Diagnosing and Treating Myeloproliferative Neoplasms

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Welcome and Introductions
Disclosures

Jason Gotlib, MD, MS is on the Advisory Board for Incyte. He has received Grant Support from Incyte, Gilead, Novartis, Promedior, and CTI BioPharma.
Myeloproliferative Neoplasms (MPNs)

- Chronic Myelogenous Leukemia (CML)
- Polycythemia Vera (PV)
- Essential Thrombocythemia (ET)
- Primary Myelofibrosis (PMF)
- Chronic Eosinophilic Leukemia, Not Otherwise Specified (CEL, NOS)
- Chronic Neutrophilic Leukemia (CNL)
- Systemic Mastocytosis (SM)
- MPN Unclassified (MPN-U)

Myeloproliferative Neoplasms (MPNs) Are a Group of Hematologic Malignancies

- Philadelphia chromosome-negative MPNs\textsuperscript{1,2}
  - Acquired clonal stem cell disorders
    - Molecular / cytogenetic abnormalities
  - Overproduction of one or more types of blood cells in the absence of a definable stimulus
  - Extramedullary hematopoiesis (e.g. big spleen)
  - Bone marrow fibrosis
  - Propensity for transformation to acute leukemia
  - Increased risk of thrombosis and bleeding

References:

Evolution of Myeloproliferative Neoplasms

- **PV**: 10-20%
- **ET**: 5-10%
- **Post PV or ET Myelofibrosis**: 10%
- **AML**: <5%
- **Primary MF**: 15-20%

JAK2 V617F Mutation Frequency

- **Polycythemia Vera**: 95-98%, Exon 12 JAK2 ~2%
- **Essential Thrombocythemia**: 50-60%
- **Primary Myelofibrosis**: 50-60%
Mutational landscape of BCR-ABL1-negative myeloproliferative neoplasms (MPN)
Erythropoietin (EPO receptor) is a cytokine receptor that binds to the cell membrane, leading to the activation of Jak kinases. This results in the phosphorylation of STAT proteins, which translocate to the nucleus to transcribe genes involved in cell survival, migration, and proliferation.

Thrombopoietin (TPO) is another cytokine receptor that binds to the cell membrane, activating Jak kinases. This leads to the phosphorylation of CALR proteins, which also translocate to the nucleus to transcribe genes involved in cell survival, migration, and proliferation.
Mutations in genes outside of the JAK-STAT pathway in MPN patients

- JAK2 V617F
- CBL
- JAK2 exon 12
- MPL
- CALR LNK
- TET2
- ASXL1
- IDH1, IDH2
- DNMT3A
- EZH2
- SRSF2

Average number of acquired mutations in:
- PV: 6.5
- ET: 6.5
- PMF: 13

Klampflet al, NEJM 2013
## Diagnosis of MPN

<table>
<thead>
<tr>
<th>Diagnostic Procedure</th>
<th>Potential Information Obtained</th>
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| **Patient Interview**                         | • History of blood clots or bleeding?  
• Reactive (secondary) causes for a high red blood cell or platelet count?  
• Symptom burden?  
• Medical problems that can interact with MPN?  
• Relevant medications? |
| **Physical Examination**                      | • Big spleen or liver?  Signs of blood clot in leg?                                                                                                        |
| **Complete blood count and smear review**     | • Elevated white blood cell, hemoglobin, or platelet count?  
• Appearance of myelofibrosis changes in the peripheral blood?  Circulating blasts? |
| **Chemistries/liver function**                | • EPO level?  Iron deficiency?  Increased LDH?                                                                                                              |
| **Bone marrow biopsy**                        | • Bone marrow cellularity?  Increased blasts?  Appearance and number of precursor white & red blood cells, and megakaryocytes?  Increased blasts?  Grade of fibrosis if present?  
• Chromosome abnormalities?                   |
| **Molecular Testing**                         | • JAK2 V617F mutation present?  If not, CALR or MPL?  Additional poor-risk genetic mutations?                                                             |
Burdens of PV and ET

- Vascular Risks
- Treatment Side Effects
- Symptoms: itching, fatigue, erythromelalgia
- Transformation

Burdens of Myelofibrosis

- Anemia
- Enlarged Spleen
- Clonal MPN Cells & Inflammatory cytokines
- Fibrosis In Marrow
- Symptoms: Fever, Weight Loss, Night Sweats, Itching, Bone pain, Fatigue

Transformation to AML
Goals of MPN Therapy

- Cure
- Eliminate / reduce symptoms
- Decrease in splenomegaly
- Prevent future clotting / bleeding events
- Improvement of blood counts
- Cytogenetic / molecular response
- Reduce risk of evolution to AML
### Risk-Adapted Therapy for PV and ET

