What MPN Patients Have Taught US

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What Have MPN Patient Taught US?

1. Burden of having an MPN includes several clinical features including MPN associated symptoms
2. Symptoms are heterogeneous and variable across MPN subtype and risk
3. MPN symptoms correlate with disease biology, risk, possibly progression?
4. Burden of having an MPN extends beyond symptoms to distress and employment
5. Tracking symptom changes relevant for measuring value of medical treatments
6. Non pharmacologic options may have a role, alongside medicines or transplant, in MPN patient health and QoL
Assessing MPN Burden

WHO Diagnosis Does Not Tell Whole Story

**MPN Symptoms**
- MF > PV > ET
- Multifactorial
- Some ET/PV > MF
- Cytoreductive rx frequently not effective

**Baseline Health**
AGE/ Medicines Comorbidities

**Vascular Events**
- PV/ET > MF
- Counts matter
- Can be unrecognized

**Cytopenias**
- MF > ET/PV
- Anemia
  - MF 75%
  - TX Dep 25%
- TPN 30%

**Progression**
- PV/ET to MF
- PV/ET to AML
- MF to AML
- ? 2nd MDS

**Splenomegaly**
- MF > ET/PV
- Pain not always a function of size

**Cytopenias**
- MF > ET/PV
- Anemia
  - MF 75%
  - TX Dep 25%
- TPN 30%

**MPN Symptoms**
- MF > PV > ET
- Multifactorial
- Some ET/PV > MF
- Cytoreductive rx frequently not effective
MPN SYMPTOMS

- Abdominal Pain
- Early Satiety
- Inactivity
- Abdominal Discomfort
- Fatigue
- Insomnia
- Itching
- Depression
- Sadness
- Fever
- Weight loss
- Night Sweats
- Numbness
- Fatigue
- Concentration
- Tingling
- Pain
- Headache
- Cough
- Mood
- Problems
- Mood
Evolution of MPN Symptom Assessment Tools

- **MF – SAF 2009** (19 items)
- **MF – SAF 2.0** (7 items 2011)
- **JCO 2012 Brief Fatigue Inventory (BFI) – 9 Items**
- **Spleen Sx – 4 Items**
- **Constitutional Sx – 5 Items**
- **QOL 1 Item**
- **Vascular and Ψ Sx – 9 Items**

**MPN–SAF 2011** (27 items)
- **Blood 2011**
- **MPN–SAF TSS (10 items 2012)**
- **JCO 2013**

**MPN–SAF Languages**
- English
- French
- German
- Spanish
- Dutch
- Swedish
- Italian
- Portuguese
- Mandarin
- Japanese
- Hebrew
- Arabic

**MPN–SAF Languages**
MPN SAF TSS “MPN10” in Many Languages

English

Name: ________________________
Date: _________________________

Fill out the form below to track the burden of your symptoms.

Symptoms: 1 to 10, 0 if absent and 10 being worst imaginable

Please rate your fatigue (awakening, tiredness) by circling the one number that best describes your WORST level of fatigue during the past 24 hours:

Fatigue
0 1 2 3 4 5 6 7 8 9 10

(Absent) (Worst imaginable)

Circle the one number that describes how much difficulty you have had with each of the following symptoms during the past week:

Filling up quickly when you eat (lowest safety)
0 1 2 3 4 5 6 7 8 9 10

(Absent) (Worst imaginable)

Abdominal discomfort
0 1 2 3 4 5 6 7 8 9 10

(Absent) (Worst imaginable)

Inability
0 1 2 3 4 5 6 7 8 9 10

(Absent) (Worst imaginable)

Problems with concentration - compared to before my diagnosis
0 1 2 3 4 5 6 7 8 9 10

(Absent) (Worst imaginable)

Night sweats
0 1 2 3 4 5 6 7 8 9 10

(Absent) (Worst imaginable)

Rash (pruritus)
0 1 2 3 4 5 6 7 8 9 10

(Absent) (Worst imaginable)

Bone pain (stiffness, red joint pain or arthritis)
0 1 2 3 4 5 6 7 8 9 10

(Absent) (Worst imaginable)

Fever (>37.8°C or 100°F)
0 1 2 3 4 5 6 7 8 9 10

(Absent) (Anorexic)

Unexplained weight loss last 6 months
0 1 2 3 4 5 6 7 8 9 12

(Absent) (Worst imaginable)

To help you get a clear overall picture of how you are feeling, you can add up all your scores to calculate your Total Symptom Score. 

Total: ______________________

You can also fill in this form and find more expert information about myeloproliferative neoplasms online at www.spottingsonMHN.com
MPN10: allows visual assessment

Classic Signs and Symptoms of MPNs

Geyer H L, and Mesa R A Blood 2014;124:3529-3537
What is MPN Symptom Burden in Patients vs. General Population?

