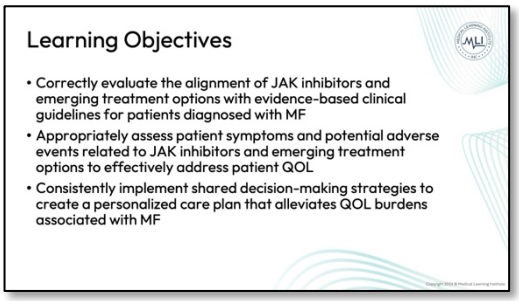
Recognizing the Profound Impact on Quality of Life: Emerging Therapy Options for Patients with Myelofibrosis

Jeanne M. Palmer, MD: Hello everybody and welcome. Today we're going to talk about Recognizing the Profound Impact on Quality of Life: Emerging Therapy Options for Patients with Myelofibrosis. My name is Jeanne Palmer, and I am a hematologist at Mayo Clinic in Arizona. I am joined by my colleague, Jennifer Andres.

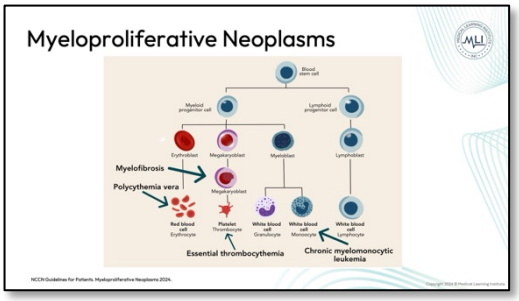
Jennifer Andres, MSN, RN, FNP-C, OCN, BMTCN: Hi, everyone. As Dr. Palmer said, my name is Jennifer Andres, I'm one of the nurse practitioners here at Mayo Clinic in Arizona, and I specialize in MDS, CML, benign hematology, and the myeloproliferative neoplasms, which include polycythemia vera, essential thrombocythemia, and myelofibrosis, which we'll be talking more about today.



Learning Objectives

Dr. Palmer: The learning objectives for today include the following. Correctly evaluate an alignment of JAK inhibitors and emerging treatment options with evidence-based clinical guidelines for patients diagnosed with myelofibrosis. Appropriately assess patient symptoms and potential adverse events related to JAK inhibitors and emerging treatment options to effectively address patient quality of life. Finally, consistently implement shared decision-making strategies to create a personalized care plan that alleviates quality of life burdens associated with myelofibrosis.

For the first part of this presentation, we will provide information about myelofibrosis with regards to its pathophysiology, as well as how we choose treatment options and how they work.



Myeloproliferative Neoplasms

To begin with, let's look at the blood system to understand where the problems occur. The blood system starts with that cell on top, which is a hematopoietic stem cell. The first breakdown it goes to is to a myeloid progenitor cell and the lymphoid progenitor cell.

The myeloproliferative diseases are characterized by dysregulation of cells in the myeloid progenitor cell line. The myeloid progenitor cells go on to make erythroblasts, which ultimately make red blood cells, make a karyoblasts, which ultimately go to make karyocytes and make platelets. Then they also go on to myeloblasts, which ultimately go on to make different types of white blood cells, including neutrophils, monocytes, among others.

Where we believe that some of the dysregulation starts is in the megakaryocytes, especially for myelofibrosis and essential thrombocythemia, and in the erythroblasts and probably also the megakaryoblasts for polycythemia vera. Now, these are defined-- when we look at these different diseases, polycythemia vera is defined as too many red blood cells, essential thrombocythemia is defined as too many platelets, and myelofibrosis is a sort of syndrome of diseases that basically is characterized by dysregulation of the cell, which ultimately results in a whole plethora of different clinical manifestations and pathologic manifestations such as fibrosis of the bone marrow. Patients may often have a high white blood cell count, anemia, a large spleen. We'll talk a little bit further about the symptoms that patients have moving forward.

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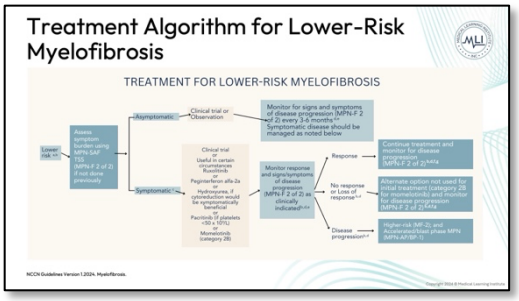
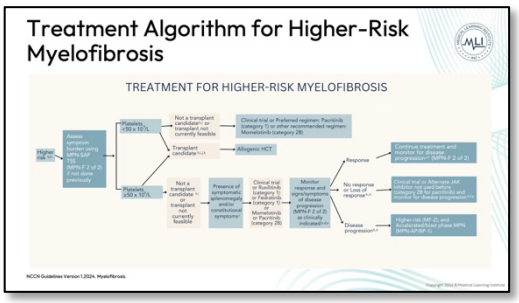


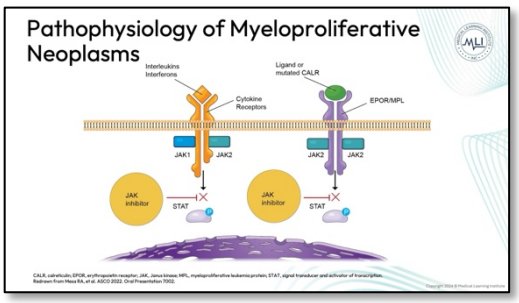
Treatment Algorithm for Lower-Risk Myelofibrosis

Today we will be focusing on myelofibrosis. When we think about the treatment algorithm for lower-risk myelofibrosis, we really go back to the NCCN guidelines, and in lower-risk myelofibrosis, we assess symptoms based on whether they're symptomatic or not. That would help us determine whether we want to try some type of treatment.



Treatment Algorithm for Higher-Risk Myelofibrosis

Higher-risk myelofibrosis, oftentimes in these patients, we assess their symptoms still and we also look at their counts as many times these patients will have low platelet counts or anemia, and that usually puts people in a higher risk category just by that by itself. In those patients, the platelet count will largely help direct their therapy, particularly if they are symptomatic. We will go more into how these different therapies play out and how we sequence them later on.



Pathophysiology of Myeloproliferative Neoplasms

To understand the pathophysiology of the myeloproliferative neoplasms, it's important to understand the JAK-STAT pathway. Dysregulation of this pathway is one of the underpinnings of this disease. What we see here is the membrane of a cell, which is characterized by the little yellow dots and sort of the hatched marks in between. Now you see a purple line that goes through it, two purple lines together, as well as two orange lines together.

What these are, these are different receptors, and how receptors work is there's something external to the cell that wants to tell it to grow. These receptors are there to get the signal and then to pass it on to the nucleus so that the nucleus produces proteins and makes a cell divide and makes it grow in the way it's supposed to grow. Examples of these are cytokine receptors, cytokines being chemicals that help modulate our immune response. For example, when we're having a cold or a flu and we feel feverish and yucky, that's our cytokines reacting. Then the EPO is erythropoietin, which drives red blood cells, and MPL is a thrombopoietin receptor which drives production of platelets. All of these, however, signal through this JAK-STAT pathway.

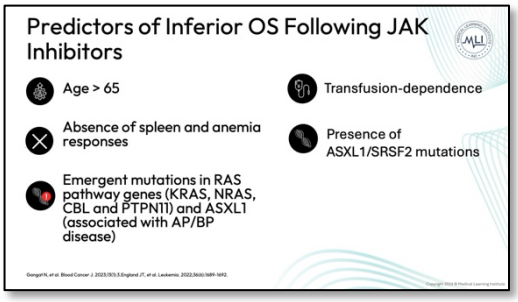
What happens when the cells get a signal coming in is the two pieces of the receptor bind together. When they bind together, they make that JAK2, which is the teal box, activate and signal through the STAT protein to make the cell grow or produce chemicals or a variety of other different things. Under normal steady state, those two parts of the receptor live apart. They just hang out waiting for a signal to come.

