Improving Care for Patients with Myelofibrosis Through Education: Nursing Practice Update

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Hello and welcome to our program, *Improving Care for Patients with Myelofibrosis through Education, a Nursing Practice Update*. I am Dr. Sara Tinsley and I work at Moffitt Cancer Center. I do research on quality of life and I take care of patients with myelofibrosis and other myeloproliferative disorders or neoplasms. I have been taking care of patients for a long time and it used to be called disorders but now they are considered neoplasms. In today's activity, I will help you assimilate a knowledge of the disease pathology and current and emerging treatments.

Disclosures

- Consultant: Incyte, Jazz
- Speaker's Bureau: Celgene, Incyte, Jazz, Novartis, Takeda

These are my disclosures.

Key Topics for Discussion

- Discuss physiology, etiology, diagnosis, prognosis, and risk-stratification of myelofibrosis (MF)
  - Considerations for patient/family education
- Describe current and emerging treatments for MF
  - Adverse events/key safety issues
  - Monitoring/management of pharmacologic treatment-associated adverse events
- Outline strategies to improve education of patients with MF and their families
  - Tools and resources

These are the key topics for discussion. First, we will go over the physiology, etiology, how you diagnose a person with myelofibrosis. We will look at the prognosis or staging systems for myelofibrosis and the risk stratification, and we will really focus on the considerations for patient and family education. We know that this is a difficult disease for our patients and family members to understand, and then explain to other people so that they can help them in their care. We will also go over the current and emerging treatments for myelofibrosis. We are making strides in helping patients live better with the disease. We will look at the key safety issues associated with those treatments and we will look at the monitoring and management of pharmacologic treatments and the associated adverse events. And at the end, we will go over the strategies to improve the education of the patients with myelofibrosis and their families and we will go over some resources.

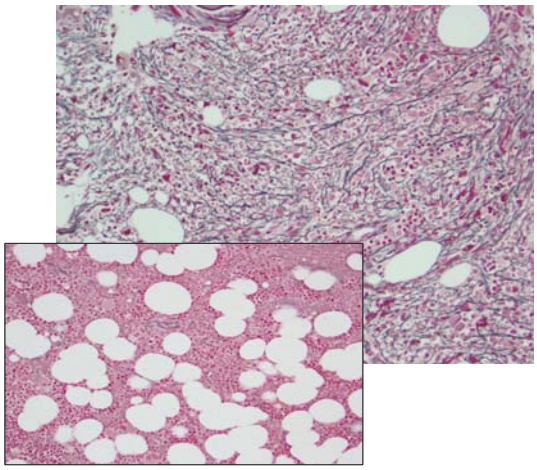
What Is Myelofibrosis?

"Myelo"– originating from bone marrow

"Fibrosis" – thickening or scarring of tissue

- Myelofibrosis is:
  - Characterized as scarring or thickening of bone marrow
  - Diagnosed from bone marrow biopsy
  - Often referred to as a chronic leukemia
  - Known to progress to AML (10%-20% of cases)
  - Observed to have variable prognosis depending on individual patient risk factors

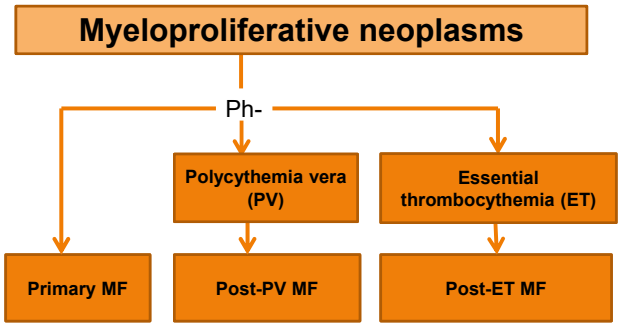
Photos courtesy of pathology department at Moffitt Cancer Center
Mughal TI, et al. *Int J General Med.* 2014;7:89-101.



What is myelofibrosis? First, let's breakdown the word. "Myelo" means it is originating from the bone marrow and "fibrosis" means thickening or scarring of the bone marrow tissue. If you look at the illustrations on the right, you can see a normal bone marrow at the bottom without those reticulum fibers and then a fibrotic marrow at the top where you can see those little fibers going throughout the bone marrow and that is really the fibrosis. There are special stains that they do of the core piece of the bone marrow biopsy and then stain them so that you can see the fibrotic tissue. Myelofibrosis is scarring or thickening of the bone marrow. You diagnose it from a bone marrow biopsy. They also attempt an aspiration, but it is pretty common for patients with myelofibrosis to not be able to get an aspirate, also called a dry tap. So, you have to diagnosis it from a bone marrow biopsy. It is referred to frequently as a chronic leukemia. It can progress to acute myelogenous leukemia in about 10% to 20% of cases and each patient has a variable prognosis depending on their risk factors and that is why we do risk stratification.

Characteristics of MF

- Overproduction of bone marrow stem cells
- Absence of Philadelphia chromosome (Ph-)
- Can result in too many or too few blood cells
- Anemia and splenomegaly
- Increased inflammation resulting from overactive *JAK* signaling pathways



Mughal TI, et al. *Int J General Med.* 2014;7:89-101.; Barbui T, et al. *Blood Cancer J.* 2018;8:15.

Disorder versus cancer. It was originally called a disorder but this was changed to neoplasm in 2008 according to the World Health Organization. These myeloproliferative neoplasms are characterized by over production of bone marrow stem cells and they also have the absence of the Philadelphia chromosome which you may recall is translocation of chromosomes 9 and 22, that makes this Philadelphia chromosome that is BCR-ABL positive. So this falls into a group of disorders or cancers that are negative for that 9;22 translocation along with polycythemia vera, where patients make too many red blood cells, and essential thrombocythemia where patients make too many platelets. As you will see illustrated on the right but over time, both polycythemia vera and essential thrombocythemia can progress to post PV myelofibrosis and post ET myelofibrosis. Anemia is common when they get into the myelofibrotic stage of the illness, and splenomegaly is also common. There is also increased inflammation associated with the disease that is a result of overactive Janus associated kinase signaling pathways.

Incidence and Prevalence of MF

- Considered rare disorder
- Incidence (number of newly diagnosed cases/year) in the US is 1.0 per 100,000 people
- Prevalence of 2.0 per 100,000 people/year in the US or 13,000
- Fewer women than men affected ~47%

Mehta J, et al. *Leuk Lymphoma*. 2014;55(3):595-600.

