Current Status of MPN Guidelines: Response and Treatment

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MPNs: A historical view—the pre-JAK2 era

G. Heuck describes MF “Two cases of leukemia with peculiar blood and bone marrow findings”

Epstein and Goedel describe ET, noting a pt with extreme increase in platelets and bleeding

Vaquez and Osler describe PV

Dameshek coins the term, “MPD” and speculates on a shared pathogenesis

Nowell and Hungerford

The Ph Chromosome

PVSG established: Conduct of pivotal clinical trials in PV

A change in cancer therapy

1879
1892-1903
1931
1951
1960
1967
1996
MPNs: The JAK2 discovery era

- **2005**
  - Reports of the JAK2 V617F mutation in ET, PV, and MF patients

- **2006**
  - Reports of the MPL mutation in <10% ET and MF patients

- **2007-2011**
  - JAK-inhibitor clinical trials: Approval of the first specific MF treatment

- **2013**
  - Another “driving mutation:” CALR in ET and MF pts who lack JAK2 mutations

- **2014**
  - JAK-inhibitor clinical trials: Approval of the first specific PV treatment
  - Refined prognostic assessment and evaluation of novel drugs

- **MPN symptom burden assessment**
New mutations, evolving diagnostic criteria, new ways to assess symptoms, updated epidemiology, new prognostic assessments, new approved drugs, and many important clinical trials underway.....
Clinical Practice Guidelines

Created by expert panels that collect, organize, interpret and assess scientific evidence during a comprehensive review

Recommendations based on high and (low) quality evidence, and when lacking, based on expert/consensus opinion

Goals:

- Optimize patient care
- Help physicians weigh options when evidence is limited, no consensus exists, or both (!)
- Highlight research priorities

*Routinely updated to incorporate new information*
## Selected Existing MPN Guidelines and Consensus Statements

<table>
<thead>
<tr>
<th>Source</th>
<th>Content</th>
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<tbody>
<tr>
<td>International Working Group for MPN Research and Treatment/ELN (IWG-MRT/ELN)</td>
<td>Response assessment in Myelofibrosis</td>
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<tr>
<td></td>
<td>Response assessment in ET and PV</td>
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<tr>
<td>European Leukemia Net</td>
<td>Definition of Hydroxyurea Resistance or Intolerance</td>
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<td>European Leukemia Net</td>
<td>Guidance regarding approach to diagnosis and treatment of ET, PV, and MF</td>
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<tr>
<td>Austrian/German Society of Hematology/Oncology</td>
<td>Management of Venous Blood Clotting Events: Primary and Secondary</td>
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</tbody>
</table>
Why are response criteria needed?
Many novel treatment strategies are emerging!

- IFN + JAKi
- JAKi prior to HSCT
- Early/Low Risk MF
- High-Risk and/or Accelerating MF
- HMT followed by JAKi
- Selected Novel MF treatment strategies
- Selected Unique Targets
- Ameliorating the burden of anemia
- JAKi with: Danazol, IMIDS, Epo Stim agents, Sotatercept
- Synergistic combinations
- Telomerase CALR Abnormal splicesome machinery
- JAK-inhibitors +: HSP90i, HDACi, mTOR/PI3K/AKTi, Aurora Kinase A i

Stein et al. Leukemia 2014
Response criteria help objectively assess the value of new drugs/clinical trials

1). Include response categories that suggest that the natural history of the disease is being modified

<table>
<thead>
<tr>
<th>Response</th>
<th>Symptoms and Splenomegaly</th>
<th>Blood</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>Resolution of MPN symptoms and splenomegaly</td>
<td>Normal blood counts Hgb &gt; 10 g/dl Plts &gt; 100,000 Neutrophils &gt; 1000</td>
<td>-Restored productivity -Absence of scarring -Absence of immaturity</td>
</tr>
</tbody>
</table>

**Partial response:**

*Remission in the blood and resolution of symptoms/splenomegaly, but not necessarily in the bone marrow*

*Remission in the marrow, but incomplete improvement in blood counts*
Response criteria help objectively assess the value of new drugs/clinical trials

2). Objective evaluation of a drug’s ability to improve the MF-symptom burden

<table>
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<tr>
<th>Response</th>
<th>MF-Symptoms</th>
<th>Splenomegaly</th>
<th>Anemia</th>
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</table>
| Clinical Improvement      | 50% improvement in baseline symptom score, using valid instrument | --Modest spleen becomes non-palpable  
  --50% reduction in marked splenomegaly 
  Confirmed by imaging | 2 gram increase in hemoglobin  
  *Achieving transfusion-independence |

**Clinical improvement requires improvement in 1 aspect without worsening another**

- Transfusion-dependence: 6 units of blood in 12 weeks
- Transfusion-independence: Hgb >8.5, and no transfusion in 12 weeks
New treatments also emerging in ET and PV!