When a signal comes, such as erythropoietin or thrombopoietin or something that activates those receptors, it pulls the two receptors together, the JAK2 is activated, and it signals to the cell to grow. As soon as that signal externally is gone, the two receptors pop apart and wait for the next signal to come. When there's a mutation in one of these, for example, the JAK2V617F mutation, which is the most common driver mutation, that makes those two receptor pieces stick together and continue to signal, even if there's nothing external telling it to do so.

Then when we look at the second most common mutation is the calreticulin mutation. What that is, that's actually a protein that lives external to the cell. It's that green circle you see, which is on the top part of the

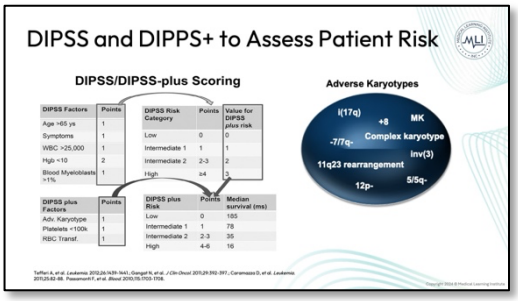
slide, which is external to the cell. By that being there, that also drives abnormal signaling. It keeps the signal going, even if the rest of the body doesn't think it needs to be.

Then the final mutation that's far more rare is the MPL mutation, and that's the thrombopoietin receptor. That's that purple line that you see the receptor there. When that's mutated, that also drives atypical signaling. This is important, because when we talk about these different treatments and disease, one of the major things we do, as you'll see by that yellow circle, is we block that pathway. That's one of the ways that we are able to treat this disease and make people feel better.



Predictors of Inferior OS Following JAK Inhibitors

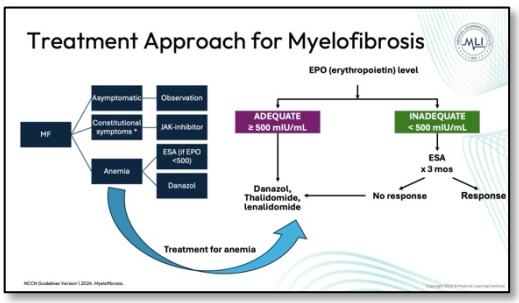
JAK inhibitors are a wonderful treatment for this disease, but there are predictors of inferior overall survival. These are things such as age of greater than 65, which unfortunately includes the majority of patients who have myelofibrosis, transfusion dependence, absence of a spleen or anemia response, presence of an ASXL1 or SRSF2 mutation, both of which are considered higher risk mutations. We're also finding that there may be other mutations present in different pathways that may also impact the ability of JAK inhibitors to work and may also make the cell more prone to progress into more dangerous diseases, such as accelerated phase or blast phase.



DIPSS and DIPPS+ to Assess Patient Risk

One of the ways we try to assess risk in patients coming in to see us is we calculate something called the DIPSS or DIPPS score. You'll often hear people talking about the DIPPS score, especially when thinking about how we decide on bone marrow transplant. This score is based on a conglomerate of both clinical factors, such as age and symptoms, as well as laboratory factors, such as blood counts. By calculating scores based on the numbers you see there, you can ultimately decide to give them an either low risk, intermediate one risk, intermediate two risk, or high risk.

Now I think that understanding these symptoms is extremely important to understanding how the disease will behave. I do want to exercise caution in using these survival numbers, because these were both created prior to JAK inhibitors being clinically available, and they do appear to prolong survival. So, these are probably not accurate at this stage in the game. That being said, I feel like these risk factors are clearly very important.



Treatment Approach for Myelofibrosis

When I see a patient who has myelofibrosis, at first, I try to say, are you symptomatic or not? Because if they're symptomatic, that's when I really want to think about the JAK inhibitors. Then I determine the appropriate one based on their clinical situation. If they're asymptomatic, especially if they don't have low blood counts, it's often observation. Sometimes patients present with severe anemia, and I'm sure Jennifer can weigh in on that because we see a number of these patients together. In that case, we look at whether they have erythropoietin or not, and consider either danazol, an ESA. Even though luspatercept is not FDA-approved for myelofibrosis, it is FDA-approved for MDS, so sometimes we try that.

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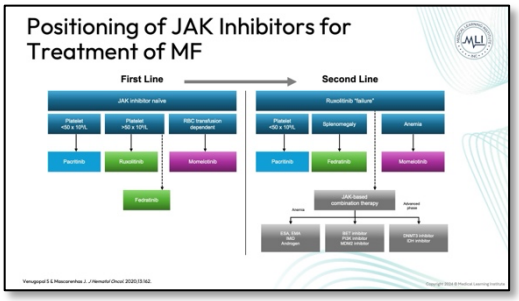
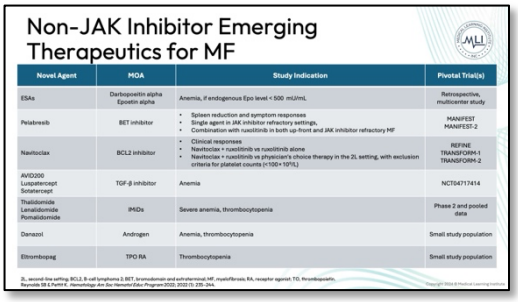


Positioning of JAK Inhibitors for Treatment of MF

Positioning of JAK inhibitors for the treatment of myelofibrosis is definitely something that is a moving target and individualized per provider. I think we know that in terms of patients who are frontline, we most frequently will use ruxolitinib up front, as long as their platelets are greater than 50. If they have red blood cell transfusion dependence, you consider momelotinib. If their platelets are less than 50, pacritinib is generally the choice.

For the second line treatment, you can either go to pacritinib or momelotinib, or fedratinib, depending on how their platelets and red blood cells look. That's considered the ruxolitinib failures. When we look at these JAK combinations, these again are things most of which are still in clinical studies and there's more to be seen on that.


Non-JAK Inhibitor Emerging Therapeutics for MF

Novel Agent	MOA	Study Indication	Pivotal Trial(s)
ESAs	Darbopoetin alpha Epoetin alpha	Anemia, if endogenous Epo level < 500 mU/mL	Retrospective, multicenter study
Pelabresib	BET inhibitor	• Spleen reduction and symptom responses • Single agent in JAK inhibitor refractory settings, • Combination with ruxolitinib in both up-front and JAK inhibitor refractory MF	MANIFEST MANIFEST-2
Navitoclax	BCL2 inhibitor	• Clinical responses • Navitoclax + ruxolitinib vs ruxolitinib alone • Navitoclax + ruxolitinib vs physician's choice therapy in the 2L setting, with exclusion criteria for platelet counts (<100×10^9/L)	REFINE TRANSFORM-1 TRANSFORM-2
AVID200 Luspatercept Sotatercept	TGF-β inhibitor	Anemia	NCT04717414
Thalidomide Lenalidomide Pomalidomide	IMiDs	Severe anemia, thrombocytopenia	Phase 2 and pooled data
Danazol	Androgen	Anemia, thrombocytopenia	Small study population
Eltrombopag	TPO RA	Thrombocytopenia	Small study population

2L, second-line setting; BCL2, B-cell lymphoma 2; BET, bromodomain and extraterminal; MF, myelofibrosis; RA, receptor agonist; TO, thrombopoietin.
Reynolds SB & Parikh K. *Hematologic Am Soc Hematol Educ Program* 2022; 2022 (1): 235–244.

Non-JAK Inhibitor Emerging Therapeutics for MF

There are different medications that are currently being studied for the treatment of myelofibrosis. These are drugs such as ESAs, which are erythropoietin-simulating agents that have been used for MDS for a number of years as well as for patients with renal failure. These can be used in patients whose EPO level, erythropoietin level is less than 500. Again, we don't have any prospective studies for this, but we do have some retrospective studies.

