An Overview of US-Based MPN Guidelines: A First Look

Brady L. Stein, MD MHS
Assistant Professor of Medicine
Division of Hematology/Oncology
February 25, 2017
“Medicine is a science of uncertainty and an art of probability.”

- William Osler
MPNs: A historical view—the pre-JAK2 era

Vaquez and Osler describe PV
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
Nowell and Hungerford

1879
1892-1903
1931
1951
1960
1967
1996

The Ph Chromosome

PVSG established: Conduct of pivotal clinical trials in PV

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

A change in cancer therapy
MPNs: The JAK2 discovery era (post 2005)

- Reports of the JAK2 V617F mutation in ET, PV, and MF patients
- Reports of the MPL mutation in < 10% ET and MF patients
- JAK-inhibitor clinical trials: Approval of the first specific MF treatment
- Another “driving mutation”: CALR in ET and MF pts who lack JAK2 mutations
- WHO Revision -Advanced Clinical Trials: JAKi IFNs Anti-fibrotics Combos
- JAK-inhibitor clinical trials: Approval of the first specific PV treatment
- MPN symptom burden assessment
New mutations, revised diagnostic criteria, new ways to assess symptoms, updated epidemiology, new prognostic assessments, new approved drugs, and many important clinical trials underway.....
Practicing hematologists/oncologists could use practical, updated advice on approach to diagnosis, symptom and risk assessment, supportive care, and management strategies.
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*
An overview of the process
1. Implicit plea to NCCN-our review article

“Historical views, conventional approaches, and evolving management strategies for the MPN”

- Introduce important themes to an the NCCN audience
- Approach to diagnostic challenges
- Approach to prognostic assessment
- Introduction of symptom monitoring tools
- Overview of treatment options
2. Explicit Plea to NCCN—our commentary

“Myeloproliferative Neoplasms are in need of US-Based Guidelines”

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

Published JNCCN 2015
3. Dr. Mesa invited to give a formal proposal to NCCN—they accepted!

4. MPN specialists from participating centers invited as panelists
Drafting the guidelines

- Present draft algorithms regarding MPN diagnosis and MF treatment
- Each committee member reviews and edits the draft algorithms
- Teleconference to discuss queries

Live meeting

Draft review

- Each member institution solicits feedback from colleagues re: preliminary draft

Institutional review

Final review

- Address institutional comments
- Committee reviews a final draft for approval

Chair: Dr. Mesa; Co-chair: Dr. Jamieson; NCCN team and panelists
Themes: Symptoms and Risk Group

1. Symptom assessment (and reassessment!)
   Emphasize use of **MPN-symptom assessment tool** at diagnosis, and throughout follow-up

   Symptoms have a significant impact on decision-making in the algorithms!

2. Risk assessment

   Treatment strategies can differ based on risk—this is especially the case when considering transplant
How we assess symptoms: TSS

1. Patient reported assessment
   *Absent to Worst Imaginable (0-10)*
   Fatigue (worst level last 24 hrs)
   Filling up quickly when you eat (early satiety)
   Abdominal discomfort
   Inactivity
   Problems w/ concentration compared to prior to my MPD
   Numbness/Tingling Night sweats
   Itching (pruritus)
   Bone pain (diffuse not joint pain or arthritis)
   Fever (>100 F)
   Unintentional weight loss last 6 months

*Emphasize need to combine subjective (symptoms) and objective (blood counts, spleen, etc) assessments*
How we assess risk: Myelofibrosis

“IPSS or Dynamic IPSS”

Age > 65
Constitutional symptoms (fever, night sweats, weight loss)
Anemia
High white cell count ≥1% circulating blasts

*Dynamic IPSS-plus

Transfusion-dependence
Platelets < 100
Abnormal chromosome testing

Low risk
Int-1 risk
Int-2 risk
High risk

We are moving towards use of molecular genetic markers to add precision

IPSS: newly diagnosed pts; dynamic can be assessed throughout disease
How we assess response

1). 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</td>
<td>-Restored productivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hgb &gt; 10 g/dl</td>
<td>-Absence of scarring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plts &gt; 100k</td>
<td>-Absence of immaturity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neutrophils &gt; 1000</td>
<td></td>
</tr>
</tbody>
</table>

Partial response:
Remission in the blood and resolution of symptoms/splenomegaly, but not necessarily in the bone marrow, or remission in the marrow, but incomplete improvement in blood counts

*Guidelines emphasize that the response may not meet these thresholds, but still can be meaningful to our patients

Tefferi et al, Blood 2013
### How we assess response

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

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

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

*Guidelines emphasize that the response may not meet these thresholds, but still can be meaningful to our patients*
Diagnosis/Workup

Guidelines include tables outlining WHO Diagnostic Criteria for ET, PV and MF, as well as post-ETMF, and post-PVMF.
Suspicion for MPN: Key points

Key to establish the proper MPN diagnosis, giving overlapping symptoms and lab tests

- History taking: Assess MPN symptoms and clotting and/or bleeding history
- Physical Examination: Measure spleen (by palpation)
- Blood counts and chemistry testing
- Molecular testing (*JAK2, MPL, CALR*)
- *Bone marrow testing*
- Other tests, based on need: Bleeding evaluation?

