Practical Considerations in the Treatment Myeloproliferative Neoplasms: Prognostication and Current Treatment

Indy Hematology

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UC Irvine
March 9, 2019
Disclosures: Angela Fleischman

- Incyte – speaker’s bureau
2019 In Perspective for Myeloproliferative Neoplasms (MPNs)

Dr. William Dameshek First Categorizes Myeloproliferative Diseases


JAK2 V617F Mutation Discovery

First FDA Approved Drug for MF

First FDA Approved Drug for PV

Calreticulin Mutation Discovery

First NCCN Guidelines for MF, ET & PV

Updated Prognostic Scoring Tools for MF

Better Understanding of Role of Interferon

Many new Novel Treatments In Development
The Molecular Anatomy of MPNs: Few Patients Without an Evident Clone

- **PV**: JAK2 V617F
- **ET**: MPL, JAK2 exon 12, CALR exon 9, LNK, SH2B3, CBL
- **PMF**: JAK2 V617F, MPL, CALR exon 9, LNK, SH2B3, CBL

Noncanonical mutations:
- JAK2
- MPL
- Clonal TN
- Nonclonal TN
- ?? Unclear if clonal or nonclonal

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A354. Safety and Efficacy of Combined Ruxolitinib and Thalidomide in Patients with Myelofibrosis: Initial Results of a Phase II Study

A349. A New Prognostic Score for Advanced SM Based on Clinical and Genetic Characteristics of 210 Consecutive Patients

A353. Phase 2 Study of the Safety and Efficacy of INC8050465, a Selective PI3K Inhibitor, in Combination with Ruxolitinib in Patients with MF

A689. Comprehensive Clinical-Molecular Transplant Risk Model for Myelofibrosis Undergoing Allogeneic Stem Cell Transplantation

A577. Randomized Trial of Pegylated Interferon Alfa-2a Versus HU Therapy for the Treatment of High Risk PV and ET

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A578. Mutation-Enhanced International Prognostic Systems for Essential Thrombocythemia (MIPSS-ET) and Polycythemia Vera (MIPSS-PV)
# IPSS and DIPSS Scoring System for MF

**International Prognostic Scoring System (IPSS) At diagnosis**

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Number of risk factors</th>
<th>Median survival, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>11.3</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>1</td>
<td>7.9</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>High</td>
<td>≥3</td>
<td>2.3</td>
</tr>
</tbody>
</table>

**Dynamic International Prognostic Scoring System (DIPSS) during treatment**

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Number of risk factors</th>
<th>Median survival, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>Not Reached</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>1–2</td>
<td>14.2</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>3–4</td>
<td>4</td>
</tr>
<tr>
<td>High</td>
<td>5–6</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**Scoring criteria for IPSS and DIPSS**

- Age >65 years: 1 point each
- Constitutional symptoms: 1 point each
- Hemoglobin <10 g/dL: 1 point each
- WBC count >25 x 10^9/L: 1 point each
- Blood blasts ≥1%: 1 point each
- 2 points for Hgb <10 g/dL in DIPSS
GIPSS is based exclusively on mutations and karyotype.

MIPSS70+ version 2.0 utilizes both genetic and clinical risk factors. MIPSS70+ version 2.0 requires an online score calculator (http://www.mipss70score.it).

GIPSS features four and MIPSS70+ version 2.0 five risk categories.
What about prognostic scoring in PV/ET?

Cohort of 2035 patients
- 1321 patients with ET
- 356 with PV
- 309 with MF
- 49 with other MPN

Sequenced coding exons from 69 myeloid cancer genes in patients with myeloproliferative neoplasms, comprehensively annotating driver mutations and copy-number changes.

Developed a genomic classification for myeloproliferative neoplasms and multistage prognostic models for predicting outcomes in individual patients.
Genomic Subgroups in MPN and Phenotypic Characteristics

Grinfeld et al, NEJM 2018
https://cancer.sanger.ac.uk/mpn-multistage/
Mutation-Enhanced International Prognostic Systems for Essential Thrombocythemia (MIPSS-ET) and Polycythemia Vera (MIPSS-PV)

Ayalew Tefferi et al

- Spliceosome mutation information enhances survival prediction in ET and PV and identifies those at risk for fibrotic progression

- TP53 mutations predict leukemic transformation in ET
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Interferon-alpha in MPN

A579. Randomized Trial of Pegylated Interferon Alfa-2a Versus HU Therapy for the Treatment of High Risk PV and ET

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Results of the Myeloproliferative Neoplasms - Research Consortium (MPN-RC) 112 Randomized Trial of Pegylated Interferon Alfa-2a (PEG) Versus Hydroxyurea (HU) Therapy for the Treatment of High Risk PV and ET

John Mascarenhas et al

Randomized, open label, phase 3 clinical trial


n=168

Planned analysis
75 subjects treated for 1 year

INTERIM ANALYSIS

HU n=39
PEG n=36

FINAL ANALYSIS

HU n=86
PEG n=82

Pts who achieved a PR/CR at 12 months continued therapy for up to a maximum of 6 years

Primary objective
- Compare the CR rate following HU vs. PEG at 12 months with 3 month confirmation.