Pelabresib is a new drug that is not yet approved for any indication. It's a class of drugs called a BET inhibitor, which works on a slightly different signaling pathway. We talked about the JAK signaling pathway and that's where the JAK inhibitors work. There are a number of other pathways that could drive the progression of disease, and so a lot of these other targets really are approaching that. It has been tested both as an add-on drug to ruxolitinib as well as up-front with ruxolitinib. It's had some favorable effects, but it's not yet FDA-approved or clinically available.

Navitoclax is a drug that's considered BCL2 inhibitor. This drug has been shown to work as an add-on agent or up-front. That being said, it also is not yet clinically approved, and we're waiting to see what happens with that.

There are TGF-β inhibitors, and these all work on part of the signaling pathway that drives fibrosis and inflammation. These are supposed to help with anemia, and especially with the AVID-200, potentially help with the formation of fibrosis.

Thalidomide, lenalidomide, and pomalidomide are very rarely used and primarily for patients who have severe anemia.

Danazol is an androgen-like agent, which can be used for patients with anemia and thrombocytopenia.

Eltrombopag is something that we generally do not use off a clinical trial because it does activate the thrombopoietin receptor, which we know ultimately can be part of the driving of this disease. That would be something that would be considered an extreme thrombocytopenia.

Patient Discussion

Jennifer helps me manage a number of these patients and has a great deal of expertise in doing so. We have plenty of situations like this, where we have a male with high-risk myelofibrosis who resides in a rural community with a small hematology-oncology team which is not really up to date on the evolving standards of care. Frequently, we have trouble

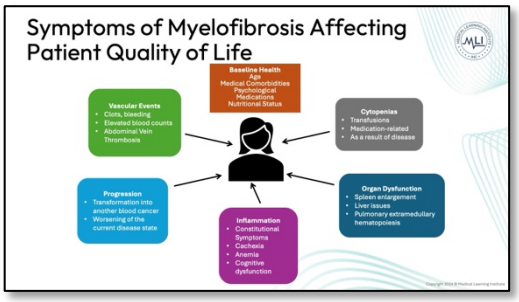
getting things like blood transfusions and stuff done. I will say, a lot of them really live far away because we have a very large catchment area actually going into California and to New Mexico and to Nevada. We have a number of patients in this situation. When you see these patients with me, how do you assess what we're going to do, like if they're on JAK inhibitors and we're thinking of changing the dose?

Ms. Andres: Right. First of all, we take a look at their blood counts. That's a big factor. We take a look at their symptom burden. In a little bit, we'll be going over the MPN-SAF total symptom score and looking at some of the main things that can affect patients. Then, as Dr. Palmer also said, looking at, based on the blood counts and their symptoms, what might be the best medication? Whether it's the JAKAFI [ruxolitinib] upfront or if their platelets are low, the pacritinib or VONJO, or if they're anemic, perhaps now we have the momelotinib or OJJAARA that is FDA-approved.

Their social situation can also play a part. As Dr. Palmer mentioned, we do have some patients that are in other states, and so we really try to work closely, if they do have a local hematologist, we'll work closely with them to make sure that we are giving the patient the best care and monitoring and follow-up as possible.

Dr. Palmer: Yes, I think this is one of those things where if we have somebody on ruxolitinib and we say, maybe we should go up on the dose because they're not responding as well. Sometimes, for example, if they live far away and we know that they can't get good access to transfusions, you may be a little bit more reluctant to do that because we know they might end up with severe anemia externally. I think that can be one of the challenges of managing these patients. I think having some of these newer drugs has made things a lot better because we are able to manage them with different drugs that may not have the same impact on their peripheral blood counts.

The next part of our presentation is going to be talking about making appropriate treatment selections for patients with myelofibrosis. This is recognizing the gaps in myelofibrosis care that can influence patient quality of life. I'm going to have Jennifer talk a little bit about what type of symptoms we see in our patients.



Symptoms of Myelofibrosis Affecting Patient Quality of Life

Ms. Andres: Yes. As we discussed, there's a number of things that can affect our myelofibrosis patients and how they're feeling and their quality of life. Starting at the top in the orange rectangle there, certainly their age, other comorbidities, psychological components, the medications they're on and their nutritional status, all of those play a key role.

Certainly, when we are meeting these patients for the first time, we are assessing all of those and making sure that we can-- if they have a comorbidity, if there's a specialist that they should be seeing so that they're getting optimal care for that. If there are psychological issues, do they need to see our psychiatry team, or perhaps do we need to rope in our social work team? Medications. Some patients don't realize that simple over-the-counter medications can certainly have impacts on their level of fatigue and things like that. Then as far as nutritional status, we also have a nutritional team that we can refer patients to if needed.

Then going clockwise to the cytopenias, we take a look at all the cell lines. The red blood cells or the hemoglobin, the white blood cells, the infection fighters, and then the platelets. Some patients, depending on their hemoglobin, may require blood transfusions. Typically, we will transfuse if the hemoglobin is less than seven. In cases where patients are symptomatic, we may transfuse if the hemoglobin is less than eight.

Some of those cytopenias may be medication-related or as a result of their underlying disease. As far as platelets, we typically will transfuse if the platelet count is less than or equal to 10, as that is when they would

have the highest risk for spontaneous bleeding. In some cases, if they are febrile or having an active bleed, such as a nosebleed, we may transfuse if they are less than or equal to 20. Then certainly if they are going to be having some a procedure done, like a colonoscopy, typically we'd like the platelet count to be above 50,000 for that.

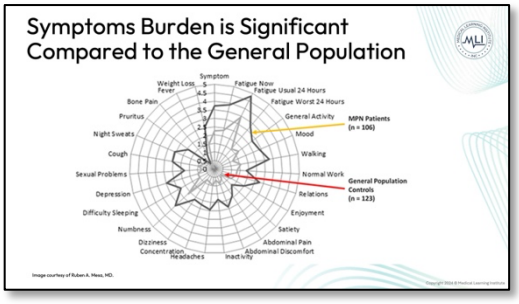
Then going down to the blue rectangle there, organ dysfunctions. The spleen is definitely something that we keep an eye on for our patients. Splenomegaly can cause a number of symptoms for patients, such as what we call early satiety or getting full quickly, which can then in turn affect their ability to eat and can cause them to lose weight without trying. We certainly keep an eye on that.

Liver issues can play a role as well. Sometimes the liver can also get enlarged. Then there's something called pulmonary extramedullary hematopoiesis, where the disease might be affecting their breathing. We sometimes will do imaging to evaluate for that. A lot of times, in person, we can try to palpate for the spleen. A normal spleen sits under the rib cage where you're not able to feel it, but in a lot of these patients that have significant splenomegaly, we are able to feel it below that midclavicular line under the rib cage.

Coming down to the pink-purple square there, inflammation. We'll be talking about some constitutional symptoms in a little bit, and that can be things such as fatigue and night sweats. As I had mentioned earlier, there is a symptom assessment form that we utilize. We try to ask our patients that every time we see them so that we can evaluate whether things are improving, if they're the same, or if things are perhaps getting worse, where we may need to think about an alternative treatment. Then as I mentioned before, nutrition is very important, making sure that they are maintaining a healthy, adequate weight. Then we talked about anemia as well. Cognitive dysfunction is something that we also want to keep an eye on.

Then coming around to the blue square there, progression. As Dr. Palmer mentioned, we are always keeping an eye out for whether or not they may be progressing. We do have patients that may start out with polycythemia vera, and that may evolve into what we will then call a secondary myelofibrosis or post-PV myelofibrosis. Then, same for the essential thrombocythemia, that can evolve into post-ET myelofibrosis, whereas, if patients have primary myelofibrosis, then that is their initial diagnosis. Some of our patients can eventually progress to leukemia, although that's rare. So, we're always looking at the blood counts and making sure that we're not seeing any signs of progression. Then as well, looking at the current state of the disease. As we had talked about earlier, that involves looking at their blood counts, symptoms, and the whole picture.

Then lastly, vascular events. One of the big things we're trying to prevent with our patients is them having a blood clot or bleeding, and so where patients that have platelets too high or too low can have bleeding or blood clots. Then we're always as well assessing for if they're having any abdominal symptoms or a blood clot in the abdominal area that might cause thrombosis. I'm going to have Dr. Palmer speak to this next slide about symptom burden and its significance compared to the general population.