*Diagnosis is based on World Health Organization 2016 revision*
Treatment Algorithms

Low risk MF
Int-1 MF
Int-2/High Risk MF
Anemia algorithm
Higher risk situations
Low risk MF

Assess symptom burden

Asymptomatic
Watch and Wait (or Clinical trial)

(If this changes)

Symptomatic
-Ruxolitinib
-Interferons
-Clinical trial

Monitor for progression of Sx and Rx response *Each 3-6 months*

If progression, then follow to next algorithm

If therapy inadequate, can use another choice on this list

*Sx: Symptoms; Rx: Treatment*
**Intermediate-1 risk MF**

Assess symptom burden

Observation
- If Symptomatic:
  - Ruxolitinib
  - Clinical trial
  - *Transplant

Monitor for progression of Sx and Rx response
*Each 3-6 months*

If progression, then follow to next algorithm

If therapy inadequate, can use another choice on this list

*If there was a risky genetic marker, for example*  

Sx: Symptoms; Rx: Treatment
Intermediate-2/High risk MF

Transplant candidate?

- Not a transplant candidate
  - Prioritized sx burden: Spleen/Symptoms

- Not a transplant candidate
  - Prioritized MF sx/burden: Symptomatic anemia

- Low plts: Consider clinical trial
  - Plts > 50k
    - Ruxolitinib
    - Clinical Trial

- Follow MF-anemia algorithm

Allo Stem Cell transplant

Monitor for progression of Sx and Rx response
*Each 3-6 months*
Management of MF-anemia

Exclude other causes of anemia
(Iron/B12/folate, blood cell destruction)

Treat reversible causes, if present
Transfusion of red cells as form of support

- Epo Level < 500 U
- Epo Level > 500 U

Epo Stimulating Agents
Examples:
Procrit
Aranesp

Clinical trial is an upfront consideration here, or in the event that therapy is inadequate

Androgens:
Danazol or another androgen
IMIDs
Thal/Lenalidomide (w/ Prednisone)
MPN-Accelerated Phase
Blasts 10-19% in peripheral blood or bone marrow

MPN-Blast Phase
Blasts 20% in peripheral blood or bone marrow

Yes

Transplant Candidate?
Hypomethylating Agent or chemotherapy with hope to induce remission or control disease prior

No, not a candidate

- Clinical trial
- Hypomethylating Agent (an example here is Vidaza or Dacogen)
- Low intensity induction chemotherapy (per NCCN AML guidelines)

If on ruxolitinib, may be continued for control of splenomegaly/symptoms
Other helpful information

Special considerations regarding use of Ruxolitinib
Special considerations for use of Ruxolitinib

Monitoring recommendations
  Symptom assessment at baseline and during follow-up
  Blood count monitoring recommendations
  Caution about premature discontinuation/rebound

Dosing recommendations
  Initial, based on platelet count
  Modifications based on insufficient response
  Modifications based on low platelets/white cells

Side effects to watch for:
  Infection, Skin Cancer, Weight gain, cholesterol changes
NCCN Evidence Blocks

• Evidence blocks will be added soon to the NCCN guidelines

• These blocks are a graphic representation of the panel’s scores of efficacy, safety, quality of evidence, consistency of evidence, and affordability of each regimen recommended in the algorithms

• The aim of evidence blocks within the guidelines is to assist clinicians when discussing and selecting treatment options with patients.
Next steps

Annual review/update of MF guidelines, to incorporate changes in clinical practice

1st draft of ET and PV guidelines underway
   First conference call to review draft 1 in late January

Emphasis on:
   Diagnosis
   Prognostic assessment
   Treatment based on risk and symptoms
   Special situations: Thrombosis, Surgery, Pregnancy
Thank you—to our patients

“He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all”

--William Osler
Acknowledgements

Ruben Mesa

My Northwestern Colleagues

MPN Research Foundation

MPN Advocacy International

Jim and Antje Hjerpe/MPN-NET

My patients.....

My family!
Outside of work....

Before the playoffs

The Grateful Dead 50 yr anniversary concert
Thank you for your attention!