So, how common is it? Actually, it is very uncommon. It is considered a rare disorder. The incidence of number of newly diagnosed cases per year in the United States is 1:100,000 people. The prevalence is 2:100,000 people per year in the United States or approximately 13,000. There are fewer men than women affected, approximately 47%.

Diagnosis of Myelofibrosis

History Examination	Physical Examination	Laboratory Evaluation
• Evaluation of hemorrhagic/ thrombotic history • Evaluation of CV risk factors • Transfusion and medication history • Review of symptoms	• Assess for hepatosplenomegaly	• CBC with differential with peripheral smear • Comprehensive metabolic profile • Uric acid • LDH • Erythropoietin level • Iron studies • HLA typing for individuals who may be eligible for ASCT

How do we diagnose it? First, we want to take a good history and you are asking them specifically about hemorrhagic or thrombotic events. You want to know any cardiovascular risk factors, are they are being treated for hypertension or hyperlipidemia, have they had a prior coronary artery bypass graft or have other cardiovascular diseases. You want to know if they have had any transfusions and what frequency are they being transfused and how many units of red blood cells have they had in their history and then really go over their symptoms in detail because that is a key piece of the risk stratification and really knowing how we can help patients with our current treatments that we have available. Then, on the physical examination we want to really pay attention to hepatosplenomegaly on your abdominal exam and we frequently measure both the liver and the spleen if they are enlarged, and you would frequency assess for hepatosplenomegaly by measuring at the midclavicular line and the number of centimeters that it extends below the costal margin. Other important takeaways or things to really pay attention to when you are doing a history and physical exam is the CBC with differential and the peripheral smear. When you look at the differential, you want to take note if there are any immature cells, blast cells or leukemic cells, you want to pay attention to if they are present or absent. Also, myelocytes, metamyelocytes and other abnormal cells that are floating around in that differential. You want to look for nucleated red blood cells. Other labs that you want to look for are the comprehensive metabolic profile, a uric acid, LDH, and erythropoietin level, iron studies, and if you think that this person may be eligible or good candidate for allogeneic stem cell transplant, you want to do HLA typing.

Diagnosis of Myelofibrosis

- Bone marrow biopsy with aspiration is essential for diagnosis of myelofibrosis
- Reticulin and trichrome stain graded as MF0-MF3
- Histology shows hypercellularity for age-matched comparisons and megakaryocytic proliferation
  - Marrow rules out other causes for abnormalities in blood counts

Instruments for bone marrow biopsy

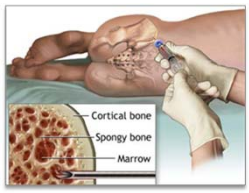
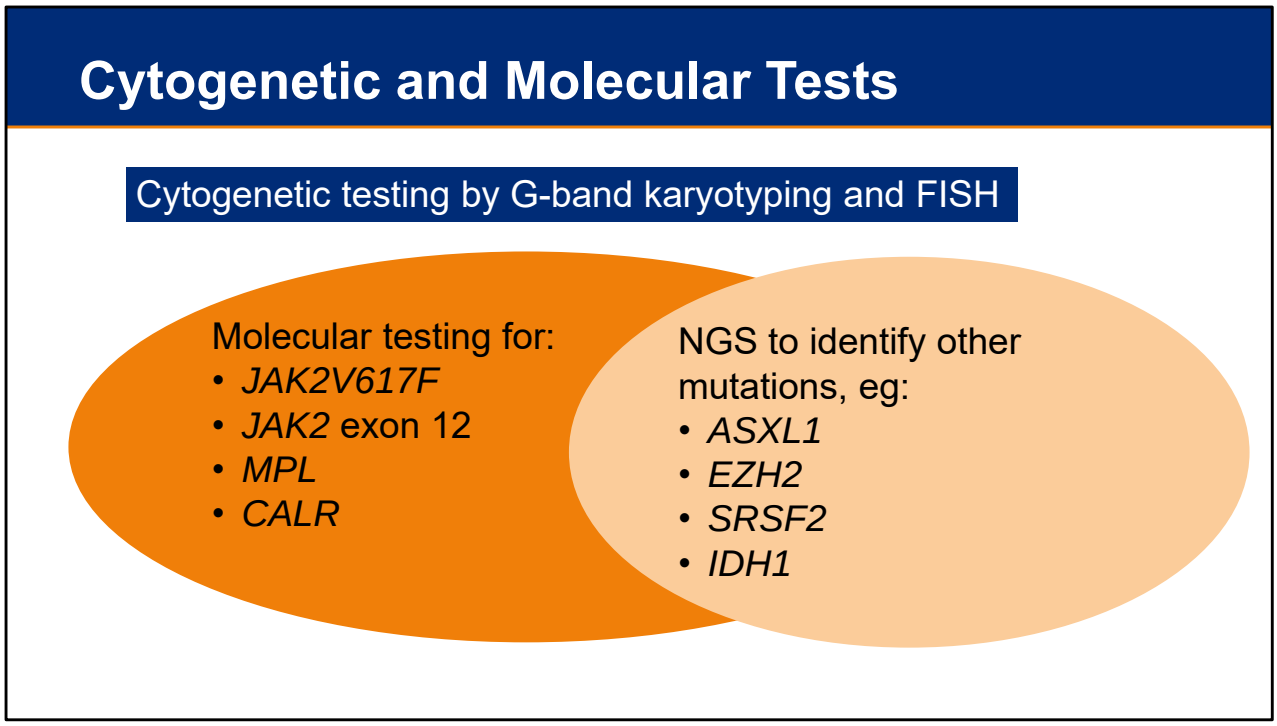


Diagram of lateral position for bone marrow biopsy

When diagnosing myelofibrosis as we discussed previously, you really have to have a bone marrow biopsy and an aspiration if possible to look for other forms of reactive causes for anemia or fibrosis. We do a reticulin and a trichrome stain and it is graded on a system of MF0 to MF3, with the higher the grade corresponding to increased levels of fibrosis. When you see the histology, it shows a hyper cellular bone marrow for age match comparisons. As we age, our bone marrows become less cellular, you subtract your age from 100 and that is how cellular your bone marrow should be. So a 50-year-old with myelofibrosis, may have a 70% cellular bone marrow. Also, it is typical to see megakaryocytic proliferation. Megakaryocytes are immature forms of your platelets and it is very common for patients with myelofibrosis to have an increased number of megakaryocytes and when you this bone marrow biopsy, you ruling out other causes for abnormalities in the blood counts. On the left, you will see the instruments used for bone marrow biopsies and then on the right you will see a lateral positioning for bone marrow biopsy, and then the different areas of cortical bones, spongy and then bone marrow. They are also using drills for bone marrow biopsies but not is not illustrated.