<u>Symptoms Burden is Significant Compared to the General Population</u>

Dr. Palmer: One of the things you may notice is when we talk about a lot of these symptoms, a lot of these symptoms are things that people have at baseline. For example, fatigue, who isn't tired sometimes with our busy lives? What this diagram shows is the general population and the MPN population and comparing just how they even answer questions to the same survey. You'll see in the center, there's a gray line. They're like a jagged little line that goes around. That's the general population. Then when you look at the dark black line that certainly captures a bigger space, you'll see that patients with MPN inherently just have a higher symptom burden, even if you're asking some of these same questions that are quite common to different people.

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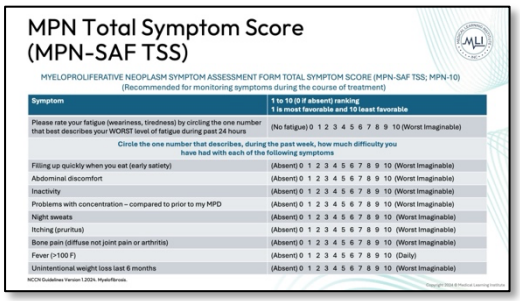


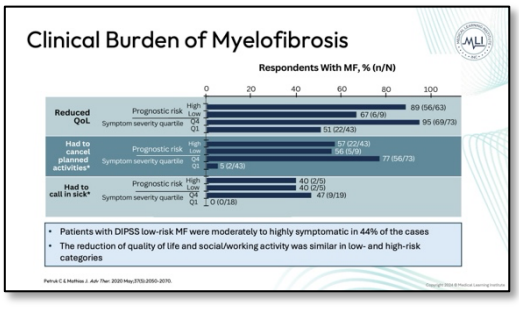
MPN Total Symptom Score (MPN-SAF TSS

Ms. Andres: This is one of the tools that we utilize in clinic. We recently were able to get it where it's sent electronically, so our patients can fill it out prior to the visit if they're able to, but we use a 0 to 10 scale. Zero would be that that particular symptom is not bothersome and 10 would be that it's the worst imaginable. For example, the top one there says, *Please rate your level of fatigue or tiredness by circling the one number that best describes your worst level of fatigue in the last 24 hours*. A lot of patients may come in and say, "Oh, I'm just so tired, I can't do anything. I can barely get out of bed." So, they would give it a 10. Then we have other people who come in and say," I feel great, I'm able to do everything and I would give it a zero." Then we have those people that are in between. Fatigue is one of the symptoms.

Going down the list, we ask them about if they get full quickly when they eat and abdominal discomfort. Some of those go back again to the spleen enlargement. If they're having spleen enlargement, sometimes those symptoms may be more bothersome. If they're having spleen enlargement, that's when we would want to tie in one of those JAK inhibitors, such as the JAKAFI, which again, we often use first-line. Or if they are anemic, we might do the OJJAARA [momelotinib]. Or, again, if their platelet counts are low, we have the pacritinib as an option.

Then the next is related to their activity level. We also ask about their concentration, whether or not they're having night sweats, itching, bone pain, fevers, or unintentional weight loss. This symptom form is very helpful because we can see, and I've seen in clinic, and I'm sure Dr. Palmer has as well, where we'll have a patient come in and they're not in any medication and their symptom score is very high. The higher the total score, the worse their symptoms.

After we start them on some kind of a JAK inhibitor, a lot of times we do see improvement in the score. Sometimes we see an improvement by 50%. Sometimes it takes a little bit longer. This is just one way that we can capture how the patients are doing. Certainly, as Dr. Palmer said, we have to also take it with a grain of salt because we know some of these symptoms, like fatigue, can certainly be multifactorial and different things can play a part in it.



Clinical Burden of Myelofibrosis

Dr. Palmer: I think this is a complicated slide, but the take-home message of it is this. We talked about the DIPSS risk and the high-risk and the low-risk patients. What this is showing is that sometimes that high-risk or low-risk doesn't actually play into whether patients will have symptoms. Even if a patient has low-risk disease, they still can be quite symptomatic. On the converse side, they can actually have high-risk disease and not have many symptoms at all depending on the patient. I think making sure to assess this, irregardless of the patient's risk score, is very important.

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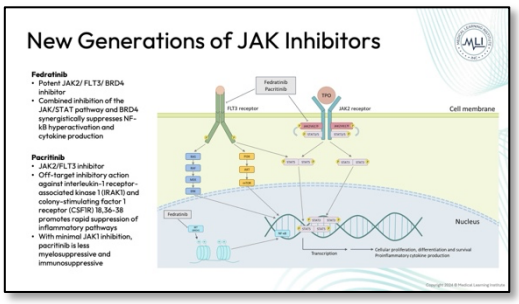
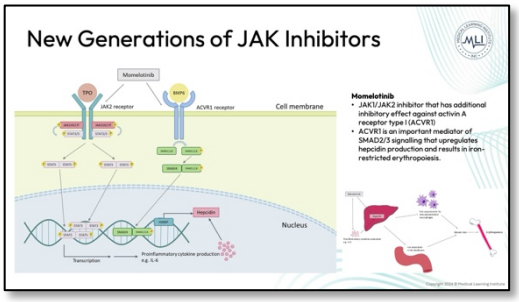


New Generations of JAK Inhibitors

We have been talking a lot about the different JAK inhibitors that are available and this is just taking a little bit of a deep dive into things other than the JAK2, the JAK inhibition, that probably help us and help these drugs work well. We know fedratinib affects JAK2 which helps a lot with symptom burden. I think one of the other things that's notable is it does have FLT3 inhibition, which FLT3 is something we'll sometimes see in AML that doesn't necessarily play into our decision to use Fedratinib although it does contribute to some of the side effects.

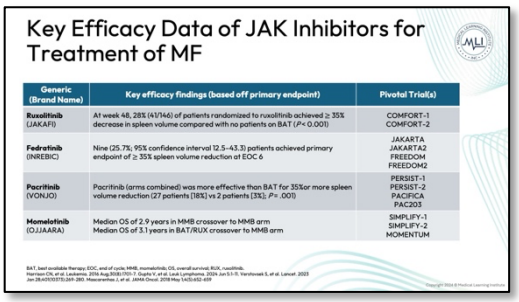
Then pacritinib also does a FLT3 inhibition, but it does three other things actually that are pretty important. The first one is IRAK1, and this is actually felt to help with the ability of us to use this drug with low platelets. Then there is CSF1R which also can help suppress some of the inflammatory pathways. Both fedratinib and pacritinib have less JAK1 inhibition. When we talk about JAK inhibitors, it's usually JAK1 and JAK2. We know JAK1 inhibition really contributes to the low blood counts.



New Generations of JAK Inhibitors

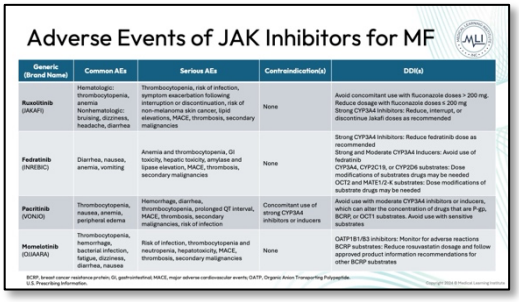
One of the most exciting things that's come out recently with the JAK inhibitors is the inhibition of the ACVR1 pathway. The reason that this is important is not because it has another set of initials you have to remember but because ACVR1 is actually very critical in iron homeostasis. Now, as a medical student and possibly in nursing school and nurse practitioner school, you learn about iron metabolism and think you don't have to remember it anymore.

Well unfortunately, or fortunately, we do have to learn it again because this is really a critical piece of how a drug like momelotinib works and we're actually finding that pacritinib probably has that same ACVR1 inhibition. Basically, by inhibiting ACVR1 you decrease the hepcidin which ultimately makes the bone marrow able to grow better and make more red cells. This has been a fantastic thing for our patients. They can go from needing transfusions and being very anemic to actually having a close to normal hemoglobin.