#### Polycythemia vera

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<thead>
<tr>
<th>Risk group</th>
<th>Age ≥ 60 or history of thrombosis</th>
<th>Treatment</th>
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<td>Low</td>
<td>No</td>
<td>Low-dose aspirin + phlebotomy</td>
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<tr>
<td>High*</td>
<td>Yes</td>
<td>Low-dose aspirin + phlebotomy + cytoreduction</td>
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<td>(hydroxyurea or [PEG]-interferon-alpha)*</td>
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#### Essential thrombocythemia

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<th>Risk group</th>
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<th>Treatment</th>
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<td>Low</td>
<td>No</td>
<td>Low-dose aspirin</td>
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<tr>
<td>High*</td>
<td>Yes</td>
<td>Low-dose aspirin + cytoreduction</td>
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<tr>
<td></td>
<td></td>
<td>(hydroxyurea or [PEG]-interferon-alpha)*</td>
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*Extreme thrombocytosis (> 1-1.5 million) is a risk factor for bleeding (consider screening for aVWD before starting ASA)*

* Anagrelide is typically employed as second line therapy for control of platelets

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*Ruxolitinib approved in 2014 as 2nd line therapy for patients with PV with inadequate response or intolerance to hydroxyurea*
PV: Thrombosis Risk and Hct

![Graph showing the relationship between Hct and vascular occlusive episodes per million over 10 years.]

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Events and Intensity of Treatment in Polycythemia Vera

Roberto Marchioli, M.D., Guido Finazzi, M.D., Giorgina Specchia, M.D., Rossella Cacciola, M.D., Ph.D., Riccardo Cavazzina, Sc.D., Daniela Cillon, M.D., Ph.D., Valerio De Stefano, M.D., Elena Elli, M.D., Alessandra Iurlo, M.D., Ph.D., Roberto Latagliata, M.D., Francesca Lunghi, M.D., Monia Lunghi, M.D., Rosa Maria Marfisi, M.S., Pellegrino Musto, M.D., Arianna Masciulli, M.D., Ph.D., Caterina Musolino, M.D., Ph.D., Nicola Cascavilla, M.D., Giovanni Quarta, M.D., Maria Luigia Randi, M.D., Davide Raperzzi, M.D., Marco Ruggeri, M.D., Elisa Rumi, M.D., Anna Rita Scortechini, M.D., Simone Santini, M.D., Marco Scarano, Sc.D., Sergio Siragusa, M.D., Antonio Spadea, M.D., Ph.D., Alessia Tieghi, M.D., Emanuele Angelucci, M.D., Giuseppe Visani, M.D., Alessandro Maria Vannucchi, M.D., and Tiziano Barbui, M.D., for the CYTO-PV Collaborative Group®

Optimal Hct Target <45% in the Treatment of PV: Cyto-PV Study

- Baseline characteristics balanced between both groups
- ~50% had received an initial diagnosis of PV within 2 years before randomization
- 67% were at high risk because of advanced age or previous thrombosis
- 25% had thrombotic events >12 months before randomization

Low Hct group
n = 182
More intensive treatment (target Hct level <45%)

High Hct group
n = 183
Less intensive treatment (target Hct level 45%–50%)

Cardiovascular Mortality or Major Thrombosis Was Significantly Lower in Patients With PV and Hct Level of <45%

The rate of death from cardiovascular events or major thrombosis is 4-fold lower in patients who maintain Hct level target of <45% compared with those with a target of 45%–50%
Indications for Cytoreduction in PV and ET

- High-risk patients
- Poor tolerance of, or frequent phlebotomy
- Symptomatic /progressive splenomegaly; severe disease symptoms
- Platelet count > 1.5 million or progressive increase in the WBC count
- Hydroxyurea or IFN-α is first-line cytoreductive therapy at any age for PV/ET
- Hydroxyurea should be used with caution in young patients (age <40 yrs)
- Pipobroman, busulfan, and $^{32}$P are second-line therapies; used for patients with short life expectancy because they increase the risk of leukemia

Barbui et al, J Clin Oncol, 2011

Pegylated interferon-α-2a
In PV and ET:
Hematologic and Molecular Response Rates

Quintas-Cardama et al, Blood, 2013
RESPONSE Trial in PV: Ruxolitinib vs. Best Available Therapy

Vannucchi et al., NEJM, 2015

RESPONSE Trial: Symptom Assessments

Vannucchi et al., NEJM, 2015
Core Issues with Available Drugs for PV

<table>
<thead>
<tr>
<th>Tolerability</th>
<th>Hydroxyurea (HU)</th>
<th>[PEG]-IFN-α (HU-resistant/intolerant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually good tolerance</td>
<td>Decreased tolerability &amp; drop out</td>
<td>Well-tolerated</td>
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</tbody>
</table>

| Disease Natural History | “Cosmetic” | Potential for disease modification | No evidence for disease modification |