*MOSAICC Population Vs. Controls*

Image courtesy of Ruben A. Mesa, MD
Definitions

HRQOL in MPNs?

- MPN related symptoms
- Medication related toxicities
- Problems from prior MPN complications
- Stressors from having their MPN
  - Financial
  - Emotional
  - Intrapersonal
- Co-morbidities
- Hassle of medical care
What Have MPN Patient Taught US?

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6. Non pharmacologic options may have a role, alongside medicines or transplant, in MPN patient health and QoL
What is “Symptomatic” in MF, enough to consider Rx?

Analysis of 425 MF with MPN-10, DIPSS Risk, Spleen Size

Table 1: Ordinal logistic regression models of DIPSS risk score (N=420) by symptoms in JAK2-naïve myelofibrosis patients.

<table>
<thead>
<tr>
<th>Model</th>
<th>DIPSS Risk AIC</th>
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<tbody>
<tr>
<td>TSS &gt;20</td>
<td>936.657*</td>
</tr>
<tr>
<td>Worst single symptom score &gt;5</td>
<td>935.281*</td>
</tr>
<tr>
<td>Worst single symptom score &gt;6</td>
<td>942.198</td>
</tr>
<tr>
<td>Worst single symptom score &gt;7</td>
<td>942.684</td>
</tr>
<tr>
<td>TSS &gt;20 &amp; single score &gt;5</td>
<td>938.510</td>
</tr>
<tr>
<td>TSS &gt;20 &amp; single score &gt;6</td>
<td>943.335</td>
</tr>
<tr>
<td>TSS &gt;20 &amp; single score &gt;7</td>
<td>944.867</td>
</tr>
</tbody>
</table>

*Optimal models based on lowest AIC.

Single Item
>5 (out of 10)

TSS
>20 (out of 100)

Meeting Threshold – Higher WBC, Blasts, Lower Platelets (even < DIPSS Cutoffs)

Scherber et. al. ASH 2016
What is “Symptomatic” in ET or PV in HU Failure, enough to consider Rx?

*Analysis of 838 PV/ 867 ET with Disease Features*

**Table 1: Ordinal logistic regression models of DIPSS risk score (N=420) by symptoms in JAK2-naïve myelofibrosis patients.**

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Mesa et. al.
BMC Cancer
2016;16:167

Fig. 1 Impact of MPNs on QoL, work, and activities of daily living. MPN impact was stratified by calculated prognostic risk score and symptom severity quartile in respondents with (a) MF, (b) PV, and (c) ET. ET = essential thrombocythemia; MF = myelofibrosis; MPN = myeloproliferative neoplasm; PV = polycythemia vera; Q1 = quartile 1; Q4 = quartile 4; QoL = quality of life. * ≥ 1 day in the preceding 30 days.
Investigating MPN Heterogeneity-Geyer 2014

**Regular Article**

**Blood 2014**

**MYELOID NEOPLASIA**

Distinct clustering of symptomatic burden among myeloproliferative neoplasm patients: retrospective assessment in 1470 patients

Holly L. Geyer,1 Robyn M. Emanuel,1 Amy Lou C. Dueck,2 Jean-Jacques Kladjan,3 Zhijian Xiao,4,5 Stefanie Slot,6 Sonja Zwigger,6 Federico Badmann,7 Ana Kerguelen Fuentes,8 Dolores Hernández-Maraver,9 Konstanze Dörner,9 Claire N. Hamilton,10 Deepthi Radia,10 Pablo Musi,11 Carlos Bessis,12 Francisco Cervera,13 Peter L. Johansson,14 Björn Andreasson,14 Alessandro Rambaldi,15 Tiziana Bartoli,15 Alessandro M. Vannucchi,16 Francesco Passamonti,17 Jan Samuelsson,18 Gunnar Birgegard,19 and Ruben A. Mesa20

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• Prospective Study
• 1470 MPN Patients
• DIPSS/IPSET/Leukemia 2013 PV Criteria
Investigating MPN Heterogeneity-Geyer 2014

Heterogeneity = Clusters?

High symptom burden in low and int. 1 risk MF

TSS Increases by clusters
• Did not correlate with PV or ET Risk categories

Risk scores are not direct surrogates for symptom burden
Impact of Disease Duration on Symptoms

Conclusion: Disease duration should be investigated as an alternative marker of burden in future survival studies.