It is very important for you to do cytogenetic and molecular testing on the specimen and so these have to be ordered. Cytogenetics can be done by G-banding where they take naturally dividing cells and do a karyotype of those, and that is usually 20 cells and they take dividing cells and they line them up in numerical order and see if there are any structural abnormalities, that is referred to as G-banding, karyotyping, or FISH, also known as fluorescence in situ hybridization where you have to tell them what your fishing for as another way of doing chromosomal abnormality evaluation but you do have to tell them what you are looking for in your FISH and then they drop a panel that will pick up those abnormalities that you are looking for. For example, 17p deletion, you would tell them that when you do your FISH, when you submit a FISH test for a person with myelofibrosis. The molecular testing really is for the JAK2 V617F, JAK2 exon 12, MPL and CALR. We also performed next-generation sequencing for myeloid disorders to identify other mutations that can be associated with myelofibrosis. This is also now being incorporated into our prognostic models, the latest versions. The ones that are really key to take a look at are the ASXL1, EZH2, SRSF2, IDH1 and IDH2.

Diagnostic Criteria for PMF by WHO

- Diagnosis of PMF requires meeting all three major criteria, and at least one minor criterion confirmed in two consecutive determinations

Major criteria

- Presence of *JAK2, CALR*, or *MPL* mutation or in absence of these mutations, presence of another clonal marker, or absence of reactive MF
- Proliferation an atypia of megakaryocytes, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3 on a scale of 0-3
- Not meeting WHO criteria for BCR/ABL1 CML, ET, PV, MDS, or other myeloproliferative neoplasms

Minor criteria

- Anemia not attributed to comorbid condition
- Leukocytosis >11 x 10^9/L
- Palpable splenomegaly
- LDH increased to above upper normal limit of institutional reference range
- Leukoerythroblastosis

Arber DA, et al. *Blood.* 2016;127:2391-2405.

These are the diagnostic criteria for primary myelofibrosis according to the World Health Organization. You see there are two columns. For a diagnosis of primary myelofibrosis, they have to meet all three major criteria and at least one minor criterion confirmed in two consecutive determinations. So you see, those molecular mutations are included in the major criteria and the presence of the proliferation of an atypia of those megakaryocytes which are your platelet precursors and they also have to have either reticulin and/or collagen fibrosis at a grade of 2 or 3 on a scale of 0 to 3 and they do not meet the criteria for the BCR ABL1 that we talked about that would be diagnostic for CML not being ET or a PV patient or myelodysplastic syndrome or other myeloproliferative neoplasm. The minor criteria include anemia that is not caused by another comorbid condition, a leukocyte count greater than 11, palpable splenomegaly and increased LDH above upper normal limit of the reference range for your institution, and a leukoerythroblastosis picture on that you get that from the differential on your CBC.

Causes of Myelofibrosis

- Primary myelofibrosis
  - Underlying cause of primary myelofibrosis has not yet been determined
  - Risk factors include
    - Prior exposure to benzene, toluene, or ionizing radiation
    - Aging bone marrow
- Secondary myelofibrosis
  - Evolved from prior PV or ET
  - The longer a person has been diagnosed with PV or ET, the more likely to develop secondary myelofibrosis over time

What are the causes of myelofibrosis? For most patients we do not really know why they developed myelofibrosis, so we do not know what the underlying cause is in the majority of our diagnosed patients. Risk factors that you want to obtain history on when you are seeing a new patient is their prior exposure to benzene, toluene, or ionizing radiation. It is associated with an aging bone marrow, so it is frequently diagnosed in our older individuals. We discussed secondary myelofibrosis which is really an evolution on the disease process for patients with polycythemia vera or essential thrombocythemia and you will be able to determine that they are evolving into a fibrotic stain stage of disease if their blood counts start to change. You can also get a good idea that this happening if their spleen start to rapidly increase. Then is usually the time we will order a repeat bone marrow biopsy. It is also associated with having to adjust like what their normal dose of Hydrea has been for many years, that is like a red flag for this person's disease is changing. And then of course the longer a person has been diagnosed with PV or ET, then they are more likely to develop this secondary myelofibrosis over time.

