12th Joyce Niblack MPN Conference

Gaps and Guidelines



Ruben A. Mesa, MD Executive Director, Mays Cancer Center Mays Family Foundation Distinguished University Presidential Chair mesar@uthscsa.edu Twitter: @mpdrc





Consulting: Novartis, La Jolla, Samus, Sierra Oncology, Blueprint, Abbvie, BMS, Genentech, Roche

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What is a treatment guideline?





MPNs 2021

- Burden of Having an MPN
- Essential Thrombocythemia
- Polycythemia Vera
- Myelofibrosis
- Complementary Approaches



Assessing MPN Burden

WHO Diagnosis Does Not Tell Whole Story





Evolution of MPN Symptom Assessment Tools



MF, myelofibrosis; MPN, myeloproliferative neoplasm; QOL, quality of life; SAF, symptom assessment tool; TSS, total symptom score. *Scherber et al. *Blood* 2011;118:401-408. †Emanuel et al. *J Clin Oncol.* 2012;30:4098-4103.



MPN Recent Phase 3 Trials MPN Symptom Assessment

Disease	Drug (Trial)	MPN Symptom Tool
MF	Ruxolitinib (COMFORT 1)	MF-SAF 2.0
	Ruxolitinib (COMFORT 2)	FACT-LYM
	Fedratinib (JAKARTA)	MF-SAF
	Pacritinib (PERSIST 1&2)	MPN-SAF
	Momelotinib (SIMPLIFY 1&2)	MPN-SAF
	Pomalidomide (RESUME)	FACT-AN
	Ruxolitinib (RETHINK)	MPN-10
PV	Ruxolitinib (RESPONSE)	MPN-SAF
	Ruxolitinib (RELIEF)	MPN-SAF
	PEG INFa2a (MPD-RC 112)	MPN-SAF
ET	Ruxolitinib (MAGIC)	MPN-SAF
	PEG INFa2a (MPD-RC 112)	MPN-SAF

ET, essential thrombocytopenia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PEG INFa2a, Pegylated interferon alfa-2a; PV, polycythemia vera; SAF, symptom assessment tool.

Symptoms Change During the Natural History of MPNs



Inflammation in MPNs Inflammation Drives Clonal Proliferation



Fleischman, *et al. Blood* **118**, 6392-6398 (2011). Koschmieder et. al. Leukemia 2016

What do symptoms tell us about MPN Biology?





Fatigue





Cancer, vol. 92, no. 6, pp. 1684–1688, 2001. Cancer, vol. 104, no. 4,pp. 788–793, 2005. Brain, Behavior, and Immunity, vol. 21,no. 3, pp. 251–258, 2007. Cancer, vol. 106, no. 4, pp. 751–758, 2006. [American Journal ofPsychiatry, vol. 158, no. 8, pp. 1252–1257, 2001.

Abdominal Symptoms



Constitutional Symptoms



Microvascular Symptoms



Treatment Goals

- Avoiding thrombosis and bleeding?
- Improving MPN associated symptoms?
- Increase activity?
- Decreasing splenomegaly?
- Improving anemia?
- Improving low platelets?
- Decreasing progression?
- Preventing progression?
- Live longer?



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PV/ET: When Do Problems Occur?



Management of ET 2021



Treatment Gaps - ET

1. What is the optimal front line therapy for ET?

2. How do we prevent disease progression?

3. What is the role of JAK inhibition?

Pipeline – PV and ET

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American Society of Hematology Helping hematologists conquer blood diseases worldwide

Symptom Burden and Quality of Life in High-Risk ET and PV Patients Receiving Hydroxyurea or Pegylated Interferon Alfa-2a: Results of MPN-RC 111 and 112 Trials

Gina L. Mazza

on behalf of

Carolyn Mead-Harvey, John Mascarenhas, Abdulraheem Yacoub, Ronald Hoffman, Heidi E. Kosiorek, Josef T. Prchal, Richard T. Silver, Tiziano Barbui, Amylou C. Dueck, Ruben A. Mesa

Results – Patients

Charactaristic	MPN-	RC 111	MPN-RC 112		
Characteristic	ET (<i>n</i> = 64)	PV (<i>n</i> = 50)	ET (<i>n</i> = 79)	PV (<i>n</i> = 87)	
Sex (% Female)	51%	48%	50%	33%	
Age in Years (Median, Range)	65 (20 – 85)	64 (26 – 84)	60 (18 – 83)	62 (20 – 88)	
Months Since Dx (Median, Range)	38 (0 – 291)	55 (1 – 394)	3 (0 – 48)	3 (0 – 84)	
Prior Thrombosis (%)	31%	22%	25%	29%	
Splenomegaly (%)	19%	56%	11%	37%	

Results – Symptoms

- MPN-RC 111 patients had significant improvement of TSS, fatigue, abdominal pain, abdominal discomfort, dizziness, numbness, night sweats, and fever
- MPN-RC 112 PEG patients had significant **worsening** of fever
- MPN-RC 112 HU patients had significant **worsening** of inactivity
- MPN-RC 111 and 112 PEG patients had significant **worsening** of PEGrelated symptoms

Conclusions

- Although no statistical comparisons were made across trials, overall improvements were seen in MPN-RC 111 but not MPN-RC 112
- Patients with high baseline symptom burden experienced the greatest improvements in symptom burden and quality of life during treatment with PEG or HU
 - These results may explain the improvements seen in the more advanced MPN-RC 111 patients compared to MPN-RC 112 patients

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Management of Myelofibrosis 2021

JAK Inhibitor Landscape 2021

A selection of novel agents/targets being developed in MPN particularly MF

Takeaway 1:

Effective MF Therapies May Prolong Overall Survival

Questions? MF and Survival

1. Is survival benefit across all responders to JAKi?

- 2. Do all patients who experience clear response for splenomegaly and/or symptoms have improved survival? Mechanism?
- 3. What might be better surrogates of OS benefit? What thresholds of clinical benefit will predict OS benefit?