- 757 fit criteria for early disease duration (0-5 yrs)
- 353 fit criteria for intermediate disease (6-10 yrs)
- 333 fit criteria for late disease duration (>10 yrs)

Mean age was 62 years

1443 PV, ET, MF Patients

Increased Average MPN-SAF TSS Score with Longer MPN Duration

Increased Spleen-Related Symptoms with Longer MPN Duration

Worsened Fatigue Related Symptoms with Longer MPN Duration

Worsened Constitutional Symptoms with Longer MPN Duration

Once Size Does Not Fit All: *The MPN Gender Study* 

- **Females**
  - Lower rate of thrombocytopenia (8% vs 14%, p<0.001).
  - Higher TSS (adjusted mean 23.9 vs 20.6, p<0.001)
  - Higher symptom scores for 15/18 items
  - Prominent symptoms: *fatigue, bone pain, abdominal discomfort, and microvascular related*

- **Males**
  - Higher mean age than females (mean 60.7 yrs [SD 12.6] vs 59.3 yrs [SD 14.4]; p=0.02)
  - Higher rate of requirement for red blood cell transfusion (7% vs 5%, p=0.02)
  - Higher mean white blood cell count (mean 9.5x10^9/L [SD 8.2 x10^9/L] vs mean 8.5 x10^9/L [SD 6.1x10^9/L]; p=0.004)

**Females demonstrate...**

- Higher levels of fatigue
  - Younger
  - Lower red blood counts
  - Lower transfusion rates

- More Abdominal Symptoms
  - Male=female abdominal thrombosis rates

**Microvascular symptoms**

- Previous reports show more macrovascular symptoms

**Higher Total Symptom Scores**

- Male=female QOL score
MPN Insomnia

- Included 1992 MPN Patients
- BFI, MPN-SAF, and EORTC QLQ-C30
- Pearson correlations and analysis of variance/t-tests, multivariate regression models were used

### RESULTS

- Insomnia is highly prevalent and severe
- Insomnia correlates with most other MPN-related symptoms and functional domains bearing a multi-faceted impact on overall quality of life.
- Cause of MPN-related sleep complaints is likely complex.
  - Emotional roots
  - Cognitive roots
  - Physical roots

### Table 5. Multivariate analysis between insomnia and MPN-SAF items

| Item                          | Pr>|t| |
|-------------------------------|----------|
| BFI Worst Fatigue             | 0.13     |
| Early Satiety                | 0.12     |
| Abdominal Pain               | 0.66     |
| Abdominal Discomfort         | 0.22     |
| Inactivity                   | 0.22     |
| Headaches                    | 0.0001   |
| Concentration                | 0.22     |
| Dizziness/Vertigo/Lightheaded| 0.24     |
| Numbness/tingling             | <0.0001  |
| Depression/sad mood          | <0.0001  |
| Sexuality                    | 0.006    |
| Cough                        | 0.09     |
| Night sweats                 | <0.0001  |
| Itching/pruritus             | 0.0042   |
| Bone pain                    | 0.07     |
| Fever (>100 F)               | 0.01     |
| Unintentional weight loss    | 0.75     |
| Overall Quality of Life      | 0.03     |

Insomnia is highly prevalent and severe in MPN patients. MPN-related insomnia correlates with most other MPN-related symptoms and functional domains, bearing a multifaceted impact on overall quality of life. Correlations between insomnia and emotional, cognitive, and physical complaints including depression/sad mood, concentration problems, night sweats, and numbness/tingling in the extremities suggest that the cause of MPN-related sleep complaints is likely complex. Future studies should evaluate the impact of interventions on MPN-associated insomnia as well as its biological underpinnings.

RESULTS

Sexuality complaints are highly prevalent. Close associations exist between sexuality and function within emotional, cognitive, and social domains. Symptom correlates with overall functionality and quality of life. Likely multifactorial in origin, these complaints are influenced by metabolic/endocrine/inflammatory, psychosomatic, and other factors. The study included 1908 MPN patients, using the BFI, MPN-SAF, and EORTC QLQ-C30. Pearson correlations and analysis of variance/t-tests, multivariate regression models were used to assess relationships. The results support the need for further investigation and management.
What Have MPN Patient Taught US?

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4. Burden of having an MPN extends beyond symptoms to distress and employment
5. Tracking symptom changes relevant for measuring value of medical treatments
6. Non pharmacologic options may have a role, alongside medicines or transplant, in MPN patient health and QoL
What do symptoms tell us about MPN Biology?

- Mood Disorders
- Anxiety over Uncertainty
- Cytokine Driven Symptoms
- Spleen/Inflammation