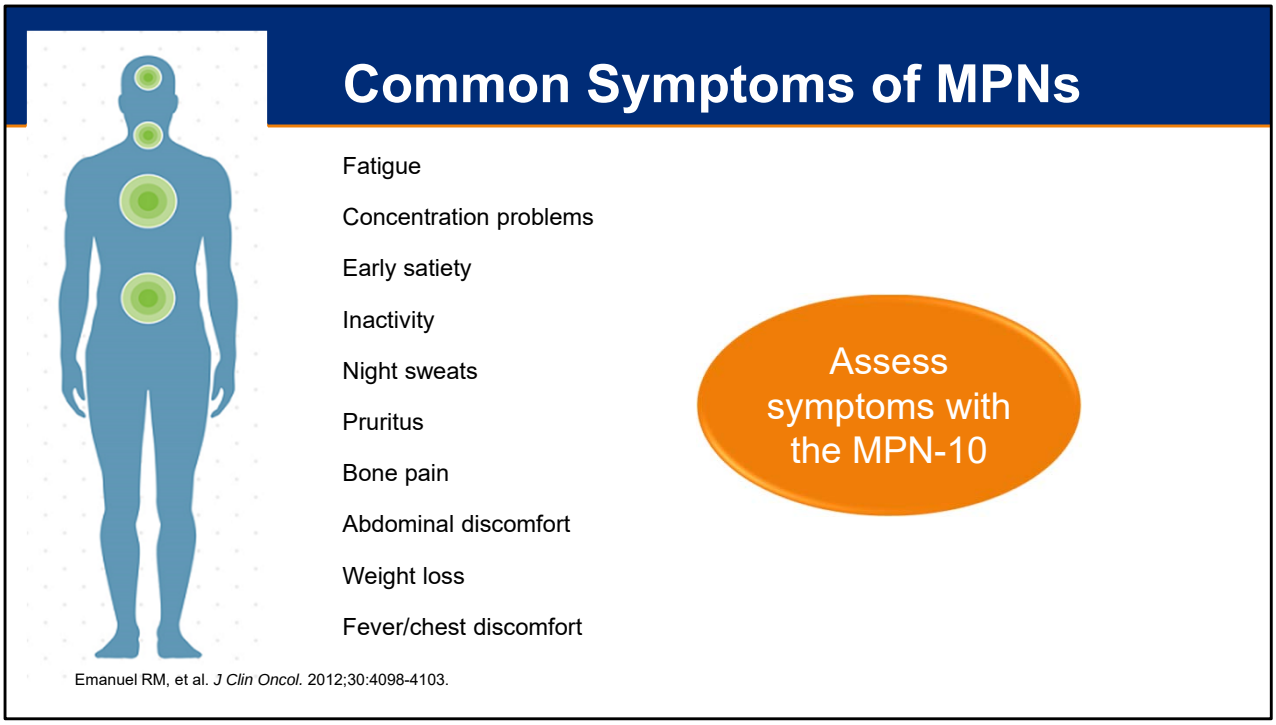
Drivers of Myelofibrosis

Mutational Drivers in MF	
Mutation, %	Frequency in MF
JAK	50
MPL	5-10
CALR	35

- Excessive inflammatory cytokines
- Damaged intracellular signaling mechanisms
- Increased *JAK1* signaling (occurs even when *JAK* mutation status is negative)
- 10% of cases without driver mutation (termed “triple negative”)

Rumi E, et al. *Blood.* 2014;124:1062-1069.; Vannucchi AM, et al. *Leukemia*. 2013;27:1861-1869.; Tefferi A, et al. *Leukemia*. 2014;28:1472-1477.; Guglielmelli P, et al. *Leukemia*. 2014;28:1804-1810.

What are the drivers of myelofibrosis? We have touched on this but just to really emphasize this point, we did not know about this when I first started taking care of patients and the better we are with our mutation analysis, then we have been able to determine what the underlying drivers of the disease are and thus the change from being classified as a disorder to a neoplasm. It is overactive Janus associated kinase activity or JAK mutations which occur in about 50% of our patients with myelofibrosis. There is also the MPL or myeloproliferative leukemia virus mutation which can occur in 5% to 10% of patients and there is CAL reticulin mutation which occurs in 35% of patients with myelofibrosis. There is excessive inflammatory cytokines that are part of the disease process that lends itself to all these symptoms that patients’ experience, extreme fatigue being the top reported symptom. We also have damaged intracellular signaling mechanisms, referred to as SOCS, and increased JAK1 signaling which occurs even when the JAK mutation status is negative, and 10% of the cases are without a driver mutation and these are referred to as triple-negative myelofibrosis.



What are the symptoms? I really think that nurses are great at talking to patients and really going over their symptoms. There are 10 common disease-related symptoms for myeloproliferative neoplasms and we have a quality of life tool to measure those referred to as MPN 10 and they are as you can see in descending order, fatigue, concentration problems, early satiety, usually associated with an enlarging spleen inactivity, night sweats, pruritus, bone pain. Patients will frequently ask me is this part of my disease or am I just getting old? And I will tell them it could a little bit of both since these are older patients and we know that osteoarthritis is also associated with aging. Abdominal discomfort even for patients that do not have an enlarged spleen, they can get spleen-related symptoms usually in that left upper quadrant beneath the spleen, they can have weight loss and fever.

The Role of Nurses in the Care of Patients with MF

- Nurses are key members of the healthcare team whose role includes:
  - Assisting patients in recognition and evaluation of symptoms
  - Evaluating how these symptoms change over time
  - Discussing with and educating patients regarding symptom management

Emanuel RM, et al. *J Clin Oncol.* 2012;30:4098-4103.

Myeloproliferative Neoplasm Assessment Form
Total Symptom Score (MPN-SAF TSS)

Symptom	1 to 10 (0 if absent) ranking 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past 24 hours	(No Fatigue) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes, during the past week, how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (early satiety)	(Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration compared prior to my MPD	(Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/tingling (in my hands and feet)	(Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint or arthritis)	(Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

*Question used with permission from the MD Anderson Cancer Center Brief Inventory
About this form
The article describes the development and use of this form as published in the November 20, 2012 edition of the *Journal of Clinical Oncology*

This is the form for that MPN 10, also referred to MPN Symptom Assessment Form and they grade these on a scale of 0 to 10, with 0 being absent and 10 being the worst imaginable degree of that symptom and as I stated earlier, I am really a firm believer in the nurse's role in assessing these symptoms. We are the key members of the healthcare team or the frontline. We spent time educating our patients. We can help them recognize that some of those bone pain symptoms are part of the disease and not always just their arthritis, and another key piece of the routine consistent measuring of the symptoms in a consistent systematic fashion is that you will be able to see as they change over time which will correlate with changing disease like if their symptoms are increasing, then they may be progressing to a more advanced stage of disease, and then educating patients on different strategies for minimizing or helping deal with those symptoms.

The MPN Landmark Survey: US Findings

- The survey included 207 patient respondents with MF, and 156 physician respondents treated patients with MF
- Findings revealed gaps between patient-physician perception of goals of therapy and emphasize a need to improve communication and patient education about MF
- 81% of patients with MF reported diminished QoL due to disease-related symptoms

MF-related Symptoms, %	Patients (n=207)
Fatigue	81
Night sweats	28
Abdominal discomfort	26
Difficulty sleeping	25
Weight loss	25
Early satiety	21
No symptoms	19

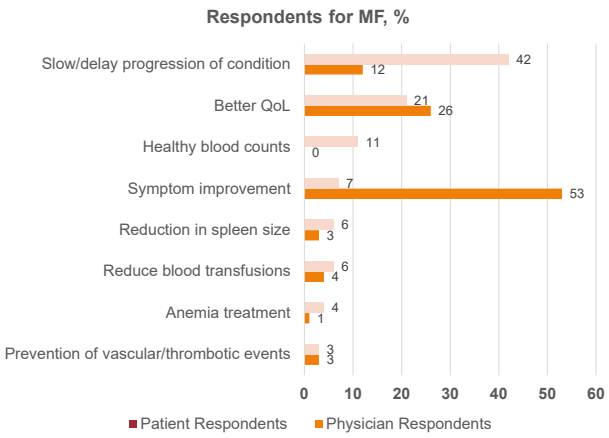
Mesa RA, et al. *Cancer.* 2017;123:449-458.