Myelofibrosis
Prognostic Scoring Systems

- Age >65
- Hb < 10 g/dL
- WBC > 25,000/mm³
- Constitutional symptoms
- Peripheral blood blasts >1%
- RBC transfusion dependence
- Platelet count < 100,000/mm³
- Unfavorable cytogenetics

IPSS
DIPSS Plus

Cervantes et al, Blood, 2009
Gangat et al, J Clin Oncol, 2011
DIPSS Plus

<table>
<thead>
<tr>
<th>Risk Level</th>
<th># Adverse Points</th>
<th>Median Survival</th>
<th>Time (months)</th>
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<tbody>
<tr>
<td>Low risk</td>
<td>0</td>
<td>185 months</td>
<td>15.4 yrs</td>
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<tr>
<td>Intermediate-1 risk</td>
<td>1</td>
<td>78 months</td>
<td>6.5 yrs</td>
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<tr>
<td>Intermediate-2 risk</td>
<td>2-3</td>
<td>35 months</td>
<td>2.9 yrs</td>
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<tr>
<td>High risk</td>
<td>4-6</td>
<td>16 months</td>
<td>1.3 yrs</td>
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Gangat et al., J Clin Oncol, 2011

Conventional Medications for MF

**Medicines for MF Anemia**
- Prednisone
- Androgens
- EPO
- Thalidomide +/- prednisone

**Medicines for MF Spleen**
- Hydroxyurea
- Busulfan
- 2-CDA
- Splenectomy
- Splenic Radiation

**Medicines for Anemia & Spleen**
- Lenalidomide +/- prednisone

**Medicines for MF Symptoms**
- Previously None
Myelofibrosis (MF) in 2016

1. Only the JAK inhibitor ruxolitinib is FDA-approved for MF (2011)

2. No medicine has been proven to cure, or definitively alter the natural history of MF

3. Allogeneic stem cell transplant can cure MF, but carries significant risks (use must be selective)

### JAK2 inhibitors tested in clinical trials in patients with myelofibrosis

<table>
<thead>
<tr>
<th>Agent</th>
<th>JAK family target</th>
<th>Non-JAK family target</th>
<th>Heme toxicity</th>
<th>Non-heme toxicity</th>
<th>Heme response</th>
<th>BMR</th>
<th>CMR</th>
<th>Trial phase</th>
<th>NCT#</th>
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<tr>
<td>Ruxolitinib (INCB18424)</td>
<td>JAK1/2</td>
<td>Hg Plts</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>III</td>
<td>III</td>
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<td><strong>FDA New Drug Application</strong></td>
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<tr>
<td>Pacritinib (SB1518)</td>
<td>JAK2</td>
<td>FLT3</td>
<td>Hg</td>
<td>GI</td>
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<td>No</td>
<td>III</td>
<td>III</td>
<td>NCT01773187, NCT02055781</td>
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<td>Mometinib (CT387)</td>
<td>JAK2/2</td>
<td>JNK1/2</td>
<td>Plts</td>
<td>Neuro</td>
<td>Anemia</td>
<td>No</td>
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<td>Vandetanib (LY2784644)</td>
<td>JAK2 V617F</td>
<td>Hg</td>
<td>Renal TLS</td>
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<td>No</td>
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<td>BMS-911543</td>
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<td>Plts</td>
<td>Lipase</td>
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<td>No</td>
<td>I/II</td>
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<td>AZD12480</td>
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Courtesy of J. Mascarenhas ASH 2015
Ruxolitinib in Myelofibrosis: True/False

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Managing the side effects of anemia and thrombocytopenia

- Consider starting at the lower-dose range (10 mg BID) and dose-escalate
- Options to mitigate drug-induced anemia and/or RBC transfusions:
  - Erythropoietin (Procrit), danazol
Splenomegaly in MF Patient Pre-Therapy

Splenomegaly after 2 Months of Therapy
Duration of Spleen Response (COMFORT-II trial)

Loss of response: no longer a ≥ 35% reduction that is also a > 25% increase over nadir

- Median duration of response: ruxolitinib, 3.2 years
- The Kaplan-Meier estimated probability of maintaining response:
  - 3 years, 0.51 (95% CI, 0.38-0.62)
  - 5 years, 0.48 (95% CI, 0.35-0.60)

For patients who achieved a ≥ 35% reduction at any time during randomized treatment; crossover patients are not summarized.