MPN Symptoms
A Baseline, Patients with Myelofibrosis vs. Healthy Controls

V617F−

V617F+

S. Verstovsek, H. Kantarjian, R. Mesa, et. al. NEJM 2010;363:1117-27
Inflammatory Cytokines and Chemokines in the MPNs

Symptom Burden
- B2MG
- Ferritin
- VCAM1
- TNF-RII
- TIMP1
- PAL1
- Leptin

Disease Advancement
- BMP1
- BMP6
- BMP7
- BMP-Rcp2
- IL-12
- TNF-1
- IL-8

Inferior Survival
- INF
- IL8
- IL12
- IL15
- IP10
- TNF-1

Splenomegaly
- HGF
- MIG
- IL1RA

Prominent Clonal expansion/blasts
- TNFa

<table>
<thead>
<tr>
<th>Inflammatory marker*</th>
<th>Impact</th>
<th>Disorder</th>
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<tbody>
<tr>
<td>B2M1CG</td>
<td>Symptoms</td>
<td>MF</td>
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<tr>
<td>BMP1</td>
<td>Disease advancement</td>
<td>PMF</td>
</tr>
<tr>
<td>BMP6</td>
<td>Disease advancement</td>
<td>PMF</td>
</tr>
<tr>
<td>BMP7</td>
<td>Disease advancement</td>
<td>PMF</td>
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<tr>
<td>BMP-Rec2</td>
<td>Disease advancement</td>
<td>PMF</td>
</tr>
<tr>
<td>CD40L</td>
<td>Loss of appetite</td>
<td>MF</td>
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<tr>
<td>CRP</td>
<td>Thrombosis; atherogenesis</td>
<td>PV, ET</td>
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<tr>
<td>Ferritin</td>
<td>Pruritus</td>
<td>MF</td>
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<td>FGF</td>
<td>Marrow fibrosis</td>
<td>PV, ET, PMF</td>
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<td>HGF</td>
<td>Spheromegaly</td>
<td>PMF</td>
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<td>IFN</td>
<td>Associated with JAK2V617F; inferior survival; transfusion requirements, vascular complications</td>
<td>MF</td>
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<tr>
<td>IL-12</td>
<td>Inferior survival</td>
<td>MF</td>
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<td>IL-15</td>
<td>Inferior survival</td>
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<td>IL-1B</td>
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<td>MF</td>
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<td>IL-1RA</td>
<td>Spheromegaly</td>
<td>PMF</td>
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<td>IL-2R</td>
<td>Inferior survival; transfusion requirements</td>
<td>MF</td>
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<td>IL-8</td>
<td>Elevated blast; constitutional symptoms</td>
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<td>IL-8</td>
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<td>IP-10</td>
<td>Inferior survival</td>
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<td>LEPTIN</td>
<td>Symptoms; weight loss</td>
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<td>MIG</td>
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<td>PALI</td>
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<td>RANTES</td>
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<td>TIMP1</td>
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<td>TNFRII</td>
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<td>VCAMI</td>
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<tr>
<td>VEGFβ</td>
<td>Marrow fibrosis</td>
<td>PV, ET, PMF</td>
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</tbody>
</table>

Cytokines & MPNs

Geyer et. al. 2015
Mediators of Inflammation
The Sequelae of Inflammation in MPNs

- Inflammation
  - Fatigue
  - Weight loss
  - Fevers
  - Night sweats

- Thrombosis
  - Visceral Clots = Abdominal Pain
  - Pulmonary Clots = Cough
  - Cerebral Vein Thrombosis = Headache

- Bone Marrow Fibrosis
  - Bone Pain

- Extramedullary Hematopoiesis
  - Abdominal Pain
  - Early Satiety
  - Nausea
  - Constipation

- Splenomegaly
  - Abdominal Pain
  - Early Satiety
  - Nausea
  - Constipation

- Extramedullary Hematopoiesis
  - Abdominal Pain
  - Early Satiety
  - Nausea
  - Constipation
LANDMARK Study in ET
Goals (Patients (N=226) & Physicians)

Mesa et. al.
BMC Cancer
2016;16:167
LANDMARK Study in PV
Goals (Patients (N=382) & Physicians)

Mesa et. al. BMC Cancer 2016;16:167
LANDMARK Study in MF
Goals (Patients (N=207) & Physicians)

Respondents for MF, %

- Slow/delay progression of condition
- Better QoL
- Healthy blood counts
- Symptom improvement
- Reduction in spleen size
- Reduce blood transfusions
- Anemia treatment
- Prevention of vascular/thrombotic events

Mesa et. al. BMC Cancer 2016;16:167
MF Patient vs physician-reported most important goal for therapy

PV Top 5:
- Slow/delay progression (25%, 6%)
- Prevention of vascular/thrombotic events (24%, 43%)
- Healthy blood counts (18%, 2%)
- Better QOL (12%, 11%)
- Symptom improvement (9%, 20%)

ET Top 5:
- Prevention of thrombotic event (35%, 57%)
- Slow/delay progression (21%, 4%)
- Healthy blood counts (17%, 4%)
- Better QOL (14%, 18%)
- Symptom improvement (9%, 14%)

USA MPN Landmark Study: Mesa et. al. Cancer 2016
Treatment goals - Patients vs. Physicians view (*Q36 + Q31*)

ET and PV patients wish to slow disease progression whilst physicians are more concerned about thrombotic events. In all diseases both Patients & Physicians look for symptom improvements.