- Pegylated interferon
- JAK-inhibition
- HDAC inhibition (Givinostat)

- JAK-inhibition
- HDAC inhibition
- Pegylated interferon

*Delay onset of transformation?*

*Reduce Splenomegaly*

*Treat high counts*

*Manage risk of vascular complications*

*Relieve constitutional and systemic symptoms (fatigue and itching)*

In Contemporary Management of Myeloproliferative Neoplasms, Editors B Stein and B McMahon, Jaypee Brothers 2014
**Response criteria in ET and PV**

Aim: To provide response definitions in ET and PV that are clinically relevant, practical and reproducible

<table>
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<tr>
<th>Complete Response</th>
<th>Symptoms and Splenomegaly</th>
<th>Blood counts</th>
<th>Vascular concerns</th>
<th>Bone Marrow</th>
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</table>
| **ET and PV**     | Durable (3 months) resolution of MPN-symptoms and splenomegaly | PV: Hct < 45% w/o phlebotomy  
ET and PV: Plts < 400,000  
WBC < 10,000 | No bleeding or clotting events | ET: Absence of scarring and normal megakaryocyte number (parent of plts)  
PV: Absence of scarring, improvement to normal degree of efficiency |

**Partial response:** Improvement in symptoms, blood counts, and vascular concerns, but no remission in the bone marrow

Barosi, et al Blood 2014
Clinical trial goals can differ from an individual patient’s goals!

- Address High or Low Blood Counts
- Prevent bleeding/clotting
- Relieve Splenomegaly
- Relieve MPN Symptoms
- Improve Quality of Life!
- Delay Progression
**Consensus Definition:**

- “**Hydroxyurea Resistance/Intolerance**”

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<td><strong>Need for phlebotomy to keep Hct &lt; 45%</strong></td>
</tr>
<tr>
<td><strong>Plts &gt; 400,000 and WBC &gt; 10,000</strong></td>
</tr>
<tr>
<td><strong>Failure to shrink the spleen or improve symptoms of splenomegaly</strong></td>
</tr>
<tr>
<td>-- Low white cell counts (neutrophils &lt; 1000)</td>
</tr>
<tr>
<td>-- Low plts (&lt; 100,000)</td>
</tr>
<tr>
<td>-- Anemia (&lt; 10 g/dl)</td>
</tr>
<tr>
<td>Leg ulcers, GI symptoms, lung inflammation, fever</td>
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</table>

*At least one required

After at least 3 months, and at least 2 grams daily of Hydroxyurea

Barosi et al, Br J Haematology 2010

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Diagnosis

Use of World Health Organization Criteria (2008)

Patient communication

Guidance on communication of expectations and natural history of the disease

Risk classification

Age and prior history of thrombosis for ET/PV

Prognostic scoring systems for MF (IPSS, DIPSS, DIPSS-plus)

Goals of therapy

- **ET**
- **PV**

Manage Cardiovascular Risk Factors

**Aspirin?**
- In those with small vessel disturbance
- For all, if tolerated...

**Cytoreduction?**
- HU or IFN in high risk patients
- *Consider lowering plts if > 1.5 million due to bleeding risk*
- Anagrelide or IFN 2nd line

*HU or IFN in high risk patients, or in those with progressive increase in WBC, Plts >1.5 million, symptomatic splenomegaly, uncontrolled sx*

HU or IFN 2nd line

HU=hydroxyurea; IFN=interferon

Barbui, T et al: JCO 2011

Treatment of Myelofibrosis: (Covered later today!)

How to treat anemia

How to treat splenomegaly

When to consider surgery

How to address constitutional symptoms

Making decisions about transplantation

Treatment of special situations:

Pregnancy (Covered later today!)

Blood clotting in unusual locations

Management of itching

Published prior to approval of JAK-inhibitors for MF and PV!
Management of MPN-associated venous blood clotting complications

Protection: Special situations
- Protective blood thinners around the time of surgery
- Hold aspirin if possible
- Control MPN (blood counts) to the best ability

Initial Treatment
- Anticoagulation for at least 3-6 months, along with best control of the MPN
  - Many options in 2015 *(Discussed today)*
  - Avoid Aspirin unless benefit > risk when on blood thinner

Extended treatment
- For those w/ abd. vein clotting, recurrent events, or life-threatening events
- Best MPN control/ASA and continued re-evaluation

Consensus Statement from the German and Austrian Society of Hematology and Oncology: Annals of Hematology 2014