Secondary objectives
- Toxicity and tolerability PR rates
- Incidence of specific pre-defined Toxicities and tolerance to therapy
- Impact of therapy on key biomarkers
- Survival and incidence of myelodysplastic syndrome, myelofibrosis, or leukemic transformation
- Incidence of major cardiovascular events.

2016

CR rate at 12 months was 33% (HU) and 28% (PEG); p=0.6 - did not cross stopping boundary

ORR was 69% (HU) and 81% (PEG)

WHO = World Health Organization
CR = Complete Response
PR = Partial Response

Abstract 577, ASH 2018
Complete response (CR)
- Platelet count ≤ 400 x 10^9/L AND
- No disease-related symptoms* AND
- Normal spleen size on imaging AND
- WBC ≤ 10 x 10^9/L

Partial response (PR)
In patients who do not meet criteria for complete response
- Platelet count ≤ 600 x 10^9/L OR >50% reduction from baseline

No response (NR)
Any response that does not satisfy partial criteria

*Disease-related symptoms: microvascular disturbances, pruritus, headache
### MPN-RC 112 Response: 12 MONTHS

**Arm A (HU): 86 pts**  
PV: 44, ET: 42  

**Arm B (PEG): 82 pts**  
PV: 43, ET: 39  

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**Response at 12 months**  

<table>
<thead>
<tr>
<th>CR</th>
<th>ET</th>
<th>PV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19 (45.2%)</td>
<td>13 (29.5%)</td>
<td>32 (37.2%)</td>
</tr>
<tr>
<td>PR</td>
<td>11 (26.2%)</td>
<td>17 (38.6%)</td>
<td>28 (32.6%)</td>
</tr>
<tr>
<td>NR</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>UE*</td>
<td>11 (3 **)</td>
<td>12 (3 **)</td>
<td>23 (6 **)</td>
</tr>
</tbody>
</table>

**TOTAL**  
42  
44  
86

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<table>
<thead>
<tr>
<th>CR</th>
<th>ET</th>
<th>PV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17 (43.6%)</td>
<td>12 (27.9%)</td>
<td>29 (35.4%)</td>
</tr>
<tr>
<td>PR</td>
<td>10 (25.6%)</td>
<td>25 (58.1%)</td>
<td>35 (42.7%)</td>
</tr>
<tr>
<td>NR</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>UE*</td>
<td>9</td>
<td>4</td>
<td>13</td>
</tr>
</tbody>
</table>

**TOTAL**  
39  
43  
82

ORR: 69.8%  
75.0% accounting for withdrawals

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Abstract 577, ASH 2018
24 Month Response Data

- When considering all 106 patients who were eligible to receive treatment for 24 months (due to study closure)

<table>
<thead>
<tr>
<th></th>
<th>HU (n=54)</th>
<th>PEG (n=52)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ET</td>
<td>PV</td>
<td>Total</td>
</tr>
<tr>
<td>CR</td>
<td>6</td>
<td>5 (25%)</td>
<td>11 (20.4%)</td>
</tr>
<tr>
<td>PR</td>
<td>2 (8%)</td>
<td>9 (30%)</td>
<td>11 (20.4%)</td>
</tr>
<tr>
<td>ORR</td>
<td>8/24 (33.3%)</td>
<td>14/30 (46.7%)</td>
<td>22/54 (40.7%)</td>
</tr>
</tbody>
</table>

Abstract 577, ASH 2018
Spleen reduction by ultrasound

In patients with spleen > 13 cm at baseline:

**Hydroxyurea**

- Median -5.2% (-24.1 to 16.9%)
- 4/37 (10.8%) HU normalized spleen

**Pegasys**

- Median -5.7% (-36.7 to 53.8%)
- 6/36 (16.7%) PEG normalized spleen

In patients with spleen > 13 cm at baseline:
Bone marrow response by Treatment Arm and Disease type
Best Response (n=113)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>CR</th>
<th>PR</th>
<th>NR</th>
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</thead>
<tbody>
<tr>
<td>HU - ET</td>
<td>12</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>PEG - ET</td>
<td>8</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>HU - PV</td>
<td>6</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>PEG - PV</td>
<td>2</td>
<td>13</td>
<td>19</td>
</tr>
</tbody>
</table>

HU 18/54 (33.3%) vs. 10/59 (16.9%) for PEG, p=0.052

ET - disappearance of megakaryocyte hyperplasia
PV - presence of age-adjusted normocellularity and disappearance of trilinear hyperplasia

