

Myelofibrosis: Charting the Course for Care

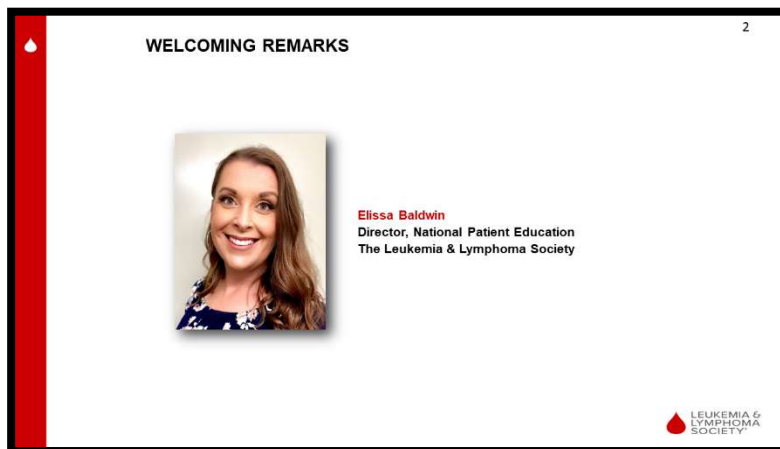
Speaker: Swati Goel, MD




**MYELOFIBROSIS:
CHARTING THE
COURSE FOR CARE**

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Elissa Baldwin: Hello, everyone, and welcome to Myelofibrosis: Charting the Course for Care.



WELCOMING REMARKS 2



Elissa Baldwin
Director, National Patient Education
The Leukemia & Lymphoma Society



My name is Elissa Baldwin with the Patient Education Team at The Leukemia & Lymphoma Society, and I will be your moderator today.

We will have a question-and-answer session after the presentation, where our speaker will answer questions that came into our LLS Information Specialists and online Community.

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We would like to acknowledge Abbvie for their support of this program.



I am now pleased to introduce our speaker for this lecture.

Doctor Swati Goel is a hematologist/oncologist at Montefiore Einstein Comprehensive Cancer Center in New York City. She leads the Myeloproliferative Disorder Clinic and is an Associate Professor in the Department of Oncology and Medicine at Montefiore Einstein. Her area of clinical and research focus is in myeloproliferative neoplasms (MPN), where she has been the Principal Investigator for several clinical trials including myelofibrosis, polycythemia vera and essential thrombocythemia.

On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise. Dr. Goel, I am now privileged to turn the program over to you.

Myelofibrosis: Charting the Course for Care

Speaker: Swati Goel, MD



Dr. Swati Goel: Hello everyone. My name is Swati Goel. I'm an Associate Professor of Medicine in Montefiore Einstein Comprehensive Cancer Center. Today I will talk to you about myelofibrosis.

What is myelofibrosis?

- Myelofibrosis(MF) is a rare Bone marrow disorder. Bone marrow is the spongy tissue inside the bone and the factory where our blood cells are produced.
- MF causes scarring of the bone marrow leading to abnormal production of blood cells
- As it becomes difficult for the scarred and stiff bone marrow to produce normal cells, blood cell production may move to the spleen (causing enlargement) or to other areas of the body

So, what is myelofibrosis? Myelofibrosis is a rare bone marrow disorder. Bone marrow is the spongy tissue inside the bone, and it is the factory where all our blood cells are produced. Myelofibrosis causes scarring of this bone marrow, which leads to abnormal production of blood cells. As it becomes difficult for the scarred and stiff bone marrow to produce normal cells, blood cell production may move to spleen causing enlargement or to other areas of the body.

Myelofibrosis: Charting the Course for Care

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Epidemiology

- Primary myelofibrosis is an uncommon disease, with an annual incidence of approximately 0.5-1.5 cases per 100,000 individuals in the United States.
- About 16 to 18 thousand people are living with Myelofibrosis in US.
- It can occur at any age but more common in people over 50 years of age

So, how common is this myelofibrosis? Primary myelofibrosis is an uncommon and rare disease with an annual incidence of approximately .5 to 1.5 cases per 100,000 individuals in the United States of America. At this time, about 16 to 18,000 people are living with myelofibrosis in the US. It may occur at any age, but it is commonly found in people over 50 years of age.