*(Selected) Practical Tips*
## Selected Existing MPN Consensus/Guidelines

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| IWG-ELN                                     | Response assessment in ET, PV, and MV  
*Designed for use in a clinical trial setting, not in clinical practice*                                                                                                                                   |
| ELN                                         | Definition of Hydroxyurea Resistance or Intolerance  
*Inadequate response may have a broader meaning in clinical practice*                                                                                                                                     |
| ELN                                         | Guidance regarding approach to diagnosis and treatment of ET, PV, and MF  
*Based on expert consensus, and published prior to JAK-inhibitor approval (2011 for MF, 2014 for PV)*                                                                                                   |
| Austrian/German Hematology-Oncology Society | Management of Venous Blood Clotting  
*Practical, yet less of an evidence base here (not the fault of the society!)*                                                                                                                          |

FYI: British Committee for Standards in Haematology also has guidelines for investigation and management of ET, PV, and MF, as well as guidance on MPN molecular markers.
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- Highlight research priorities
- Routinely updated to incorporate new information

Alexis Thompson, MD: Op Ed for the Hematologist, 2014
Practicing hematologists/oncologists could use practical, updated advice on approach to diagnosis, symptom and risk assessment, supportive care, and management strategies.
PV practice patterns in the pre-JAK2 era

PV practice patterns, 2002

Survey of ~1000 American Society of Hematology members

- Red cell mass, Epo level and blood gas most commonly used for diagnosis
- Most respondents used a target Hct ≤ 44%, though 16% used a target of 50 or 55%.
- ~65% treated only when a plts > 1 million, while a ~20% used a lower threshold, or treated only those with symptoms (12%).
- Hydroxyurea (HU) was most commonly used to treat increased platelets and 55% and 15% percent of respondents avoided interferon (IFN), and aspirin (ASA), respectively as treatments
PV practice patterns in the post-JAK2 era

Survey of practice patterns in the diagnosis and treatment of PV in 2014

Stein, BL et al, American Society of Hematology 2014, poster presentation
**Query** | **Respondents answer**
--- | ---
Indications for cytoreduction: | --Blood clotting: 75%
--Small vessel disturbance: 73%
--Age > 60 years: 59%

Agent of choice: | Hydroxyurea, 89%

Age restriction for cytoreduction: Concerns regarding younger age? | *50% prescribed regardless of age
34% avoided in those < 40 yrs
16 yrs vs. < 15 yrs experience (67% vs. 31% regardless of age)

Do you universally prescribe aspirin? | 79% universally prescribed, but more likely in those with <15 yrs experience vs. > 16 years experience (91% vs. 69%)
US Guidelines: Myeloid Neoplasms

Represented by the National Comprehensive Cancer Network:
--Diagnosis/Workup
--Supportive Care
--Treatment
Comprehensive, contemporary US-based MPN Guidelines....

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Commentary for the Journal of the National Comprehensive Cancer Network

“Myeloproliferative Neoplasms are in need of United States-Based Guidelines”

Brady L. Stein, Susan O’Brien, Peter Greenberg and Ruben A. Mesa

Commentary accepted, JNCCN 2015
Collaborators from NCCN member institutions
“Historical views, conventional approaches, and evolving management strategies for the MPN”

- Impact of mutations \((JAK2 \text{ V617F, CALR, MPL})\)
- Appropriate settings for testing
- MPN “mimicry”

“Occult MPN”—
\((\text{presentation with abdominal vein thrombosis})\)

Distinguishing ET from PV and early MF

This is a review, not a guideline!
"Historical views, conventional approaches, and evolving management strategies for the MPN"

Risk assessment for thrombosis

Age, blood clotting history

Mutational status, CV risk factors

? WBC count, allele burden, and other?

Prevention and treatment

Options, efficacy and safety of agents to lower counts (HU)

Interferon

Phlebotomy, blood thinning (duration?), anti-platelet agents

Special situations: Pregnancy, Surgery

Assessing risk for and managing thrombosis

This is a review, not a guideline!
“Historical views, conventional approaches, and evolving management strategies for the MPN”

Use of JAK-inhibitors in MF and PV

Ruxolitinib in MF and PV

Novel JAK-inhibitors in clinical trials (momelotinib, pacritinib)

Positive effects, Side effects

The role and timing of stem cell transplant

Pre-transplant therapy, donor options, use of prognostic scoring systems (IPSS, etc)

This is a review, not a guideline!
“Historical views, conventional approaches, and evolving management strategies for the MPN”

**Supportive Care**

*Symptom management*

*Addressing low blood counts*

*Treating anemia, iron overload*

*Massive splenomegaly (surgery vs radiation)*

*Other MPN’s need guidance as well!*

*Mastocytosis, Hypereosinophilia, Chronic Neutrophilic Leukemia*

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This is a review, not a guideline! *In commentary*
Comprehensive, contemporary US-based MPN Guidelines….

Hopefully we fill this slide in years to come!
Acknowledgements

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MPN Advocacy International
Jim and Antje Hjerpe/MPN-NET
My patients.....
Thank you for your attention!