ET - megakaryocyte hyperplasia reduced
PV - marrow cellularity and trilineage hyperplasia reduced
Reduction of MK and marrow cellularity by 30% but doesn’t meet CR

ET / PV - Does not satisfy partial histo-pathology remission

Adapted from ELN-IWG [Barosi et al. Blood. 2013 6;121(23):4778-81]

Abstract 577, ASH 2018
Summary of Grade 3/4 Adverse Events by Disease Strata

• Adverse event of Grade 3 or higher (any attribution): 60 pts (37.0%)
  - HU: 22 (27.5%)
  - PEG: 38 (46.3%)

<table>
<thead>
<tr>
<th></th>
<th>HU</th>
<th>PEG</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET</td>
<td>12 (30.8%)</td>
<td>20 (51.3%)</td>
<td>32 (41.0%)</td>
</tr>
<tr>
<td>PV</td>
<td>10 (24.4%)</td>
<td>18 (41.9%)</td>
<td>28 (33.3%)</td>
</tr>
<tr>
<td></td>
<td><strong>22 (27.5%)</strong></td>
<td><strong>38 (46.3%)</strong></td>
<td><strong>60 (37.0%)</strong></td>
</tr>
</tbody>
</table>

• Adverse event of Grade 4 or higher: 6 pts (3.7%)
  HU: n=4 (hyperuricemia, lung cancer, thrombocytopenia, sepsis)
  PEG: n=2 (hyperuricemia, dyspnea)

Abstract 577, ASH 2018
Conclusions

• Conducting independent randomized studies in MPN is challenging but necessary to establish optimal therapy

• No difference in hematologic CR between the two treatment arms at 12 and 24 months

• Toxicity is not a major reason for discontinuation in either arm

• BM pathologic responses appear more frequent in ET versus PV and no difference between treatment arms

• Meaningful differences in response and toxicity between these two agents over time were not observed and both agents appear to be effective therapies for treatment naïve ET/PV patients

Abstract 577, ASH 2018
Impact on MPN Symptoms and Quality of Life of Front Line Pegylated Interferon Alpha-2a Vs. Hydroxyurea in High Risk Polycythemia Vera and Essential Thrombocythemia

Ruben Mesa et al.

• On HU, pts experienced worsening QoL (physical, cognitive functionina, HRQoL) and some persistent or transient worsened symptoms (inactivity, concentration)

• On PEG, pts experienced worsening of fever, dyspnea, appetite loss and PEG-related symptoms including flu-like symptoms, injection site irritation, blurry vision, and visual changes (all p<0.05), but not sad mood (not corrected for antidepressants).

Suggests obtaining CHR may have negative effects on patient symptoms

Change in TSS significantly differed (p=0.01) between arms:
• Increasing symptoms on HU vs PEG at 3 and 6 mo
• Lower symptom burden on HU vs PEG at 9 and 12 mos

Abstract 3032, ASH 2018
Long-Term Efficacy and Safety of Recombinant Interferon Alpha-2 Vs. Hydroxyurea in Polycythemia Vera: Preliminary Results from the Three-Year Analysis of the Daliah Trial - a Randomized Controlled Phase III Clinical Trial

Trine Knudsen et al

- Examined the difference in efficacy and safety of low-dose r-IFNα in PV patients ≤ 60 or > 60 years of age compared to HU > 60 years of age.

- 90 newly diagnosed or previously phlebotomized PV patients only

- Patients ≤ 60 years were randomized (1:1) to r-IFNα-2a (Pegasys®) or to r-IFNα-2b (PegIntron®)

- Patients > 60 years were randomized (1:1:1) to either r-IFNα-2a, r-IFNα-2b or to HU

- Starting dose of r-IFNα-2a and r-IFNα-2b was 45 or 35 µg/week

- HU dose was 500 to 2000 mg/day.

Abstract 580, ASH 2018
Response Rates

- Overall Response Rate (ORR)
  - 68% (13/19) for HU
  - 42% (14/33) for r-IFNα ≤ 60 years
  - 39% (13/33) for r-IFNα > 60 years

- Partial Hematologic Remission (PHR)
  - 53% (10/19) for HU
  - 9% (3/33) for r-IFNα ≤ 60 years
  - 9% (3/33) for r-IFNα > 60 years

- Complete Hematologic Remission (CHR)
  - 16% (3/19) for HU
  - 33% (11/33) for r-IFNα ≤ 60 years
  - 30% (10/33) for r-IFNα > 60 years

- Maintenance of CHR
  - 11% (2/19) for HU
  - 21% (7/33) for r-IFNα ≤ 60 years
  - 18% (6/33) for r-IFNα > 60 years

Molecular Responses

47 JAK2V617F positive patients were available for molecular response analysis after 36 months of therapy

- Partial Molecular Remission (PMR)
  - 21% (4/19) of HU treated patients
  - 24% (7/29) of r-IFNα treated patients ≤ 60 years
  - 18% (6/33) of r-IFNα > 60 years