### What is your most important treatment goal for your condition?

<table>
<thead>
<tr>
<th>Goal</th>
<th>Patient</th>
<th>Physician</th>
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</thead>
<tbody>
<tr>
<td>Symptom improvement</td>
<td>18/22</td>
<td>17/24</td>
</tr>
<tr>
<td>Better quality of life</td>
<td>12/20</td>
<td>14/17</td>
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<tr>
<td>Slow/delay progression of disease</td>
<td>18/20</td>
<td>9/16</td>
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<tr>
<td>Healthy blood counts</td>
<td>14/19</td>
<td>11/15</td>
</tr>
<tr>
<td>Reduction in spleen size</td>
<td>2/12</td>
<td>2/14</td>
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<tr>
<td>Prevention of vascular/thrombotic events</td>
<td>17/20</td>
<td>14/20</td>
</tr>
<tr>
<td>Reduce blood transfusions</td>
<td>5/17</td>
<td>6/14</td>
</tr>
<tr>
<td>Anaemia treatment</td>
<td>4/1</td>
<td>3/8</td>
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<tr>
<td>Haematocrit level less than 45%</td>
<td>11/0</td>
<td>11/0</td>
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<tr>
<td>Reduce frequency of phlebotomy treatment</td>
<td>0/3</td>
<td>2/12</td>
</tr>
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*International MPN Landmark Study – Harrison et. al. ASH 2016*
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MPN “Fatigue” Project 2014
Collaborative Internet Based Trial with MPN Forum

ANY MPN Patient
• Survey online
• MPN Forum
• MPN Advocacy
• MPN Research Foundation
• CMPD Ed Foundation

Register/ Online Consent

Online 70 Item Survey
• Demographics
• MPN History
• MPN-SAF (MPN10)
• Brief fatigue inventory (BFI)
• Profile of mood states (POMS-Short)
• Patient Health Questionnaire (PHQ-2)
• Mental Health Inventory (MHI-5)

Patients
1788 MPN patients/ 1676 Eval.
ET 33%, PV 39%, MF 25%
68% Female, median age 59. MPN10 Score average 28.4 (range 0-83)

Psych Comorbidity
23% high likelihood of depression (≥ 3 on PHQ-2)
Prior diagnosis depression (32%), anxiety (29%), stress (26%), grief (15%)
22% on therapy for mood disorder in last 6 months

MPN Correlation
Higher BFI, MPN-SAF, MPN10 scores all correlated with increased depressive symptoms (p<0.0001)
<table>
<thead>
<tr>
<th>Item</th>
<th>PHQ ≥3 (high likelihood of depression)</th>
<th>PHQ &lt;3 (low likelihood of depression)</th>
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<tbody>
<tr>
<td>MPN-SAF items and scoring</td>
<td></td>
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</tr>
<tr>
<td>MPN-TSS (MPN-10, mean score)*</td>
<td>41.1 (16.7)</td>
<td>24.7 (15.9)</td>
</tr>
<tr>
<td>Brief Fatigue Inventory (BFI)*</td>
<td>6.3 (1.7)</td>
<td>3.8 (2.3)</td>
</tr>
<tr>
<td>Worst Fatigue (last 24-hours)*</td>
<td>7.8 (1.9)</td>
<td>5.8 (2.7)</td>
</tr>
<tr>
<td>Early Satiety*</td>
<td>4.1 (3.1)</td>
<td>2.5 (2.8)</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>2.8 (3.1)</td>
<td>1.4 (2.2)</td>
</tr>
<tr>
<td>Abdominal discomfort*</td>
<td>3.6 (3.1)</td>
<td>2.1 (2.5)</td>
</tr>
<tr>
<td>Inactivity*</td>
<td>5.6 (2.6)</td>
<td>2.8 (2.7)</td>
</tr>
<tr>
<td>Headache*</td>
<td>3.8 (3.3)</td>
<td>2.2 (2.7)</td>
</tr>
<tr>
<td>Concentration difficulties*</td>
<td>6.1 (2.6)</td>
<td>3.4 (2.9)</td>
</tr>
<tr>
<td>Dizziness*</td>
<td>4.2 (3.3)</td>
<td>2.3 (2.6)</td>
</tr>
<tr>
<td>Numbness*</td>
<td>3.8 (3.3)</td>
<td>2.7 (3.0)</td>
</tr>
<tr>
<td>Insomnia*</td>
<td>5.4 (3.3)</td>
<td>3.7 (3.0)</td>
</tr>
<tr>
<td>Sad mood*</td>
<td>6.2 (2.3)</td>
<td>2.4 (2.4)</td>
</tr>
<tr>
<td>Sexual difficulties*</td>
<td>6.2 (3.4)</td>
<td>3.7 (3.4)</td>
</tr>
<tr>
<td>Cough*</td>
<td>2.9 (3.1)</td>
<td>1.5 (2.4)</td>
</tr>
<tr>
<td>Night sweats*</td>
<td>4.0 (3.5)</td>
<td>2.4 (2.9)</td>
</tr>
<tr>
<td>Pruritus*</td>
<td>3.8 (3.5)</td>
<td>2.5 (2.9)</td>
</tr>
<tr>
<td>Bone Pain*</td>
<td>3.9 (3.6)</td>
<td>2.2 (2.9)</td>
</tr>
<tr>
<td>Fever*</td>
<td>0.7 (1.8)</td>
<td>0.2 (1.1)</td>
</tr>
<tr>
<td>Weight loss*</td>
<td>1.5 (2.7)</td>
<td>0.8 (2.0)</td>
</tr>
<tr>
<td>Overall quality of life (QOL)*</td>
<td>5.8 (2.1)</td>
<td>3.1 (2.2)</td>
</tr>
<tr>
<td>Mental Health Inventory Score*</td>
<td>16.5 (4.3)</td>
<td>23.3 (3.9)</td>
</tr>
<tr>
<td>POMS-B Subscales</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tension-anxiety*</td>
<td>11.5 (4.0)</td>
<td>16.2 (3.2)</td>
</tr>
<tr>
<td>Vigor-activity*</td>
<td>3.3 (3.0)</td>
<td>6.8 (4.4)</td>
</tr>
<tr>
<td>Fatigue-inertia*</td>
<td>5.3 (3.9)</td>
<td>11.2 (5.1)</td>
</tr>
<tr>
<td>Depression-dejection*</td>
<td>10.6 (4.4)</td>
<td>17.0 (3.1)</td>
</tr>
<tr>
<td>Confusion-bewilderment*</td>
<td>11.2 (4.0)</td>
<td>15.2 (3.0)</td>
</tr>
<tr>
<td>Anger-hostility*</td>
<td>12.6 (4.6)</td>
<td>16.7 (3.3)</td>
</tr>
<tr>
<td>POMS-B total score*</td>
<td>54.6 (16.0)</td>
<td>83.2 (16.0)</td>
</tr>
</tbody>
</table>