Key Efficacy Data of JAK Inhibitors for Treatment of MF

We talked a little bit about this before, so I won't belabor this slide. This is again going over some of the different studies that have been done for ruxolitinib, fedratinib, pacritinib, and momelotinib, all demonstrating why they are effective treatments for our patients.



Adverse Events of JAK Inhibitors for MF

The adverse events of these patients, this is something that Jennifer and I have to watch for very closely in them.

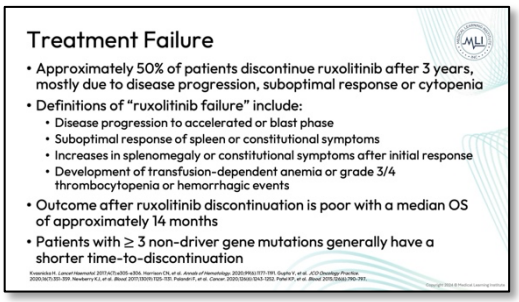
I think when we think about, what are some of these different adverse events, we have ruxolitinib. The main thing we always worry about with that is low blood count. This is particularly bad within the first few months that patients are on it and eventually they come back to a sort of steady state level. That probably is the most

important thing to be watching for. There are other side effects such as non-melanoma skin cancer, there can be hyperlipidemia, and almost all patients on ruxolitinib gain weight which is a very important thing for people to be aware of. It is important to make sure you look at the other drugs they're taking as there's a lot of drug-drug interactions.

With fedratinib, it can also cause low blood counts, but the biggest thing that's unique to fedratinib is the GI side effects. They can be very, very severe. Patients can have really bad diarrhea; they can have nausea. So, it's important that patients are aware of that and are given medicines to help prevent that such as Imodium or anti-nausea medications like Compazine. It also can have a lot of drug-drug interactions, so it's important if they start any new medications that they're made aware.

Pacritinib can also cause a fair amount of nausea and diarrhea. Now, in some earlier studies, there were some cardiovascular events and bleeding. This has not seemed to borne out in the more recent studies but it is worth keeping in mind, especially the bleeding, as these patients will have low platelets which is the main indication to use it. Also important to watch what drugs they're taking.

Finally, with the momelotinib, they can have some lower blood counts so that you certainly don't see the same degree of anemia you see with some of the others. They can have some diarrhea and nausea but it's less prevalent. In some earlier studies, there might have been a risk for some neuropathy, that hasn't seemed to borne out in the more recent studies, and there can be a little bit of hepatotoxicity. Again, watch for drug-drug interactions.



Treatment Failure

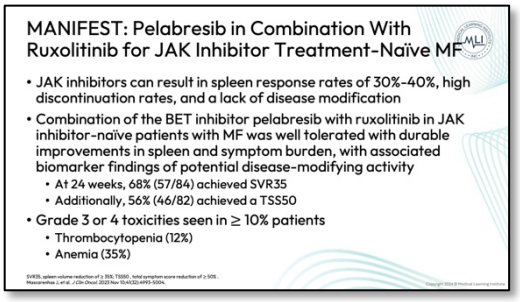
Treatment failure is a really hard one to define and to act upon and so when we look at half the people who are on the initial ruxolitinib studies had discontinued ruxolitinib because it's not working anymore, it was three years. That means that half the people will fail ruxolitinib within three years. Usually disease progression, sometimes cytopenia, sometimes people just don't want to take it because they've gained too much weight and they're really upset about it.

There's a lot of ways that people are trying to define ruxolitinib failure to standardize this, but ultimately, that's what becomes one of the shared decision-making things of as a patient. Many times, they'll say, "Well, geez, I'm on--" I say, "You're on ruxolitinib, your hemoglobin's dropping, your spleen's getting bigger," and they say, "Well, I still don't feel that bad and I really don't want to try a new medication." This is where some of that shared decision-making is important.

Now, there have been studies done of what happens when patients do fail ruxolitinib necessitating a change. Now, some studies demonstrated that they have a very poor survival after that. I will comment, these studies were all done before we had momelotinib, pacritinib, fedratinib. I think that we have to take that survival data with a grain of salt and certainly not tell patients when they failed ruxolitinib, "You only have a year left," because I think that that's probably not true currently. We do know that this is a bad prognostic sign. If we're thinking of when somebody needs a transplant, that would be one of the things that might prompt us to say, "Now it's time to move to more aggressive therapy."

When we think about what can contribute to treatment failure, having high-risk mutations, which we briefly touched upon earlier, but there's mutations aside from the JAK2 pathway mutations that may convey a higher risk. This is something that patients often will pay close attention to, and providers do as well. There's not much you can do about that, but it does help you predict how people may do.

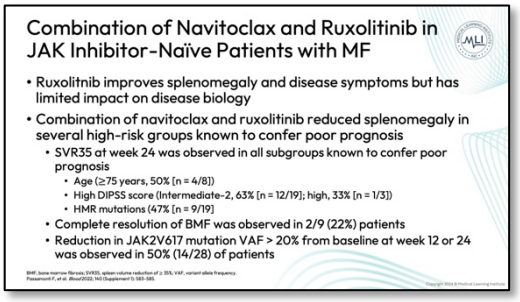
Recognizing the Profound Impact on Quality of Life: Emerging Therapy Options for Patients with Myelofibrosis



MANIFEST: Pelabresib in Combination with Ruxolitinib for JAK Inhibitor Treatment-Naïve MF

There have been a couple of different studies looking at new drugs that you may be able to add to JAK inhibitors to make them work more effectively. One of them is pelabresib, which is a BET inhibitor, which I briefly mentioned earlier. This actually can result if somebody who has failed or progressed through ruxolitinib, which usually for studies is defined as increase in spleen size. You can actually see a response rate of 30% to 40% by adding this pelabresib onto it.

Unfortunately, there are side effects as always with these, and those can be things like thrombocytopenia or anemia. Pelabresib currently isn't an upfront treatment comparing ruxolitinib alone to ruxolitinib and pelabresib combination therapy. Some data has been presented from that that is very favorable, but we're still waiting to see what's going to happen in the long term.



Combination of Navitoclax and Ruxolitinib in JAK Inhibitor-Naïve Patients with MF

Another drug that might be on the horizon is a drug called navitoclax. Navitoclax is actually a pretty interesting drug in that it allows the cell signaling that makes cells die off when they're misbehaving or mutated. It allows that signaling to occur. Venetoclax is a drug you'll often see in treatment for CLL or for AML. This is in that same general family, but it's just a different variation on it.

The combination of navitoclax with ruxolitinib has been quite effective in patients as an add-on therapy. There is upfront data looking at it compared to ruxolitinib alone that shows some very favorable results with regards to spleen response, but we're still waiting to see whether this is going to have a long-term benefit.

Patient Discussion

Now for a patient care discussion. This is a male patient, could be a female patient, with myelofibrosis who's been successfully treated with ruxolitinib. However, they've been requiring lots of dose adjustments because of blood counts for the most part. Now the patient's fairly unhappy with both disease and treatment-related factors that influence quality of life. What kind of symptoms, Jennifer, do we end up seeing or do you see with these patients who are starting to fail ruxolitinib?

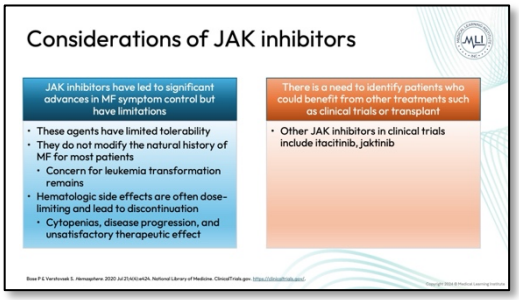
Ms. Andres: As Dr. Palmer mentioned, one of the big things is the weight gain. We have had patients gain a substantial amount of weight to the point that they just say, "I would rather stop the medication than continue on it." At that point, we would also take a look at what other symptoms they may or may not be having. Then we could take a look at, again, if their counts are changing, would one of the other JAK inhibitors maybe be appropriate at that point in time?