There was this landmark survey of all the myeloproliferative neoplasms or the classic ones and this was the large scale analysis of both patients and physicians, and really you cn see the differences between the patients and the physicians. There were 207 patients with myelofibrosis and 156 patients that took care of them or had at least two or more patients with myelofibrosis in their practice, 81% of patients had myelofibrosis symptoms that really reduced their quality of life. As we discussed previously, fatigue occurred in most patients 81% of them, night sweats, abdominal discomfort, sleeping difficulty, which would not really make you think that is part of their disease process but it is, and weight loss, early satiety and 19% of them had no symptoms, so for sure the majority of patients experienced symptoms.

Improving Care for Patients with Myelofibrosis Through Education: Nursing Practice Update

The MPN Landmark Survey: US Findings

- Results from the survey of the 156 physician respondents showed:
  - Agreement with patients in the top five symptoms
  - Fewer than 10% of physicians reported difficulty sleeping as a problem
  - Overestimation of emotional impact of disease
  - Overestimation of education provided about upcoming treatments
  - Differing top therapy goals in disease management with patients



Mesa RA, et al. *Cancer.* 2017;123:449-458.

The patients really agreed with the top 5 most commonly experienced symptoms but less than 10% of the physicians reported sleeping as a problem, which you know if you do not sleep well that can contribute to fatigue, so really helping them recognize that sleep is part of their fatigue is doing them a good service, going over sleep hygiene with them. The physicians also overestimated the emotional impact of the disease and overestimated how much they educated the patients about upcoming treatments and they diferred on their top therapy goals and disease management with patients, so a different view point helps you really understand how we can help better meet the patient's need and bring those two groups together to where we have congruent goals between the physician and the patient.

Prognosis by Mutational Status

- Prognosis determined by staging

Triple-negative MF (eg, no mutations in *JAK2*, *MPL*, or *CALR*)
- Occurs in 10% of MF patients
- Associated with inferior survival

***TET2* and *TP53* mutations**
- Associated with worsened overall prognosis
- Increased rate of leukemic transformation

CALR-/ASXL+
- Associated with poor prognosis
- Refer for allogeneic transplant if otherwise healthy

Tefferi A, et al. *Leukemia.* 2014;28:1472-1477.

For prognosis, triple-negative myelofibrosis patients have inferior survival so those are patients that do not have a JAK2 mutation or an MPL or a CAL reticulin mutations, so they are triple negative, and this occurs in about 10% of myelofibrosis patients. Also TET2 and TP53 mutated patients have a worsened overall prognosis and an increased rate of leukemic transformation. CALR-/ASXL1+ patients have poor prognosis, so if they are younger and otherwise healthy, you want to refer them early in the course of their disease for allogeneic stem cell transplant evaluation if otherwise healthy, and again this gets to talking to the patient about what their goals are, do they want to live longer no matter what it takes for them even if some of the symptoms are horrible in the meantime, you know during that journey, or do they want a better quality of life, and then our prognosis is determined really by staging the patient.

Stratifying Risk with Myelofibrosis by Staging

- No difference in risk stratification for PMF, post-PV, or post-ET MF
- Risk for progression to advanced stage of disease or AML
- Four levels:
  - Low-risk (MF-1)
  - Intermediate-1 risk (MF-2)
  - Intermediate-2 risk (MF-3)
  - High-risk (MF-3)
- Prognosis and treatment based on risk level
- Symptom assessment is integral for determination of need for treatment
- Recommend referral to center specialized in managing patients with MPNs

Tefferi A. *Am J Hematol.* 2018;93:1551-1560.

Stratifying the risk, there is no difference in risk stratification for patients with primary myelofibrosis or post PV or post ET myelofibrosis and it goes from low risk to high risk with the four levels and really you're determining their risk for transformation to more advanced stages of disease or to developing acute myelogenous leukemia, so the lower their risk is, the higher their survival and the less chance of progressing to higher risk of disease or advanced stage disease. So low risk is MF1, an intermediate risk is MF2 and intermediate 2 is MF3 and high risk is also an MF3. We base our treatments on their risk level and symptom assessment is integral for determining the need for treatment and it is also incorporated into these risk stratification staging systems, and for patients who develop MPNs we really recommend that they are referred to a center specialized in treating large numbers of myeloproliferative neoplasms.

Staging in Myelofibrosis

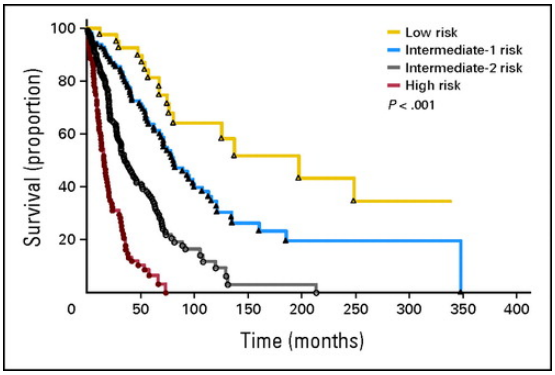
	Point/Value	
Parameter	**IPSS**	**DIPSS**
Age >65 years	1	1
Presence of constitutional symptoms	1	1
Hemoglobin <10 g/dL	1	2
WBC count >25x10^9/L	1	1
Blood blasts ≥1%	1	1
Risk group	**IPSS Score**	**Median Survival**
Low	0	11.25 years
Intermediate-1	1	7.92 years
Intermediate-2	2	4.00 years
High	≥3	2.25 years

- International Prognostic Scoring System (IPSS): recommended at diagnosis[1]
- Dynamic International Prognostic Scoring System (DIPSS): recommended if karyotyping not available[2]

[1]Cervantes F, et al. *Blood.* 2009;113:2895-2901. [2]Passamonte F, et al. *Blood.* 2010;115:1703-1708.

This illustrating two of the staging systems, the International Prognostic Scoring System which is recommended at diagnosis and then there is the Dynamic International Prognostic Scoring system which is recommended if you do not have karyotyping from the bone marrow, and survival is predicted by the score, and it guides the timing and the goals of treatment, so if you go along these lines you can see that just being older than 65 years of age get to 1 point in each of the categories, whether or not the patient has symptoms is also associated with a point of 1, hemoglobin less than 10, white blood cell count greater than 25 and then presence of blast at 1% or greater, and then you add those up and then you get your score, and you could see that the lower score, the survival is better, so a median survival for a low risk patient is 11.25 years whereas as a IPSS score of 3 or greater is associated with a much lower median survival of 2.25 years. So that helps you to be able to help the patient you know plan out whether or not they want to be treated or whether they want something else done for them. Some patients are very opposed to treatment whereas others want to do whatever it takes for them to survive longer.