Mood and MPNs
1788 MPN Patients

- MPN-SAF
- PHQ3, POMS-B
- MPN10 and every Symptom higher with Depression
- Depression not linked to MF, PV or ET risk scores

Scherber et. al. ASH 2016
Employment change due to MPNs

Impact of Living with MPN Survey Trial: Yu et. al. ASH 2016
What Have MPN Patient Taught US?

1. Burden of having an MPN includes several clinical features including MPN associated symptoms
2. Symptoms are heterogeneous and variable across MPN subtype and risk
3. MPN symptoms correlate with disease biology, risk, possibly progression?
4. Burden of having an MPN extends beyond symptoms to distress and employment
5. Tracking symptom changes relevant for measuring value of medical treatments
6. Non pharmacologic options may have a role, alongside medicines or transplant, in MPN patient health and QoL
<table>
<thead>
<tr>
<th>Disease</th>
<th>Drug</th>
<th>MPN Symptom Tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>MF</td>
<td>RUXO (COMFORT 1)</td>
<td>MF-SAF 2.0</td>
</tr>
<tr>
<td>MF</td>
<td>RUXO (COMFORT 2)</td>
<td>FACT-LYM</td>
</tr>
<tr>
<td>MF</td>
<td>Fedratinib (JAKARTA)</td>
<td>MF-SAF</td>
</tr>
<tr>
<td>MF</td>
<td>Pacritinib (PERSIST 1&amp;2)</td>
<td>MPN-SAF</td>
</tr>
<tr>
<td>MF</td>
<td>Momelotinib (SIMLIFY 1&amp;2)</td>
<td>MPN-SAF</td>
</tr>
<tr>
<td>MF</td>
<td>Pomalidomide (RESUME)</td>
<td>FACT-AN</td>
</tr>
<tr>
<td>MF</td>
<td>RUXO (RETHINK)</td>
<td>MPN-10</td>
</tr>
<tr>
<td>PV</td>
<td>Ruxo (RESPONSE)</td>
<td>MPN-SAF</td>
</tr>
<tr>
<td>PV</td>
<td>Ruxo (RELIEF)</td>
<td>MPN-SAF</td>
</tr>
<tr>
<td>PV</td>
<td>PEG INFa2a (MPD-RC 112)</td>
<td>MPN-SAF</td>
</tr>
<tr>
<td>ET</td>
<td>Ruxo (MAGIC)</td>
<td>MPN-SAF</td>
</tr>
<tr>
<td>ET</td>
<td>PEG INFa2a (MPD-RC 112)</td>
<td>MPN-SAF</td>
</tr>
</tbody>
</table>
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Aaron T. Gerds, MD, MS
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The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

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Stanford Cancer Institute

Krishna Gundabolu, MBBS
Fred & Pamela Buffett Cancer Center

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Massachusetts General Hospital Cancer Center

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### MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM

TOTAL SYMPTOM SCORE (MPN-SAF TSS-10 ITEMS)