I think one thing to keep in mind with ruxolitinib or JAKAFI is that we never want patients to stop it abruptly because it can cause rebound effects where a lot of the symptoms that were being controlled can sort of flare back up. If we ever did need to change treatments, we would taper them off of the ruxolitinib instead of having them stop completely.

Dr. Palmer: This weight gain does seem to be a ruxolitinib-specific phenomenon. It does not seem to be a class-effect thing. We don't see it as much in other JAK inhibitors. When you start to see people that are not doing as well on JAK inhibitors, how do you go about switching them to a different one?

Ms. Andres: If we're switching say from the ruxolitinib to maybe now they're more anemic so we're transitioning to the momelotinib, those, for the most part, we can just have them stop the ruxolitinib and then start the momelotinib right away. In other cases, if they're not going to be starting another treatment, as I mentioned we may just taper down on the ruxolitinib and then take a look at what other options might be appropriate. There was that previous slide that talked about things such as the danazol or the luspatercept or the erythropoietin stimulating agents such as ARANESP [darbepoetin alfa] or perhaps they might need transfusion.

We discuss all the different options with the patient, and again, it's a lot of that shared decision-making which we'll talk about in some of the later slides to see what fits in line with their goals and their quality of life.



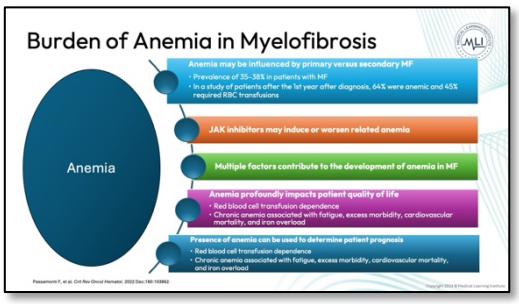
Considerations of JAK Inhibitors

Dr. Palmer: The next part of this presentation we'll talk for accounting for patient quality of life based on myelofibrosis and treatment-related factors. This is really to increase familiarity with disease and treatment-related adverse events. Considerations of JAK inhibitors. JAK inhibitors they really have been a game changer for patients with myelofibrosis, but they do have limitations.

As we've talked about, they have a limited duration of response. Unfortunately, they do not seem to modify the natural history of myelofibrosis so as they progress toward a more serious event such as AML or something like that, JAK inhibitors don't seem to slow down that progression in that trajectory. They do seem to improve survival but that's likely because of their effect on inflammation and decreased, what I consider, wear and tear on the body.

The hematologic side effects are often dose-limiting and can lead to discontinuation such as cytopenias as well as some patients don't feel well. I think it's important to note that when fatigue is the main symptom patients have and less of fatigue is very clearly related just to the inflammatory process. Often JAK inhibitors aren't as good for treating just fatigue. When you have fatigue along with night sweats, or itching, or spleen enlargement I think JAK inhibitors are more effective.

It's really important that we look at patients as a whole when we first meet them and try to say, "Okay is JAK inhibitor the right treatment for you?" It may be that clinical trials would be an important thing to do. It may be that they need a bone marrow transplant, and so all of these things should be going through somebody's mind as you're seeing this patient for the first time or when you're starting to make the decision about use of a JAK inhibitor.

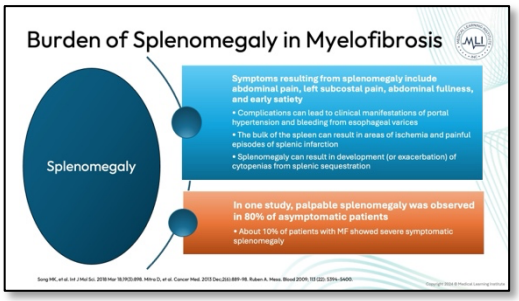


Burden of Anemia in Myelofibrosis

Anemia is one of the hardest things we deal with myelofibrosis. It's more common in patients of primary myelofibrosis versus secondary and almost every patient who has myelofibrosis will eventually become anemic. JAK inhibitors except for momelotinib in particular and pacritinib, to some degree, will potentially induce or worsen either disease-related anemia and then they also on top of it get a treatment-related anemia.

Recognizing the Profound Impact on Quality of Life: Emerging Therapy Options for Patients with Myelofibrosis

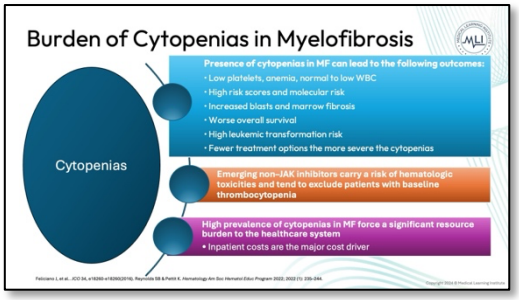
There's lots of things that contribute to the development of anemia and myelofibrosis. Their bone marrow is dysfunctional. They don't produce red cells as well. Additionally, there's a lot of inflammation which suppresses growth of red blood cells. The anemia is a huge factor on quality of life. Red cell transfusion dependence is terrible. They have to come in once a week, twice a week sometimes, to get transfusions. Chronic anemia is associated with fatigue and cardiovascular issues and then chronic transfusions associated with iron overload. Presence of anemia independently is linked to patient prognosis in a negative way.



Burden of Splenomegaly in Myelofibrosis

Ms. Andres: As we talked about in previous slides, splenomegaly can lead to things such as abdominal discomfort, particularly in that left upper abdomen, abdominal fullness, and getting full quickly. Some of the complications of these could be portal hypertension and bleeding from esophageal varices. Sometimes the spleen again can become very enlarged to the point that where it becomes very painful for these patients and that in turn can lead to cytopenias as the spleen sequesters those blood cells.

In one study, they were able to palpate a spleen in about 80% of patients who were asymptomatic, meaning that they weren't having symptoms, but the spleen was still enlarged. We do have patients that do have that splenomegaly, but again, aren't symptomatic from it. There are a few that, for whatever reason, don't want to start medication. We just monitor that spleen and monitor for any progression.



Burden of Cytopenias in Myelofibrosis

Dr. Palmer: The burden of cytopenias is huge, and we talked a little bit about it with anemia. Basically, the presence of cytopenias by itself is a poor prognostic factor. It also leads to need for blood transfusions. They have, as I said, it's a prognostic factor that can be tied into development of acute leukemia, increasing blast and marrow fibrosis, and earlier mortality related to the disease.

The other burden of cytopenias is that there's not really a lot of JAK inhibitors, aside from ones such as pacritinib or momelotinib, that can really be used to treat these patients. These cytopenias not only impact our ability to treat patients with something that can improve their quality of life, but also are a pretty big burden to the healthcare system as transfusion requirements are high, and that's use of a lot of blood, and as we know, a lot of blood is a limited resource.

Patient Discussion.

Patient is experiencing thrombocytopenia and anemia, as well as splenomegaly, and she's in clinic to discuss treatment options that will address quality of life, as well as myelofibrosis-related symptoms. What considerations do we take as a care team when we address the thrombocytopenia and anemia?

Ms. Andres: Certainly, if they have thrombocytopenia and anemia, we're looking for whether they are symptomatic from those. For example, I just saw a patient recently whose hemoglobin has been in the eight to nine range, and they actually feel okay at that level, whereas some people, at that level, would be very fatigued, short of breath, very tired. Those would be some of the things that we'd want to consider. Same for the thrombocytopenia. Are they having a lot of bruising, bleeding? Are there things we need to address from that standpoint? Those are some of the things that we would take a look at.

Dr. Palmer: Change the drug if needed, maybe.

Ms. Andres: Yes, and think about changing the drug if we needed to. As we had discussed previously, we do have JAK inhibitors that are specific for certain cytopenias, whether they do have a low platelet count or a low hemoglobin.

Dr. Palmer: When we talk about quality of life for these patients, how do you sometimes elucidate what the biggest factor involving their quality of life is?