Causation

- Myelofibrosis can be primary (without prior blood disease) or it can be secondary to blood diseases called Essential Thrombocythemia or Polycythemia Vera
- It is caused by changes in DNA called mutations. People with MF acquire these mutations at some point in their life and are not born with these mutations, nor do they pass this on to their children
- No obvious reason has been found as to why some people develop these mutations
- Exposure to industrial chemicals such as toluene and benzene and high levels of radiation can increase risk of MF

What causes myelofibrosis? Myelofibrosis can be primary without any prior blood disease, or it can be secondary to blood disease called essential thrombocythemia, which is increased platelets, or polycythemia vera, which is increased red blood cells. This disease is caused by changes in DNA which is called a mutation. People with myelofibrosis acquire these mutations or acquire these changes in DNA at some point in their life. They are not born with these mutations nor, do they pass this on to their children, to their siblings, or anyone related to them. There has been no obvious reason, which has been found, to why some people develop these mutations and develop myelofibrosis. We do know that exposure to industrial chemicals such as toluene and benzene and high levels of radiation can increase the risk of myelofibrosis.

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Presentation

People with MF might not feel anything at all, disease could be diagnosed due to blood count abnormalities or enlarged spleen. They can also feel some or all of these symptoms mentioned.

- Pain in the upper left side of belly from enlarged spleen
- Feeling tired or weak which could be from low red blood cells (condition called anemia)
- Increased risk of infections due to low white blood cells
- Increased risk of bleeding or bruising due to low platelet cells
- Night sweats, fevers and weight loss due to inflammation caused by MF
- Early satiety or feeling full after eating small portions due to enlarged spleen

People with myelofibrosis might not feel anything at all. Disease could be diagnosed due to abnormal blood counts or enlarged spleen. They can also feel some or all of these symptoms mentioned below. Pain in the upper left side of the belly, or the left side of the ribs from an enlarged spleen. Feeling tired or weak, which could be from low blood cells, a condition which is called anemia. Increased risk of infections due to low white blood cells. Increased risk of bleeding or bruising due to low platelet cells. Platelets are the clotting blood cells. They could be increased night sweats, fevers, and weight loss due to extreme inflammation caused by myelofibrosis. There could be early satiety, which means feeling full after eating just small portions due to an enlarged spleen pressing on your stomach.

Diagnosis

- MF is diagnosed based on set of criteria which include presentation, blood tests, physical exam, imaging and test called Bone marrow biopsy
- Blood tests include complete blood counts, LDH and testing for mutations(alterations) in genes especially JAK2, CALR and MPL.
- These 3 gene mutations are usually mutually exclusive, that is if one of these genes is mutated, the other 2 genes will not be mutated. These are often also called driver mutations meaning that these drive the disease process. About 5-10% of MF is caused by mutations in genes other than these 3 genes.

How do we diagnose myelofibrosis? Myelofibrosis is diagnosed based on set of criteria which include presentation of clinical symptoms, blood test, physical exam, different imaging tests, and a test called bone marrow biopsy. Blood tests include complete blood counts, chemistry test, blood tests called lactate dehydrogenase which is LDH, and testing for mutations which are the alterations in DNA in genes specially named JAK2, CALR and MPL, which is called mipple. These three gene mutations are usually mutually exclusive. That means if one of these genes is mutated, the other two genes will not be mutated. These are often called driver mutations, meaning they're driving the disease. But about 5 to 10% percent of myelofibrosis is caused by mutations in genes other than these three genes, which we call triple-negative myelofibrosis.

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Janus Kinase (JAK)



- Janus is the Roman god of all beginnings, gates, transitions, time, choices, duality, doorways, passages, and endings.
- Janus Kinase is the gene which is most commonly mutated in MF.
- A slight change in the gene called JAK2V617F mutation is responsible for about 60% of MF cases.

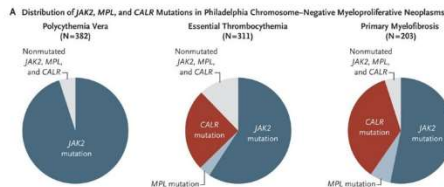
What is JAK? JAK gene is Janus Kinase gene. So, Janus is a Roman god of dualities, of beginnings, gates, transitions, choices, doorways, passages, and endings. It, this god has two faces. Janus kinase, which is the gene responsible for the production of the protein Janus kinase is the most commonly mutated gene in myelofibrosis. It has two faces like Janus, and a slight change in this gene called a point mutation, which is in the JAK2V617F location is responsible for about 60% of myelofibrosis cases.