(Recommended for monitoring symptoms during the course of treatment)

Circle the one number that describes how, during the past week how much difficulty you have had with each of the following symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filling up quickly when you eat (early satiety)</td>
<td>0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Inactivity</td>
<td>0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Problems with concentration-compared to prior to my MPD</td>
<td>0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Numbness/Tingling (in my hands and feet)</td>
<td>0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Itching (pruritus)</td>
<td>0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Bone pain (diffuse not joint pain or arthritis)</td>
<td>0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Fever (&gt;100 F)</td>
<td>0 1 2 3 4 5 6 7 8 9 10 (Daily)</td>
</tr>
<tr>
<td>Unintentional weight loss last 6 months</td>
<td>0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
</tbody>
</table>
TREATMENT FOR LOW-RISK MYELOFIBROSIS

Low risk
Risk score = 0
IPSS
DIPSS and DIPSS-Plus

Assess symptom burden using MPN-SAF TSS-10 items if not done previously

Asymptomatic
Symptomatic
Why do MPNs Progress?

- Clonal Progression (accumulation of mutations?)
- ET, PV, Early MF → Overt MF
- Microenvironment/Inflammation?
- Progressive Myelofibrosis
- Death from Stable MF (Debilitation)
- Acute Myeloid Leukemia
TREATMENT FOR INTERMEDIATE-RISK 1 (INT-1) MYELOFIBROSIS

Intermediate-risk 1 (INT-1) Risk score:
IPSS=1
DIPSS-Plus = 1
DIPSS= 1 or 2

Assess symptom burden using MPN-SAF TSS-10 items if not done previously

Observation or Ruxolitinib if symptomatic or Clinical trial or Allogeneic HCT

Monitor response and signs/symptoms of disease progression every 3–6 months

Response
Continue prior treatment

No Response or Loss of response
Disease progression
INT-2/High risk, and Advanced stage MF

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Non-Pharmacologic Approaches in the MPNs: Online-Streamed Yoga

MPN Patients Completing the Yoga Study (N=38)

12 Week Online Yoga Course

Yoga participation averaged 50.8 min/week.

Significant improvements in total symptom burden (effect size = -0.36, p=0.004)
- Anxiety (ES=-0.67, p=0.002)
- Depression (ES=-0.41, p=0.049)
- Sleep (ES=-0.58, p<0.001)
- Fatigue (ES=-0.33, p=0.04)

Patient Satisfaction:
- 68% of participants were either satisfied or very satisfied
- 75% felt that it was helpful for coping

Huberty et. al. Blood 2016 128:5478
Key Eligibility
- MPN Patient
- Not Depressed
- PS<3
- Not already doing yoga or Mindfulness
- <150 Min of weekly exercise

At Home Yoga (N=30)
- 12 Weeks
- >/= 60 Min/ Week
- Fitbit tracking (Blinded)
- Daily Logs-Yoga and activity
- Blood (2 Timepoints)
  - TNFa
  - IL6
- Saliva (2 Timepoints, 4x each timpoint)
  - Cortisol
  - MPN Sx, QOL, Sleep

Wait List Control (N=30)
- 12 Weeks
- Fitbit tracking/Blinded
- Usual Level of Activity
- Daily Logs - Activity
- MPN Sx, QOL, Sleep

MPN Yoga Team:
Arizona State University:
  Jennifer Huberty PhD
  Linda Larkey, PhD
  Ryan Eckert, B.S.
Mayo Clinic Arizona
  R. Mesa, MD
  Amylou Dueck, PhD
  K. Gowin, MD

Online Registration & Randomization

Post 12 week Cross Over
Acceptance and Commitment Therapy for MPNs - The Opportunity -

ACT in Chronic Conditions

Chronic Pain | Fibromyalgia | Chronic Fatigue

↓ anxiety | ↑ mental QOL | ↓ insomnia
↓ pain, | ↓ anxiety | ↓ anxiety
↓ pain disability | ↓ depression | ↓ fatigue
↑ QOL

ACT In Cancer

Breast Cancer | CNS Tumors

Completed Cancer Treatment | Completed Cancer Treatment
↓ Depressive | ↑ QOL
↓ Anxiety | ↑ QOL brain tumor specific

↑ QOL brain tumor specific

Padrinos, Geda, Stonnington & Mesa: Mayo Clinic
Non-Pharmacologic Approaches in the MPNs: MyACT Study: Video Intervention to reduce fatigue

190 MPN patients
Baseline Surveys and FitBit Delivered
Randomization: Age and Brief Fatigue
Index Score (4-6, 7-10)

95 patients
Intervention Group
Weeks 1-8
Weekly ACT videos

Surveys at week 4 and 8
FitBit Assessed Weekly

Washout Period
Survey at week 12
FitBit Assessed Weekly

95 patients
Wait List Control
Group

Surveys at week 4 and 8
FitBit Assessed Weekly

Survey at week 12
FitBit Assessed Weekly

Wait List Crossover
Weekly ACT Videos

Surveys at week 20
FitBit Assessed week 20

Survey at week 20
FitBit Assessed week 20

8 Weekly Video Topics

Introduction

Acceptance

Defusion

Being Present

Self as Context

Values

Committed Action

Conclusion
What about diet?