![Duration of Spleen Response (COMFORT-II trial)](image)

Novel Non-JAK2 inhibitors in clinical trials for patients with myelofibrosis

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Trial phase</th>
<th>NCT #</th>
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<tbody>
<tr>
<td>Epigenetic</td>
<td>Histone deacetylase (HDAC)</td>
<td>Vorinostat (Panobinostat)</td>
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<td>DNA methyltransferase (DNMT)</td>
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<td>Decitabine</td>
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<td>Signaling pathway</td>
<td>Janus Kinase 1 (JAK1)</td>
<td>Incib110 (Sorafenib)</td>
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<td>Checkpoint inhibitor and immunomodulator</td>
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<td>Peptide toxin</td>
<td>SL-401</td>
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*Courtesy of J. Mascarenhas ASH 2015*
PRM-151 in Myelofibrosis: Durable Efficacy and Safety at 72 Weeks

Srdan Verstovsek1, Olga Pozdnyakova2, Robert Hasserjian3, Mohamed Salama4, Ruben Mesa5, Lynda Foltz6, Vikas Gupta7, John Mascarenhas8, Ellen Ritchie9, Ronald Hoffman9, Richard Silver9, Marina Kremyanskaya8, Zeev Estrov1, Elizabeth Trehu10, Hagop Kantarjian1, Jason Gotlib11

1MD Anderson Cancer Center, Houston, TX; 2Brigham and Women’s Hospital, Boston, MA; 3Massachusetts General Hospital, Boston, MA; 4University of Utah, Salt Lake City, UT; 5Mayo Clinic, Scottsdale, AZ; 6St. Paul’s Hospital, University of British Columbia, BC, CA; 7Princess Margaret Hospital, Toronto, ON, CA; 8Mt Sinai Medical Center, New York, NY; 9Weill Cornell Medical Center, New York, NY; 10Promedior, Inc., Lexington, MA; 11Stanford Cancer Institute, Stanford, CA

Abstract 59, ASH 2015

PRM-151: Recombinant Human Pentraxin-2 (PTX-2)

- PTX-2 is an endogenous regulator of tissue repair
- PTX-2 binds to damaged tissue and monocytes/macrophages
- PTX-2 prevents and reverses fibrosis in pre-clinical models
- PTX-2 levels are low in MF patients
  - Also low in patients with renal, pulmonary and liver fibrosis

Hypothesis:“ReducL on‘of’bone‘marrow’fibrosis‘will’restore‘hematopoiesis’and’improve‘cytopenias’

Verstovsek et al, ASH 2015
A Pilot Study of the Telomerase Inhibitor Imetelstat for Myelofibrosis

Ayalew Tefferi, M.D., Terra L. Lasho, Ph.D., Kebede H. Begna, M.D., Mrinal M. Patnaik, M.D., Darci L. Zblewski, C.N.P., Christy M. Finke, B.Sc., Rebecca R. Laborde, Ph.D., Ermenet Wassie, M.D., Lauren Schimek, B.S., Curtis A. Hanson, M.D., Naseema Gangat, M.D., Xiaolin Wang, Ph.D., and Animesh Pardanani, M.D., Ph.D.


Double and triple combination therapy trials in chronic and advanced phases of myelofibrosis

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Courtesy of J. Mascarenhas
ASH 2015
Side Effect Management

Disease Symptoms

- Fatigue / Anemia
- Abdominal discomfort
- Infection
- Bleeding/bruising
- Weight loss

Toxicity

- RBC & platelet transfusions
- Procrit, danazol
- Antibiotics
- Pain medications
- Caloric supplementation
- Exercise
- Hold, reduce, or stop therapy

Treatment

The Good Patient (1):
Open Communication with your Treatment Team

- Asks questions about the disease and treatment side effects
- Details prior and current medications and allergies
- Compliant with medication
- Adheres to the schedule of visits/follow-up
- Immediately informs the team of new, concerning symptoms
- Contacts the team before taking new medications or if admitted to the hospital
The Good Patient (2):
Open Communication with your Treatment Team

- Partners with family and friends to increase support
- Patient as diarist
- Self-advocacy

Resources for MPN Education & Finding a Clinical Trial

- Your local hematologist
- MPN specialist at an academic medical center
- Patient support groups
- Online / social media

Search engine of registered clinical trials: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

- Leukemia & Lymphoma Society [www.lls.org](http://www.lls.org)
- Cancer Research & Treatment Fund, Inc.: [www.crt.org](http://www.crt.org)
- MPN Education Foundation: [www.mpninfo.org](http://www.mpninfo.org)
- MPN Research Foundation: [www.mpnresearchfoundation.org](http://www.mpnresearchfoundation.org)
- MPN Advocacy & Education International: [www.mpnadvocacy.com](http://www.mpnadvocacy.com)
Question & Answer Session

The speakers’ slides are available for download at www.LLS.org/programs

The Leukemia & Lymphoma Society (LLS) offers:

Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.

- EMAIL: infocenter@LLS.org
- TOLL- FREE PHONE: (800) 955-4572

Questions to ask your treatment team: www.LLS.org/whattoask

Free education materials: www.LLS.org/booklets

An online social network and registry for people living with or supporting someone with blood cancer.

- WEBSITE: CommunityView.LLS.org