DIPSS Plus



- Survival data of 793 patients with PMF
- Stratified by DIPSS + karyotype + platelet count + transfusion status prognostic scores
- Scale for DIPSS:
  - High risk: three adverse points
  - Intermediate-2: two adverse points
  - Intermediate-1 (unfavorable karyotype, platelets <100 x 10^9/L, and transfusion need): one adverse point

Gangat N, et al. *J Clin* Oncol. 2011;29:392-397.

This is looking at a different staging system, the Dynamic International Prognostic Scoring Plus, so it incorporates the DIPSS plus some other prognostic information. They will look at survival data of 793 patients with primary myelofibrosis diagnosis and this was done through the Mayo Clinic referral system, so the DIPSS Plus incorporates karyotyping, platelet count and transfusion status into the prognostic scores, and then you can see on the left that again your low risk disease illustrated in yellow has a longer survival and it even plateaus, whereas your intermediate-1, intermediate 2 and high-risk disease have survival that is measured in months. We have several prognostic scoring systems and you would need to use the one that is most appropriate for your patient and for which you have complete data.

Scoring for DIPSS and DIPSS-PLUS: NCCN Myelofibrosis Clinical Practice Guidelines

RISK STRATIFICATION FOR PATIENTS WITH MYELOFIBROSIS[1]

DYNAMIC INTERNATIONAL PROGNOSTIC SCORING SYSTEM (DIPSS)[3]

Progonostic Variable	Points		
	0	1	2
Age, y	≤65	>65	
White blood cell count, x10^9/L	≤25	>25	
Hemoglobin, g/dL	≥10		<10
Peripheral blood blast, %	<1	≥1	
Constitutional symptoms, Y/N	N	Y	

Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1 or 2
Intermediate-2 (INT-2)	3 or 4
High	5 or 6

DIPSS-PLUS[4]

Prognostic Variable	Points
DIPSS low-risk	0
DIPSS intermediate-risk 1 (INT-1)	1
DIPSS intermediate-risk 2 (INT-2)	2
DIPSS high-risk	3
Platelets <100 x 10^9/L	1
Transfusion need	1
Unfavorable karyotype*	1

*Unfavorable karyotype: complex karyotype or sole or two abnormalities that include trisomy 8, 7/7q-, i(17q), 5/5q-, 12p-, inv(3), or 11q23 rearrangement.

Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1
Intermediate-2 (INT-2)	2 or 3
High	4 to 6

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines. Myelofibrosis. Version 3.2019. Available at: www.nccn.org. Accessed April 14, 2020.

This is just showing you side by side from the NCCN Guidelines version 3.2019, the DIPSS and DIPSS Plus which we referred to previously in this presentation.

Goals of Treatment

- Discuss the risk/benefit of therapies with the patient
- The goal should be individualized to what is most important to the patient
- Improve symptoms and overall QoL
- Reduce spleen size
- Delay progression of MF to later stages of disease, and transformation to AML
- In some cases, cure is the goal through allogeneic transplant

- Fatigue
- Concentration problems
- Early satiety
- Inactivity
- Night sweats
- Pruritus (itching)
- Bone pain
- Abdominal discomfort
- Weight loss
- Fever

Emanuel RM, et al. *J Clin Oncol.* 2012;30:4098-4103.; Mesa RA, et al. *Leuk Lymph.* 2015;56:1989-1999.

What are the goals of treatment? I really feel like we should talk to the patients and provide them as much information as possible and then discuss what the goals of treatment are providing the pros and cons with each treatment and also they are very interested in how much it is going to cost them and how long they have to be treated, and what is the benefits. It is a risk-benefit determination and you really want to understand your patient so that you can determine what is most important to them. Some of my patients that I take care of with myelofibrosis really did not want to start any treatments or start on any clinical trials because they wanted to travel but at some point his disease progressed to the point that he could not travel any longer because he had to come in for transfusions and that was the point when he decided okay it is time for me start some kind of treatment. Of course, I have preferred that he start earlier but I took into consideration what his personal goals were. So, you really want to improve the symptoms and overall quality of life and if the patient's goal is cure, then that may be the person that needs to be referred for a consultation with our allogeneic stem cell transplant clinic at my facility. So, we want to improve the symptoms, what type of symptoms, fatigue, concentration problems, the early satiety, and you see the list that we have discussed previously. Patients will also feel better for the most part when you can reduce their spleen size, some of these spleens are the largest I have ever seen in our myelofibrosis patients, so if you can reduce that volume of spleen, you can give them improvement in their symptoms, and you really want to delay the progression of MF to later stages of the disease and really want to transform their rate of progression to acute myelogenous leukemia, and again we talked about in some cases cure is the goal and that is through in allogeneic stem cell transplant if they have an HLA identical donor, but remember, they have to have that HLA typing done early to know if they have a donor.

Treatment Options

Low/intermediate-1 risk disease without symptoms	Symptomatic with low/intermediate-1 risk	Intermediate-2/ high-risk	Non-transplant intermediate-2/ high-risk
• Observation	• Interferons • Hydroxyurea • Allogeneic transplant[1] (risk/benefit discussion)	• Discussion of goals with treatment • Refer for transplant evaluation with consideration of age, comorbidities, psychosocial status, and availability of caregiver	• Ruxolitinib[2] if platelet count ≥50,000 *or* fedratinib[3] *or* clinical trial • Clinical trial with pacritinib[4] for platelets ≤50,000

- Treatment should be tailored to risk group + includes evaluation of symptoms

[1]Scott BL, et al. *Blood*. 2012;119:2657-2664. [2]Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807. [3]Pardanani A, et al. *JAMA Oncol*. 2015;1:643-651. [4]Komrokji R, et al. *Blood*. 2015;125:2649-2655.