• Diets which emphasize anti-inflammatory properties:
  • Reduce CRP (p = 0.015) and IL-6 levels (p = 0.025).
  • Improve thrombotic markers
    • Decrease in homocysteine levels (p = 0.031)
    • Decreased white blood cell counts (p = 0.001)
    • Normalization of fibrinogen levels (p = 0.025).

• Anti-inflammatory diets have demonstrated good efficacy when utilized in nutritional intervention for high-inflammation disease states such inflammatory bowel disease.
  • In an intervention among patients with IBD (N=40), 60% had “good” or “very good” response in IBD severity after four weeks of dietary compliance
  • Of note, JAK2V617F mutations exceeded expected thresholds for IBD patients expressing thrombocytosis (23%) or erythrocytosis (10%).

• To date, no dietary interventions have been evaluated in MPN patients.

Nutrition in the MPNs

- 13% of MPN patients endorse undesired weight loss
  - MF 20% followed by PV (10%) and ET (7%)

- Analysis of the Mayo database:
  - 67% of MF patients lost weight over time
  - 27% of patients had decreased BMI category

- Patients with MPN are more likely to be deficient in LDL-C and total cholesterol compared to age-matched controls

- Hypocholesterolemia is independently associated with decreased survival PMF patients (p<0.001)

Healthy Sweets and Oils/Fats
Honey, Cacao, Olive oil, Avocado, Nuts

Pre- and Pro-Biotic Dairy
Yogurt, Kefir, Aged Cheeses

Protein
Lean Meats (e.g., fish, poultry, lean red meat), Egg, Seafood, Fatty Fish, Beans & Tofu

Soluble Fiber
Steel Cut Oats, Chia Seeds, Flaxseeds, Lentils

Fruits
All Berries, Citrus, Pineapple

Vegetables
Green Leafy Vegetables, Onions

General Avoidance of: Processed Meats, Refined Carbohydrates (e.g., soda pop), Lard, Fried foods
NUTRIENT Study: Development of a Dietary intervention

MPN Focus/Advocate Groups (N=30)
- Baseline Demographics and MPN Assessment
- Metabolic/Nutritional Assessment
- MPN-SAF Symptom Assessment
- Cytokine Analysis
- Inflammatory Marker Analysis
- Body Fat Composition

Online MPN Nutritional Questionnaire (N=1,000)
- Nutritional Habits
- Supplement Intake
- Dietary Needs
- Symptom Assessment

Determination of MPN Dietary Needs and Preferences

Creation of a MPN Dietary Educational Curriculum

Trial Assessing Feasibility and Adherence

Trial of Efficacy to Reduce Symptom Burden and Inflammatory Cytokines

Online Video Vignettes

Peer Support Forums

Online Apps
- Meal Plans
- Recipes

Tailoring to MPN Needs
- Iron Deficiency/Polycythemia
- Splenomegaly
- Early Satiety
- Constipation
- Weight loss
- Abdominal Discomfort

Nutritional References
- Caloric Diaries
- Vitamin Intake

Online Apps
- Meal Plans
- Recipes

Peers Support Forums

Online Video Vignettes
Putting It All Together – MPNs and QOL

MPN Patient
- Disease Prognosis
- Vascular Risk
- Symptom Burden
- Impact of Disease on QOL
- Patient Choice and Input
- Treatment Options

Role of Stem Cell Transplant
Reduction of Splenomegaly
Prolonging Survival
Improving Symptom Burden & QOL
Avoiding Progression
Preventing Vascular Events

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Role of Stem Cell Transplant
Reduction of Splenomegaly
Prolonging Survival
Improving Symptom Burden & QOL
Avoiding Progression
Preventing Vascular Events
The Itch

I have an itch you cannot know,
not the least hint will ever show
No bump no rash no insect bite
provides a clue as to my plight
My clothes, a shower, the air I breathe
make my skin prickle and seethe
Constant reminders it provides
of the disease my body hides
Maddening tears the burning brings,
no scratch, no pills can stop the stings
Life is good,
it could be much worse
I can live with my itchy curse
I walk the dog to pass the time,
take deep breaths and clear my mind
Pruritus is a small price
for my wonderful blessed life
Myeloproliferative Neoplasms
Multi-Disciplinary Team
Mayo Clinic, Arizona, USA

MPN Burden/
Symptom/QOL
Assessment

Improving
Transplant
Outcomes

New MPN
Drug/
Genetic
Therapies

Physical
Activity/
Behavioral
Therapies