Ms. Andres: I think a lot of what we do when we see our patients is we just talk to them about their life, their goals. I like to ask them what they do for work, who is in their family? Things like that. We will have some patients that might say to us, "I really want to try to make it to my son's wedding." or "I really want to try to feel good for my grandson's high school graduation."

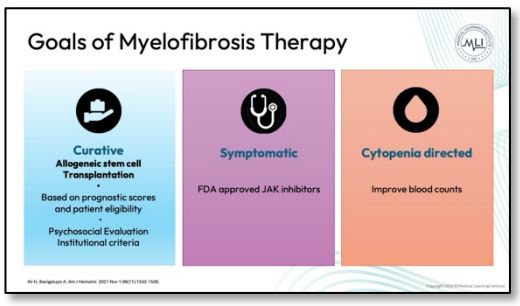
Those are some of the things that we would certainly take into consideration. For example, some people might say, "I want to be able to keep working for another few years," that kind of a thing. Those are some of the things that we would take into account. That's where it's that shared decision-making again, and determining which of the medications, or JAK inhibitors, or clinical trial might be appropriate. Like Dr. Palmer said, maybe even just having a stem cell transplant consult to see if a transplant might be the appropriate thing at that time, or if it might be more appropriate to wait a year or a few months before moving forward in that direction.

Dr. Palmer: What type of educational material? I know I see in a lot of your notes that you talk about giving patients information on different things. What do you use for resources?

Ms. Andres: Yes, so certainly, we have the NCCN that provides a lot of education and patient education. We also have our specific myeloproliferative neoplasm different forums. There's the MPN Education Foundation, and they actually do a patient conference every other year. The next one will be coming up in February of 2025 and that's the Joyce Niblack Conference. That's a great patient resource. It's good for providers too. We have a lot of our top MPN providers from all over that come and speak on all of the different MPNs and all of the latest up-to-date treatments on those.

Dr. Palmer: These patient advocacy organizations are excellent resources for patients. There's a number of them that provide webinars and patient conferences, the MPN Education Foundation, MPN Advocacy and Education. These are really important resources for patients with this disease.

In this part of the talk, we will be accounting for patient quality of life based on MF and treatment-related factors. We've been talking a lot about this, so I think one of the things we really want to delve into in this part is how do we establish trust with patients to improve outcomes and quality of life.



Goals of Myelofibrosis Therapy

One of the things when I first do a consult on a patient is I really want to know what their goals of therapy.

We talk about the short term which is what we've been talking about all along which is managing symptoms and counts but we also want to look at the big picture. Is this somebody who may eventually need a bone marrow transplant? This is something that even if somebody doesn't need a transplant right then is important that they're thinking about because there's a lot of factors that go into bone marrow transplant. Understanding whether it's the appropriate time to refer a patient for a bone marrow transplant. We also want to say do they want to improve their symptoms or do we want to improve blood counts.

Patient Discussion

Let's talk about a patient case discussion and this is a way to try to understand how we really establish trust and work with our patients. This is a male who's been experiencing diarrhea while on a current treatment option for myelofibrosis but has also felt that he has had an improved quality of life since he switched from ruxolitinib. This experiencing diarrhea could either be fedratinib or pacritinib.

I guess one of the first things that's really important before we talk about managing side effects and quality of life is establishing trust. Coming in and having to talk about your bowel movements is never fun. Coming in and also feeling confident that when they bring us their problems that we're able to address them appropriately and with an educated fashion is also very important.

Now Jennifer and I work together a lot on patients, and I see patients and then she'll often see them in between for several visits. How do you go about establishing trust? I think this is a huge important part of the healthcare team is really making sure that all members of the team are trusted by the patient so it's not just, "Oh, well, my doctor needs to be knowing about this all the time." How do you go about doing that because you do an amazing job at that?

Ms. Andres: Sure. I think it's definitely just trying to build that personal connection. When I first meet patients I just very simple basic things I say, "Hello Mr. Smith," and then I will say, "What do you like to go by? Do you like to go by John? Do you like to go by Joe?" Sometimes they might tell me, "Oh, I actually go by my middle name, which is Frank." Simple things like that where you build that rapport with them so that they don't feel like they're just another number, but they do feel like we really care about them.

I think the other thing is just being available to listen. I know when I first started as a nurse practitioner, I was able to shadow Dr. Palmer on several of her visits and she did an amazing job of that, of just letting the patient tell their story. That's where we really can glean a lot of information on how we can best tailor the treatment for that specific patient.

Like I was saying, I've recently seen a patient who we've been talking about starting medication for a number of visits and they're still not ready to start but all we can do is encourage and give them all the information. Ultimately, at the end of the day, the patient's going to make the decision that is best for them and their family. That's what we try to do with our team is just say, "We're here for you. We're here to support you whatever your decision is of how you would like to go about getting treatment."

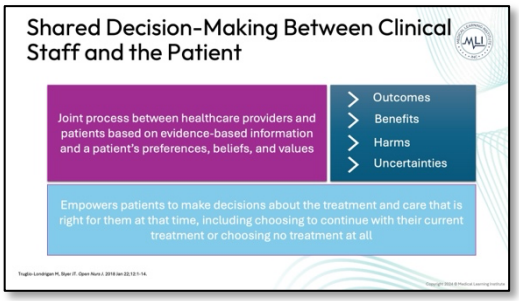
Our nurses are really great in that too. Whenever I can, if our nurses are available, I'll try to have them come in for the visit as well, just to pop in and say hello, and then that way the patient really feels supported like we're a team. I think that's one of the big things is just building that personal connection and letting them know that we truly care about them as an individual and a person.

Dr. Palmer: I think one of the things that you do especially probably better than I do with that is you always have good things in your notes about what's going on in their life like they just took a trip somewhere or in some cases, her husband just went to hospice or something like that. I think being able to do that and then when that's included in the note it helps me a lot so that when I see them, I can address that as well.

Paying attention to those types of details is really important and from that, we can really understand how their quality of life is and what's driving their quality of life. They might say, "Oh, I'm so tired and so distressed," and you think this must be their disease but it's actually that their spouse is dying from some other type of disease or just had a stroke and has been in the hospital for a long time. There's a number of different things and I think this is really, really an important piece of what we do.

In this patient case, we're talking also about managing side effects and I think them telling us about their side effects and feeling comfortable enough to continue to message us of going on now, this is going on now. The nurses that support us are some of the people who receive the highest burden of messages. I think that's a large part because we really do try to listen to the patients and make them feel that they can reach out to us. It's a very important part of the whole healthcare team. I certainly don't think I'd have nearly as many happy patients if it wasn't for the people that I work with.

In this section we're going to further discuss effective strategies for shared decision-making and myelofibrosis-related care, and again, really highlighting the value of this shared decision-making process and the unique role of a multidisciplinary team.

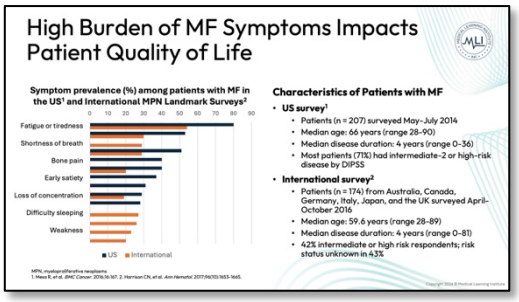


Shared Decision-Making Between Clinical Staff and the Patient

When we talk about the shared decision-making process between the clinical staff and the patient, this is really a joint process, and this is a summary slide of what I think we've been talking about for a lot of this presentation. Talking about what the outcomes are, what the benefits of a treatment are, what the harms are, and where the uncertainties are.