What are our treatment options? So our treatments are tailored to the risk group and includes the evaluation of symptoms, for our low and intermediate 1 risk groups who do not have symptoms, we can just bring them in and evaluate them periodically in our clinic on an every three-month basis from any them with the caveat that they call us if things change for them. For our symptomatic patients with lower intermediate 1 risk disease, they could be treated with interferons, hydroxyurea, or allogeneic transplant with the risk-benefit discussion that we talked about. For our intermediate 2 and high-risk disease, you really want to ask the patient what their goals are, what is most important to them and then see if that is something that we can deliver on. When they are referred for an allogeneic transplant, they consider their age, their comorbidities, their psychosocial status, their funding status, do they have a caregiver, and are they able to stay locally for the transplant, and when they go to transplant, they will go over the risk of being cured with this stem cell transplant versus the risk of dying within the first year following transplant. Those are pretty sobering numbers for many of the patients that I see. For non-transplant eligible intermediate-2 and high-risk patients, we would start ruxolitinib if their platelet count is greater than 50,000, or fedratinib which is a new kid on the block, or a clinical trial. There is also a pacritinib that is still in clinical trials that could be used for your patients who have a platelet count less than 50,000.

A Closer Look at Treatment Options: Approved JAK Inhibitors

Ruxolitinib[1]

- First in class JAK1/JAK2 inhibitor
- In the COMFORT-I study, 91% of patients treated had >50% improvement in TSS and QoL
- Reduction in splenomegaly
- Closely monitor for cytopenias experienced in the first 12 weeks

Fedratinib[2]

- JAK2 inhibitor
- Used for resistance or intolerance to ruxolitinib
- 35% SVR at 24 weeks was achieved by 36%-40% of patients in the fedratinib 400 mg and 500 mg groups, respectively
- ≥50% improvement in TSS achieved in ~35% of patients

[1]Mesa RA, et al. *J Clin Oncol.* 2013;31:1285-1292. [2]Pardanani A, et al. *JAMA Oncol.* 2015;1:643-651.

So, let's take a closure look at those treatment options. Ruxolitinib was the first in class JAK1 and JAK2 inhibitor. Remember it can be used even they are not JAK1 V617F or JAK2 exon12 mutated. We do not have to check for mutation status to get the benefit from these JAK inhibitors and the COMFORT 1 study 91% of patients treated had a 50% or greater improvement in their total symptom score and overall quality of life. They had a reduction in splenomegaly. They do need to be closely monitored for the development of cytopenias or lowering of the blood counts in the first 12 weeks. For fedratinib, the most recently FDA-approved drug for treating patients with myelofibrosis, this is a JAK2 inhibitor. It is frequently used for resistance or intolerance to ruxolitinib. The primary endpoint of the clinical trials that lead to the FDA approval were 35% reduction in spleen volume at week 24 and this was achieved by 36% and 40% of patients in the fedratinib 400 mg and 500 mg groups, and approximately 35% of patients had a 50% or greater improvement in their total symptom score. So, it not only reduces blood counts but it improves their symptom scores and quality of life.

Key Safety Issues/Adverse Events Associated with Ruxolitinib and Fedratinib

Ruxolitinib[1]

- Dose-dependent anemia and thrombocytopenia
- Diarrhea
- Muscle spasms
- Dizziness
- Dyspnea
- Increased incidence of *Varicella* infections

Fedratinib[2]

- Anemia
- Gastrointestinal symptoms
- Increased liver transaminases
- Increased serum creatinine
- Increased pancreatic enzymes
- Wernicke's encephalopathy possibly related to thiamine deficiency

[1]Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807. [2]Bewersdorf JP, et al. *Cancer Manag Res*. 2019;11:10777-10790.

The key safety issues with ruxolitinib, there is dose dependent, anemia and thrombocytopenia, so they need to be scheduled for lab work and then seen and discussed whether they need adjustment of the dose of ruxolitinib. It can cause diarrhea, muscle spasms, dizziness, and dyspnea. And there is an increase incidence of varicella infections. I think this is really a key piece for nurses to inform patients of what the symptoms are of the varicella infection and provide with phone numbers to call if this occurs. Some patients are put on preventive treatment for that and others are not if that has not been a problem for them. For fedratinib again, anemia, gastrointestinal symptoms, increased transaminases, increased serum creatinine, increased pancreatic enzymes, and there is the association with Wernicke's encephalopathy that is possibly related to thiamine deficiencies. If you think that a person is going to be started on fedratinib and is losing their response to ruxolitinib, in my clinic we are measuring thiamine levels and if they are low, starting them on replacements so that we can get them into a normal window for thiamine if we think the fedratinib is going to be their next treatment.

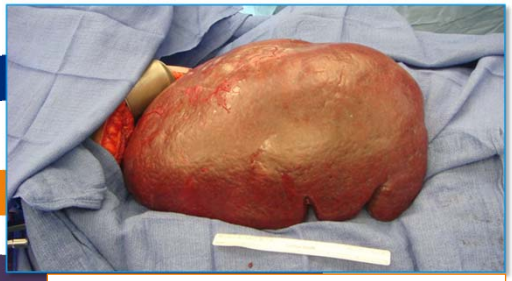
Non JAK-inhibitor Treatment Approaches

Hydroxyurea[1]
- Controls blood counts
- Reduces spleen size

Splenectomy[2]
- Used in special circumstances

Splenic irradiation[3]
- Used in advanced stage disease with painful splenomegaly

