorly matched donor
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Non-Transplant Therapies for MF in 2017

- **Ruxolitinib**
  - The first approved targeted therapy (Intermediate and High Risk MF)
  - Spleen volume reduction and improvement in symptoms and QOL
  - Main toxicities: myelosuppression and infection risk
  - Follow-up data: survival advantage compared to placebo and BAT
    - Improvement in clinical status (e.g. cachexia and systemic inflammation)
  - Ongoing study of ruxolitinib in Low and Int-1 patients with adverse mutational profile (ReTHINK)
Results of the PERSIST-2 phase 3 study of pacritinib (PAC) versus best available therapy (BAT), including ruxolitinib (RUX), in patients with myelofibrosis (MF) and platelet counts ≤100,000/µl

John Mascarenhas¹, Ronald Hoffman¹, Moshe Talpaz², Aaron T. Gerds³, Brady Stein⁴, Vikas Gupta⁵, Anita Szoke⁶*, Mark Drummond⁷*, Alexander Pristupa⁸*, Tanya Granston⁹*, Robert Daly⁹*, James P. Dean⁹, Suliman Al-Fayoumi⁹*, Jennifer A. Callahan⁹*, Jack W. Singer⁹, Jason Gotlib¹⁰, Catriona Jamieson¹¹, Claire Harrison¹²*, Ruben Mesa¹³* and Srdan Verstovsek¹⁴

Key Eligibility Criteria

Primary MF, PPV-MF, or PET-MF
Platelet counts ≤100,000/µL, prior/current JAK2 therapy allowed

1:1:1 Randomization (N = 311)

PAC 400 mg QD
PAC 200 mg BID
BAT (incl. RUX)*

Crossover from BAT allowed after progression (any time) or assessment of primary endpoint at Wk 24

Co-Primary Endpoints

% of pts achieving ≥35% SVR (independent radiologic review) from baseline to Wk 24
and
% of pts achieving ≥50% reduction in TSS** from baseline to Wk 24

*BAT includes any physician-selected treatment for PMF, PPV-MF, or PET-MF, and may include any treatment received before study entry.
**TSS, total symptom score by validated instrument 3.0 with daily patient reporting of disease-related symptoms by e-diary.

Slide courtesy of Elizabeth Hexner, MD
Spleen Volume Reduction

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PAC QD</th>
<th>PAC BID</th>
<th>BAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>-19.8</td>
<td>-21.0</td>
<td>-4.6</td>
</tr>
<tr>
<td>Median</td>
<td>-19.0</td>
<td>-23.0</td>
<td>-4.5</td>
</tr>
</tbody>
</table>

Total Symptom Score

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PAC QD</th>
<th>PAC BID</th>
<th>BAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>-18.2</td>
<td>-33.6</td>
<td>-3.9</td>
</tr>
<tr>
<td>Median</td>
<td>-27.0</td>
<td>-41.0</td>
<td>-15.0</td>
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## Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
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<th>PAC QD n=104</th>
<th>PAC BID n=106</th>
<th>BAT n=98</th>
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<tbody>
<tr>
<td>Any SAE</td>
<td>48 (46)</td>
<td>50 (47)</td>
<td>30 (31)</td>
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### SAEs referred to in the FDA clinical hold notification

<table>
<thead>
<tr>
<th></th>
<th>PAC QD</th>
<th>PAC BID</th>
<th>BAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>1 (1)</td>
<td>4 (4)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 (3)</td>
<td>0</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

January 5, 2017 FDA lifted hold on pacritinib

Slide courtesy of Elizabeth Hexner, MD
Non-Transplant Therapies for MF in 2017

46% drug-related largely irreversible peripheral neuropathy

Awaiting results:

1. Momelotinib Versus Ruxolitinib in Subjects With Myelofibrosis (SIMPLIFY-1)

2. Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects With Primary Myelofibrosis (MF), Post-polycythemia Vera MF, or Post-essential Thrombocytemia MF (SIMPLIFY-2) (post-ruxolitinib)
Non-Transplant Therapies for MF in 2017

Results of phase 1/2 studies of rux + HMA presented at ASH 2016
- Feasible
- Requires further study
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CML
- Treatment milestones
- Caveats of BCR-ABL assay
- TKI sequencing
- TKI symptom burden
## CML Treatment Milestones