Takeaway 2:

What is successful front line therapy for MF?

Comparison for 1L MF Therapy

Verstovsek et. al. NEJM 2012 Pardanani et. al. JAMA Inc 2015 Mesa et. al. JCO 2017 Mesa et. al. Lancet Hematology 2017 Mascarenhas et. al. ASH 2020

Questions? Front Line and MF

1. Does OS benefits to medical therapy alter decision for transplant in certain candidates?

- 2. Would a lower rate of response to spleen or symptoms be a good exchange for expanded additional areas of efficacy?
- 3. To justify 2 agent front line approach is a broader response needed? Deeper? In certain subsets?

Takeaway 3:

Second line – Add on to JAKi or Switch Gears All Together?

Comparison for 2L Therapy

Second Line MF Therapy

Pemmaraju et. al. ASH 2020 Verstovsek et. al. ASH 2020 Harrison et. al. ASH 2019 Verstovsek et. al. Mascarenhas et. al. Yacoub et. al. ASH 2020 Mascarenhas et. al. ASH 2020 Talpaz et. al ASH 2020

Treatment Efficacy Observed/ ENDPOINTS

Drug	Spleen	Symptoms	Anemia	Fibrosis	Molecular	PFS	OS
Ruxolitinib	Х	Х		Х			Х
Fedratinib	Х	Х		Х			
Momelotinib	Х	Х	Х				Х
Pacritinib	Х	Х					
CPI-0610	Х	Х	Х	Х			
Navitoclax	Х	Х		Х			
IMG-7289	Х	Х			Х		
Imetelstat	Х	Х					X?
Luspatercept			Х				

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Non Pharmacological Approaches for MPN Burden Relief

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Yoga In MPNs

Initial Investigation Efforts

Subsequent Investigation Efforts

- 68% of participants were either satisfied or very satisfied
- 75% felt that is was helpful for coping

Figure 3. Changes from Baseline in Patient-Reported Outcomes

Huberty et. al., Blood 2016 128:5478 Huberty et al., BMC CAM 2019 19(1)

Cognitive/Mindfulness Interventions in MPNs

Huberty et. al., JMIR Form Res 2019

Nutrition in MPNs

Initial Investigation Efforts

Correlative	Mean symptom bur	P-value	
Diet	Not Following Diet	Following Diet	Pr >lti
Diabetic diet	3.33	4.67	< 0.0001
Lactose Intolerant	3.35	3.87	0.0433
Food Intake (Dichotomous)	Never	At Least Once Per Week	Pr >iti
Alcohol	3.62	3.11	< 0.0001
Fast Food	3.24	3.59	0.0015
Fried Foods	3.22	3.46	0.0198
Rice	3.57	3.30	0.0452
Soda	3.22	3.72	< 0.0001
Food Intake		Pearson	P-value
(Continuous)		Correlation	
Alcohol	-	-0.139	< 0.0001
Baked Goods	-	-0.070	0.0212
Dairy other than Cheese (milk, cream)	-	-0.069	0.0240
Fast Food	-	0.104	0.0007
Fried Foods	-	0.086	0.0051
Pasta	-	-0.072	0.0183
Pre-made Snack Foods	-	0.067	00296
Soda	-	0.121	< 0.0001
Refined Sugars	-	0.075	0.0139
Tacos	-	0.068	0.0277

Subsequent Investigation Efforts

Foods associated with worsened symptom score in red, foods associated with improved score in green

Ongoing/Planned Trials in Cancers

Calm for Cancer App Development

Recently funded by NIH – 1 year grant to develop and beta-test a cancer-specific version of the Calm meditation app

Phase 1

• Advisory board consisting of 10 cancer patients/survivors and 10 healthcare professionals uses the app for a week and participates in a focus group to give feedback on app

Phase 2

• Calm developers utilize feedback and additional available evidence from the literature to develop cancer-specific prototype of Calm app

Phase 3

• 30 cancer patients/survivors will test the cancerspecific Calm app prototype and provide feedback for further refinement of the app to be tested again in a future RCT

Conclusions Improving Outcomes

- 1) Adequately assess the burden on the MPN and develop appropriate therapy and goals
- 2) If therapy is not beneficial change to alternative therapy or clinical trial
- 3) JAK inhibitors and interferons do have a benefit for many subsets of MPN patients, yet opportunities exist
- 4) Multiple additional pathway targeted agents are undergoing parallel testing primarily in 2nd line MF and 3rd line PV or ET
- 5) Non pharmacological therapies may augment treatment options for MPNs

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