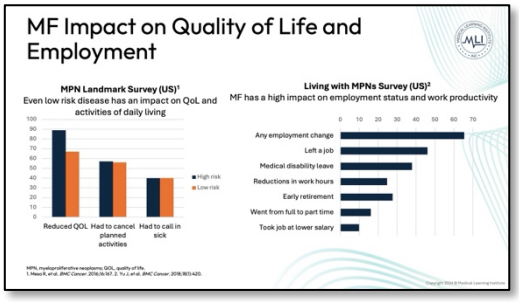
I think one of the most important things that we can do, and I think Jennifer does a great job at it, I certainly try to do that, is to really make sure that patients understand what they're dealing with so that they can make their own decisions. Then at that point, they understand, well okay, this is the pros and the cons of this decision, and patients are good at that. If you give them the option, they will often be able to say, "I understand that this is a negative effect of doing something, but this is what I want to do because it means something."

For example, a patient saying, "I would rather come in and get blood transfusions because I feel so much better on a JAK inhibitor," and therefore they understand the implications of being on that dose of a JAK inhibitor but accept what they have to do because that's going to be the best thing for their quality of life.



High Burden of MF Symptoms Impacts Patient Quality of Life

There was a landmark study that was done that studied patients with myelofibrosis to really understand the impacts of symptom burden on quality of life. In this one, we see that patients often will have fatigue, shortness of breath, bone pain. These are some of the most common symptoms that they have. The fatigue is the hard one because a number of patients have it, and we don't have really good therapies for it.

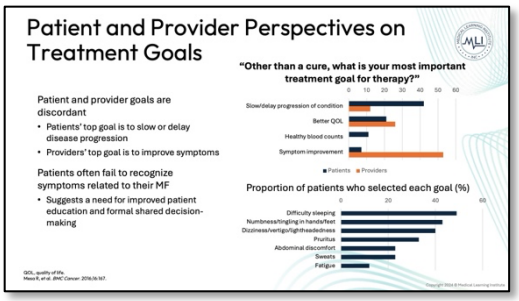


MF Impact on Quality of Life and Employment

This one I think highlights what those symptoms do to patients. This landmark survey basically looked at patients and they talked about, does this reduce your quality of life. One of the ways that they can measure this probably more accurately is have you had to cancel planned events. That's terrible if they have dinner plans and they say, "I'm just too tired I can't do this because of my disease," or they have to call in sick from work.

In this survey, they actually found that very high percentages of patients had to have some type of employment change whether it be leaving a job, medical disability leave, reduction of work hours, some patients retire earlier, and these are very critical pieces to our patients that I think we often overlook because we're so

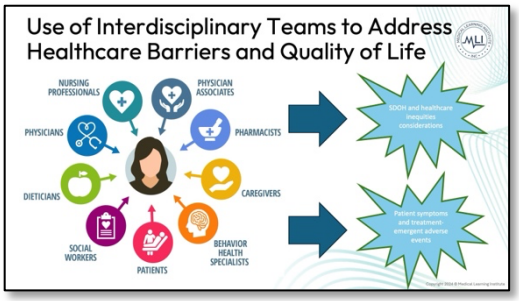
focused on numbers and drugs and stuff like that. I think understanding this and this is something we were alluding to earlier really talking to patients and saying, "What is going on in your life? What is the impact of having this disease on your life?" That's something that's important to do.



Patient and Provider Perspectives on Treatment Goals

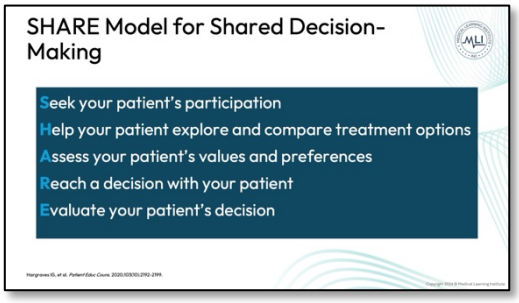
Now, one thing that's really key and we've talked a whole lot about symptoms and how to manage that, but I think this is a really important point. When they did this survey, they actually found that patients and provider goals sometimes differ. I think we've done as educators provided a really important idea to pay attention to symptoms, focus on symptoms. We focus on symptoms and making sure their symptoms are controlled.

Patients' top goal often is to slow or delay disease progression. Now, we don't have a lot of great ways of doing that, but I think it's important to acknowledge that as something that is important but focus on how we're trying to manage them in the short term. I think discussing that as part of the discussion even if you don't have an answer, a lot of times we don't like to talk about things we don't have good answers for, is really key in patient care.



Use of Interdisciplinary Teams to Address Healthcare Barriers and Quality of Life

This is a great viewpoint and Jennifer can attest to that of the importance of the healthcare team. The healthcare team is nursing professionals, physicians, dieticians, social workers, healthcaregivers, the patient's caregiver plays an incredibly important role, behavioral health specialists, pharmacists. We use these people every day and could not have the team we have and that provide good care without them. I think that's an important piece when you're starting to think about how do we take good care of patients. It's really involving everybody and making use of resources that are available.



SHARE Model for Shared Decision-Making

The SHARE model for decision-making is important. This an acronym SHARE, which makes good sense. Seek your patient's participation. Help the patient explore their treatment options. Assess the patient's values and preferences and reach a decision with your patient. Evaluate your patient's decision. Jennifer and I've talked quite a bit about that during this talk. This is a great summary of how you can approach this for patients.

Now I'll let Jennifer talk a little bit about advocating for patients as a nursing professional as she has been both a nurse as well as a nurse practitioner.

Ms. Andres: Absolutely. Nurses are an integral part of our healthcare team. As Dr. Palmer said, a lot of times they are doing that initial triaging when patients send questions in through the portal, the nurses are the ones that are trying to manage and answer as much as they can within their scope of practice. Nurses do a number of amazing things, including guiding patients through all facets of the healthcare system.

A lot of times the nurses are helping with some of those referrals that we make, trying to get patients connected to the different specialties or the social work team or the dietician, things like that. They help with that continuous monitoring and follow-up as we talked about. Our nursing staff is great about, they'll check in

with the patients and just say, "Hey, you've been on this medication for a week now or two weeks, how are you doing? How are you feeling? Is there anything you need?" Then addressing holistic needs of individuals.

Again, that comes into just knowing the patient and knowing what's important to them, knowing if they might have a faith or a value system that is a priority, or for some patients, they have a pet that's really important, so knowing about that. Then delivering culturally respectful and appropriate care. Certainly, in our area where we live, we do see a number of different populations. We have our Native American population that's here. We have patients that, as Dr. Palmer said, come to us from all different parts of the world, from West Coast, Hawaii, East Coast, all over.

Just trying our best to meet their needs and see things from their perspective so that we can provide the most culturally respectful and competent and appropriate care. Then ensuring that we are, as we've talked about, a patient-centered approach. We talk about, there's that analogy of the wheel, and we're all different spokes on that wheel, like Dr. Palmer, myself, the nurses, and the patients at the center of that. We just want to make sure that whenever we are trying to make a decision about their care, that we are certainly including them in that.

Sometimes patients, they just need time. As much as we want to try to come to a decision when we're in the office visit with them, sometimes it's just an information overload. These patients are just trying to process things for themselves. Sometimes I will say, "You know what? You don't have to make a decision just right now or today. Take some time to think about it, talk to your family, talk to the people that are important to you, and see what you think would work best and would align with your quality of life. Then we can circle back in a week or two weeks or a month."

Sometimes that is the approach that we take if a patient's not quite ready to make a decision right at that time. Certainly, our nursing team is an integral part of what we do and the care that we provide to our myelofibrosis patients.

Dr. Palmer: To summarize, I think this has been a great opportunity for Jennifer and I to share a lot of what we do, explaining the new landscape of treatment options available for myelofibrosis, and more importantly, focusing on how we take those treatment options and apply them to patients and really try to help address the patient's need, not only from medications, but also from different ways of managing them and following them that will improve their quality of life and sense of wellbeing.

I think we highlight the importance of the team approach. I think having physicians, nurse practitioners, nurses, dieticians, the whole team, is critically important and really making sure to utilize all of them is necessary to take the best care possible of patients.

I really want to thank you for joining us and listening to our presentation. Hopefully, you have learned something from us about myelofibrosis and how we can manage patients best. Thank you very much.