- Complete Molecular Remission (CMR)
  - 7% (2/29) of the r-IFNα treated patients ≤ 60 years

- Median JAK2V617F reduction from baseline
  - 38% (31-63%) for HU
  - 79% (59-92%) for r-IFNα ≤ 60 years
  - 73% (49-97%) for r-IFNα > 60 years

Abstract 580, ASH 2018
Comparable Adverse Events (AE’s) HU vs PEG

Discontinuation of treatment for any reason after 36 months of therapy
• 21% (4/19) for HU
• 52% (17/33) for r-IFNα ≤ 60 years
• 45% (15/33) for r-IFNα > 60 years

Toxicity related discontinuation
• 5% (1/19) for HU
• 30% (10/33) for both r-IFNα ≤ 60 and > 60 years

Grade 3-4 AEs
32% (6/19) of HU treated patients
27% (9/33) in r-IFNα treated patients ≤ 60 years
42% (14/33) r-IFNα treated patients > 60 years

Serious Adverse Events (SAEs)
21% (4/19) for HU
9% (3/33) for r-IFNα ≤ 60 years
24% (8/33) for r-IFNα > 60 years.

Abstract 580, ASH 2018
Evidence for Superior Efficacy and Disease Modification after Three Years of Prospective Randomized Controlled Treatment of Polycythemia Vera Patients with Ropeginterferon Alfa-2b Vs. HU/Best Available Therapy (BAT)

Heinz Gisslinger et al

Primary Outcome Measures / Primary Endpoints
• Disease response rate* at 12 months
  * defined as hematocrit <45% without phlebotomy (at least 3 months since last phlebotomy), platelets <400 G/L, leukocytes <10 G/L, and normal spleen size

Secondary Outcome Measures / Secondary Endpoints
• Disease response rate at 3, 6 and 9 months
• JAK2 allelic burden changes
• Time to response
• Duration of response
• Number of phlebotomies
• Blood parameters
• Spleen size
• Disease related symptoms
• Adverse events
• Protocol-specific adverse events of special interest

*) non-inferiority: Hematologic Response
**) benefit: durable Hematologic Response, Progression Free Survival (PFS), PV symptom relief
PROUD-PV Results

83 (Ropeg) and 70 (HU/BAT) patients completed the 36-month efficacy analysis time point

CHR
• Ropeg 70.5% vs HU/BAT 51.4%
  \[p=0.0122; \text{RR [95\% CI]: 1.38 [1.07-1.79]}\]

CHR plus symptom improvement
• Ropeg 52.6% vs. HU/BAT 37.8%;
  \[p=0.0437; \text{RR [95\% CI]: 1.42 [1.01-2.00]}\]

PROUD-PV Safety

Comparable numbers of patients experienced adverse events
• 89.8% for Ropeg
• 90.6% for HU

Treatment-related adverse events
• 74.8% for Ropeg
• 78.7% for HU

The most common (>10%) treatment-related adverse events anemia, thrombocytopenia and leukopenia occurred more frequently under HU, whereas GGT increase was mainly observed under Ropeg. No new safety signals appeared in the third year of treatment.

Abstract 579, ASH 2018
PROUD-PV molecular responses

JAK2V617F molecular response:

• 66.0% on Ropeg vs 27.0% on HU/BAT (p<0.0001; RR [95% CI]: 2.31 [1.56-3.42])
• MR strongly correlated with CHR

Ropeg was found to reduce non-JAK2V617F mutations such as TET2 burden in some patients, HU was not
Approach to Treating Myelofibrosis

- **Fatigue**
  - ruxolitinib

- **Splenomegaly**
  - ruxolitinib

- **Anemia, thrombocytopenia**
  - Supportive care
  - Danazol

- **Progression to AML**
  - transplant
Survival After Ruxolitinib Discontinuation

Median Post-Ruxolitinib Survival = 14 months

62 paired samples

- beginning of ruxolitinib
- ruxolitinib discontinuation

Average time on rux: 13.1 mo

22 out of 62 acquired new mutations while on rux

- most frequent in ASXL1, TET2, EZH2, TP53
- also found 1 new MPL mutation
My MPN Registry (Mobile MPN Monitoring): A Tool for People With PV, ET, or MF

www.mympn.org

• A digital hub for patients to record and anonymously share their unique MPN journey with the research community

• Registrants can access a secure online portal with a personalized dashboard; as they complete surveys listed on the dashboard, the registry will provide insights into how the user's MPN experience compares to other registry users

• All patient data is protected and only shared according to individual user privacy settings

• A place for eligible patients to connect with upcoming drug trials and research that will help increase our knowledge about PV, ET, and MF

ASH 2018. Abstract ID: #119033