<table>
<thead>
<tr>
<th>Month</th>
<th>Optimal</th>
<th>Warning</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>ELN: Ph&lt;sup&gt;+&lt;/sup&gt;≤35% or BCR-ABL1&lt;10%</td>
<td>Ph&lt;sup&gt;+&lt;/sup&gt; 65-95% or BCR-ABL1&gt;10%</td>
<td>No CHR or Ph&lt;sup&gt;+&lt;/sup&gt;≥95%</td>
</tr>
<tr>
<td></td>
<td>NCCN: Ph&lt;sup&gt;+&lt;/sup&gt;≤35% or BCR-ABL1≤10%</td>
<td>NA</td>
<td>Ph&lt;sup&gt;+&lt;/sup&gt; &gt;35% or BCR-ABL1&gt;10%</td>
</tr>
<tr>
<td>6</td>
<td>ELN: Ph&lt;sup&gt;+&lt;/sup&gt;0% and/or BCR-ABL1&lt;1%</td>
<td>Ph&lt;sup&gt;+&lt;/sup&gt; 1-35% and/or BCR-ABL1 1-10%</td>
<td>Ph&lt;sup&gt;+&lt;/sup&gt; &gt;35% and/or BCR-ABL1 &gt;10%</td>
</tr>
<tr>
<td></td>
<td>NCCN: Ph&lt;sup&gt;+&lt;/sup&gt;≤35% or BCR-ABL1≤10%</td>
<td>NA</td>
<td>Ph&lt;sup&gt;+&lt;/sup&gt; &gt;35% or BCR-ABL1&gt;10%</td>
</tr>
<tr>
<td>12</td>
<td>ELN: BCR-ABL1 &lt;0.1%</td>
<td>BCR-ABL1 0.1-1%</td>
<td>Ph&lt;sup&gt;+&lt;/sup&gt; &gt;0% BCR-ABL1 &gt;1%</td>
</tr>
<tr>
<td></td>
<td>NCCN: Ph&lt;sup&gt;+&lt;/sup&gt; 0%</td>
<td>NA</td>
<td>Ph&lt;sup&gt;+&lt;/sup&gt; &gt;0%</td>
</tr>
</tbody>
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Deininger Hematology 2015
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➢ Caveats of BCR-ABL assay
  - TKI sequencing
  - TKI symptom burden
Interpretation of the quantitative BCR-ABL PCR assay

A
One sample tested 96 times over several months, mean BCR-ABL1 11% IS, r 5-16%, CV 18%

Warning / Failure >10% at 3 or 6 months

BCR-ABL % IS

Optimal <10% at 3 months

Test number

B
One sample tested 146 times over several months, mean BCR-ABL1 0.11% IS, r 0.03-0.20%, CV 32%

BCR-ABL % IS

Test number
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Outcomes of patients receiving imatinib as initial therapy in CP-CML

CEFS at 7 yrs = 88%

EFS at 7 yrs = 81%
Upfront imatinib with selective early switching to nilotinib leads to excellent achievement of deep molecular response in chronic phase CML: 5 year (final) analysis of the TIDEL II study

David T Yeung et al
on behalf of ALLG
Two-cohort Imatinib->Nilotinib Treatment Schema

Cohort 1, n=105

- Trough IM <1000ng/mL
- BCR-ABL ≤ 10% IS
- BCR-ABL ≤ 1% IS
- BCR-ABL ≤ 0.1% IS

- d22
- 3mo
- 6mo
- 12mo
- 24mo

Cohort 2, n=105, directly to nilotinib

ELN Targets

- IM 800
- IM 800
- IM 800
- IM 800

Nilotinib 400mg BID

- Cohort 1, n=105

- Cohort 2, n=105, directly to nilotinib

Slide adapted from E. Hexner, ASH Update 2017
TIDEL-II as a frontline strategy

<table>
<thead>
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<tbody>
<tr>
<td></td>
<td>IM 400</td>
<td>DAS</td>
<td>IM 400</td>
</tr>
<tr>
<td>OS, 5yrs</td>
<td>90%</td>
<td>91%</td>
<td>92%</td>
</tr>
<tr>
<td>BC</td>
<td>7%</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>EMR failure</td>
<td>36%</td>
<td>16%</td>
<td>33%</td>
</tr>
<tr>
<td>5yr MMR</td>
<td>64%</td>
<td>76%</td>
<td>60%</td>
</tr>
<tr>
<td>5yr MR4.5</td>
<td>33%</td>
<td>42%</td>
<td>31%</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>37%</td>
<td>39%</td>
<td>50%</td>
</tr>
</tbody>
</table>

1. Cortes et al. JCO 2016;34:2333-40
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TKI symptom burden
Quality of Life and Medication Management in CML

- **Pre-diagnosis**
- **Diagnosis-First line TKI**
- **Higher Quality of Life (QoL)**
- **Lower Quality of Life (QoL)**
- **Time**
- **Successful management of therapy**
- **Increased QoL burden†**
- **Area of increased risk of poor adherence behavior**

*Note: The diagram illustrates the changes in quality of life over time from pre-diagnosis to post-diagnosis with the introduction of first-line TKI therapy.*
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