CALRETICULIN

Somatic *CALR* Mutations in Myeloproliferative Neoplasms with Nonmutated *JAK2*
Nangalia et al. NEJM Dec 2013

Somatic Mutations of Calreticulin in Myeloproliferative Neoplasms
Klampff et al. NEJM Dec 2013

- Most patients with ET or MF, not associated with a *JAK2* or *MPL* alteration, carried a somatic mutation in *CALR*



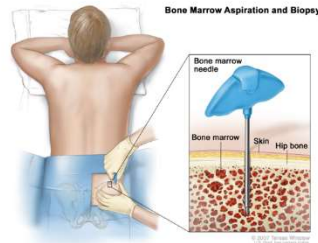
The second most commonly mutated gene is calreticulin, which we call CALR gene. This gene mutation was discovered in 2013 by different groups all over the world. Researchers found that most patients who didn't have JAK2 mutations with myelofibrosis has this CALR or calreticulin gene alteration or mutation which led to the formation of disease myelofibrosis.

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Bone marrow biopsy

Procedure done to take fluid and tissue from the hip bone. Usually, skin and bone is numbed by local anesthesia like Lidocaine and needle is inserted to take bone marrow fluid and tissue. Sometimes, the procedure can also be done under X ray or CT scan guidance under light sedation (light sleep). This test gives important information about the disease which helps in the diagnosis, prognosis and treatment strategies.



What is bone marrow biopsy? As I mentioned before, bone marrow biopsy is an important test needed to diagnose myelofibrosis. This is a procedure which is done to take fluid and small amount of tissue from your hip bone. Usually, skin and bone is numbed by local anesthesia like lidocaine, and a strong needle is inserted inside the bone marrow to take bone marrow fluid and tissue. Sometimes, this can also be done under X-ray guidance or CAT scan guidance, under light sedation with light sleep. This test gives us important information about the disease which helps us in the diagnosis of the disease, how do we prognosticate on better stage of the disease, and how do we treat the disease? This graphic shows a picture of how we usually do bone marrow. The person is either lying on their stomach or on their side and the skin, and the tissue above this hip bone is numbed with the local anesthesia and then the needle is inserted in the bone marrow to get very small amount of tissue and fluid for very important tests related to this bone marrow disease.

Additional testing

- Imaging tests like ultrasound, CT scan and MRI abdomen to evaluate spleen size and other organs like liver
- Cytogenetic analysis to look for abnormal changes in the chromosomes of the cancer cells. Normal human cells contain 23 pairs of chromosomes, for a total of 46 chromosomes. In some cases of MF, the chromosomes of the cancer cells have abnormal changes that can be seen under a microscope, such as extra or missing chromosomes, or broken or rearranged chromosomes.
- DNA sequencing to examine the exact sequence (order) of DNA. By comparing the sequence of DNA in cancer cells with the DNA in normal cells, genetic changes that are unique to the cancer cells can be found,

What other additional testing do we do in patients with myelofibrosis? Sometimes we do imaging tests like ultrasound of your abdomen, CAT scan, and MRI to evaluate spleen size and evaluate other organs like liver. There are very specialized tests sent either from blood or bone marrow to better evaluate this disease. One of these tests is called cytogenetic analysis. This looks for abnormal changes in the chromosome of the cancer cells. Normal human cells contain 23 pairs of chromosomes for a total of 46 chromosomes. In some cases of myelofibrosis, the chromosomes of the cancer cells have abnormal changes. Such as, there could be an extra chromosome, or there could be missing chromosome, it could be a broken chromosome, or a rearranged chromosome. And by this cytogenetic analysis, we are able to figure out what is different in the chromosomes of the cancer cell versus the chromosomes of the normal cells. Further sophisticated testing like DNA sequencing has been very helpful in management of myelofibrosis. This DNA sequencing is used to examine the exact sequence or the

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order of the DNA, again in the cancer cells compared to normal cells. By comparing the sequence of DNA in cancer cells with the DNA in normal cells, we are able to figure out the genetic changes that are unique to the cancer cells.