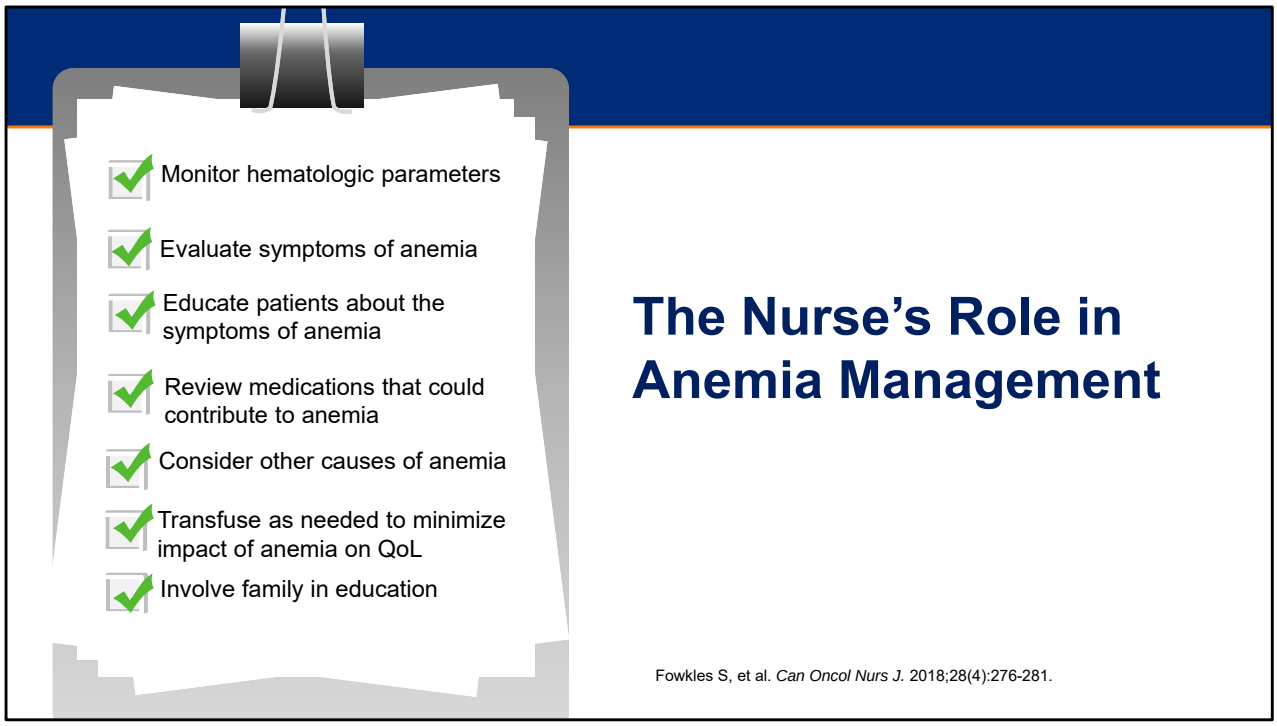
Allogeneic stem cell transplant[1]
- Curative
- High incidence of morbidity and mortality



Massively enlarged spleen, courtesy of Moffitt Cancer Center

[1]Tefferi A. *Am J Hematol.* 2018;93:1551-1560. [2]Cervantes F. *Blood Cancer J.* 2011;1(10):e37. [3]Barbui T, et al. *J Clin Oncol.* 2011;29:761-770.

Non-JAK inhibitor treatment approaches include hydroxyurea which is used to control the blood counts and also can reduce the spleen size, splenectomy in special circumstances. This is an image of a patient that I took care of who had a massively enlarged spleen and they took a picture of it for me after it was removed, you can see it was massive in size and causing the patient a lot of problems. In advanced stages of disease, when patients have painful splenomegaly, they can undergo splenic radiation, and again we talked about allogeneic stem cell transplant with the goal of cure but it is associated with a high incidence of morbidity and mortality, really individualized to that patient depending on their comorbidities and age.



The nurses were all in anemia management is really to help monitor their hematologic parameters that CBC with differential on a pretty consistent and systemic fashion and also evaluating for symptoms of anemia when they call in, may be they are not scheduled for a visit but they have increased shortness of breath and they are pale and their heart is betting really fast and you might want to bring them in for checking their CBC with differential earlier than you ordinarily would have, educate the patients about symptoms associated with the anemia, review their medication list. Many of our patients are on Plavix (clopidogrel) and aspirin, some of those are associated with bleeding, which could contribute to the anemia. Consider other causes of the anemia like we talked about bleeding or nutrition, like if they have lost 30 pounds in a short amount of time. They may have some iron deficiency that you want to replace so that they can have a higher hemoglobin, and we transfused them as needed to minimize the impact of anemia on their quality of life and again, we want to involve the family in this education process.

Communication Points for Shared Decision Making

Facilitators for shared decision making

- Consideration of patient preference for involvement in shared decision making
- Positive health care provider actions and behaviors
- Support systems use of encouragement

Barriers to shared decision making

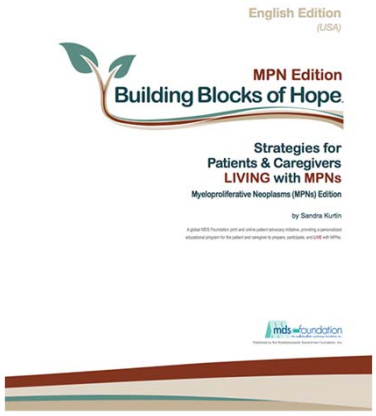
- Uncertainty in decision making regarding adverse side effects
- Poor healthcare communication

Covvey JR, et al. *Support Care Cancer.* 2019;27:1613-1637.

Decision making, again, these are communication points for that shared decision making with the patient, the family member and the physician were kind of the go-between for those two groups of people we are our patient's advocates, so we want to be facilitators of shared decision making, so we want to really lean on our understanding of what the patient values. What is the most important to them and include the patient's preference in this decision-making process. We want to have positive encouraging healthcare actions. We want to encourage the use of support systems. I have had some patients that were coming to the visit by themselves and were really getting so fatigued by the end of the day. We know that that increases the risk of falling, so I would encourage them to reach out to their children or their spouse to come with them at those visits if at all possible. I found that a lot of my female patients did not want to burden their family members, but we talked through some of that and said we really should just ask them if they will mind helping you. So, encouraging them in advocating for their own health, and we do know that the barriers to shared decision making is some of the uncertainty regarding the adverse effects, so if we can inform them to the best of our knowledge, then we can help them make a more informed decision, and then just poor health care communication, we are all very busy but if we can take the time to sit down with the patient and provide written instructions also for reinforcement, then that is really a benefit to them. It is really building that relationship.

Strategies to Improve Education

- Provide written communication to reinforce verbal communication
- Provide online resources
  - *MDS Foundation Building Blocks of Hope MPN Edition*
    https://www.mds-foundation.org/bboh/
  - *Voices of MPN*
    https://www.voicesofmpn.com/
  - *MPN Research Foundation*
    http://www.mpnresearchfoundation.org/
  - *Leukemia and Lymphoma Society – MPN*
    https://www.lls.org/



So, other strategies it is a complicated disease and difficult for patients to explain to others, so we really want to provide written communication to reinforce what was told them verbally. There are good online resources the MDS Foundation has an MPN addition ,the Building Blocks of Hope, which the patient can download or they can even order a hard copy to come through the mail. There is also Voices of MPN that is a website. There is the MPN Research that is website and the Leukemia and Lymphoma Society has an MPN link. So, those are all wonderful resources that we can provide to our patients as a way of going on it in their free time and really educating themselves and come back and ask us questions for anything they did not understand.

Thank you for joining me for this presentation. I hope you found this information useful to you in the care of your patients.