Myelofibrosis Symptom Assessment

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

Tired or weakly when you are (Early rising)	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Abdominal pain	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Abdominal discomfort	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Insatiable	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Problems with breathing	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Problems with concentration (Complete inability to read)	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Extreme "Vertigo" / Light-headedness	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Numbness/ Tingling in the hands and feet	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Difficulty sleeping	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Depression or not usual	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Problems with sexual desire or function	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Cough	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Night sweats	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Feeling agitated	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Does pain (different from joint pain or arthritis)	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Fever (≥100°F)	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
Unintentional weight loss last 6 months	(None) 0 1 2 3 4 5 6 7 8 9 10 (Worse imaginable)
What is your overall quality of life?	(As good as it can be) 0 1 2 3 4 5 6 7 8 9 10 (As bad as it can be)

© Myelofibrosis

One of the other assessments we do is something called Myelofibrosis Symptom Assessment. So, myelofibrosis is not just about the blood cells or the spleen size. It is more than that. The disease causes so much inflammation in our bodies that it can lead to multiple other symptoms. So, this is a score we often use in our clinical practice or in our clinical trials to figure out how the patient is feeling and how the patient is doing on treatment. So, we evaluate patients prior to starting treatment, in the middle of treatment, after treatment, to see how they're actually feeling and how their quality of life is. The different things which are interrogated in this survey is fatigue, early satiety, abdominal discomfort, problems with concentration, bone pains, weight loss, and again, how's the overall quality of life. The different scoring system used across the world, but it helps us better understand how's the patient with myelofibrosis is doing in their real life.

Prognosis

There are different scoring systems like DIPSS, DIPSS plus, MIPSS which doctors use to predict MF disease severity and prognosis.

These scoring systems take your age, blood work, bone marrow findings among other things into account.

People can be in different risk categories like low, intermediate and high risk based on these findings.

Approximate life expectancy can vary from 15.4 years for low risk individuals to 1.3 years for high risk.

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So, how do we tell the prognosis of this disease? How do we tell someone that you have myelofibrosis and based on the knowledge we have from the research studies over many years, what do we expect in the life with myelofibrosis? There are different scoring systems used, something called DIPSS, which is the Dynamic International Prognostic Scoring System, or DIPSS plus. There's newer systems like MIPSS, which also integrates the DNA sequencing molecular data, and these scoring systems helps doctors predict myeloid fibrosis disease severity and prognosis. These scoring systems take into account age, blood work, bone marrow findings, among other things into account. People can be in different risk categories like low risk, intermediate one, intermediate two, or intermediate risk, and high risk based on these findings. An approximate life expectancy can vary from 15.4 years for low-risk patient compared to 1.3 years for a high-risk individual living with myelofibrosis.

Complications

- Acute Myeloid Leukemia: about 15 to 20% of people with MF can transition to acute leukemia
- Portal Hypertension: Increased blood flow from an enlarged spleen can lead to high blood pressure in the portal vein (portal hypertension). This in turn can force excess blood into smaller veins in your stomach and esophagus, potentially causing these veins to rupture and bleed.
- Extramedullary hematopoiesis: Formation of blood cells outside the bone marrow can cause lumps or enlargement in organs like spleen and liver
- Increase risk of severe infections and bleeding due to decreased white blood cells and platelets

So, what are the different complications of myelofibrosis? About 15 to 20% of people with myelofibrosis can transition to a more aggressive form of cancer called acute myeloid leukemia. Another complication is something called portal hypertension. There is increased blood flow from enlarged spleen, which can lead to high blood pressure in the portal vein, which is the vein around the liver. This can in turn force excess blood into smaller veins in stomach and esophagus, which are near the liver, and they can potentially cause these veins to rupture and bleed. As we mentioned, that once our bone marrow becomes stiff and scarred, instead of the spongy normal tissue, there could be blood formation happening outside the bone marrow. This is called extramedullary hematopoiesis, which is in fact the formation of blood cells outside it's normal bone marrow, and this can cause lumps or tumors, or large ventral organs like spleen, and other organs like liver. There's always increased risk of severe infections, increased risk of bleeding due to decreased white blood cells and platelets.

Treatment for low-risk disease

- Many patients with low risk disease can be monitored without treatment
- Sometimes supportive treatment like red blood cells or erythropoietin stimulating agents are used to increase red blood cells in anemia
- JAK inhibitors can be used in patients feeling symptoms related to splenomegaly and constitutional symptoms from Myelofibrosis
- Clinical trial participation when available

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How do we treat myelofibrosis? The treatment of this disease is not a one-shot approach for everyone. Treatment depends on what the patient is feeling, how their blood counts is, what is their risk tolerance, what are the other complications in their medical life, and also depends on the risk of the disease. For most of the patients with low-risk disease, we often try a more conservative approach. Many patients can be monitored without any treatment at all. If there is no symptoms, if there's no urgency to treat this disease, we can monitor them for many years without any treatment. Sometimes we use supportive treatment like red blood cell transfusion or erythropoietin stimulating agents to increase red blood cells in anemia. Sometimes we use JAK inhibitors, which if the patients are feeling symptoms related to enlarged spleen and constitutional symptoms from myelofibrosis, these JAK inhibitor drugs can be used, and we always encourage clinical trial participation whenever available.

Treatment for intermediate-risk disease

- Many individuals with intermediate risk disease are candidates for JAK inhibitor therapy. There are currently 4 FDA approved JAK inhibitors: Ruxolitinib, Fedratinib, Pacritinib and Momelotinib. There are additional JAK inhibitors in clinical trials.
- Individuals are also considered for Allogenic stem cell transplant which is the only curative option at this time.
- Clinical trial participation is always encouraged whenever possible

How do we treat intermediate-risk disease? Many individuals with intermediate-risk disease are candidate for these JAK inhibitor therapy. There are currently four FDA JAK inhibitors, ruxolitinib, fedratinib, pacritinib and momelitinib. There are additional JAK inhibitors currently in clinical trials. Individuals are also considered for allogenic stem cell transplant, which is the only curative option at this time. And again, we strongly encourage clinical trial participation whenever feasible and whenever possible for our patients.

Treatment for high-risk disease

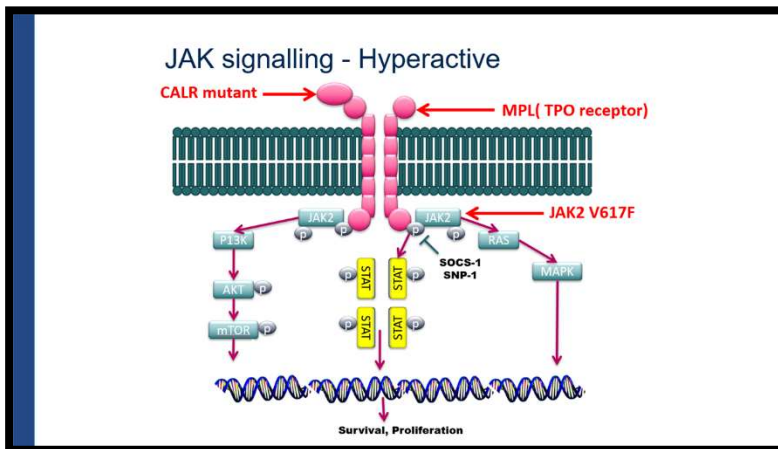
- Bone marrow transplant is the preferred treatment but it is a high risk procedure and not considered safe for older people or people with other high risk health conditions
- Jak inhibitor therapy is also used in many patients with high risk disease.
- Clinical trials when possible
- Intravenous or oral chemotherapy drugs similar to the ones used in acute leukemia or other condition called myelodysplastic syndromes

How do we treat high-risk disease? As we mentioned, the prognosis for high-risk disease is quite bleak and the survival is usually a few months to few years. If the patient can be a candidate for the procedure called bone marrow transplant, we encourage bone marrow transplant. It is a high-risk procedure with complications and it's not considered safe for very old people or people with other high-risk conditions,

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like severe kidney disease or severe heart disease. Many times, patients with high-risk disease are on JAK inhibitor therapy. And again we, we like to encourage clinical trial participation because that is the only way we can know what new treatments work, and what new treatments help our patients. Sometimes we have to use intravenous or oral chemotherapy drugs similar to the drugs we use in acute leukemia or other condition, myelodysplastic syndrome, for patients with myelofibrosis. So, we talked about JAK inhibitors, and we talked about the JAK gene, the Janus kinase gene, which is important in the formation of myelofibrosis.



But how do these JAK inhibitors work? So, this is something what we call is central to the development of myelofibrosis in our body, something called JAK signaling, which is hyperactive in myelofibrosis. This is a cell, and this is the cell membrane, and this is the JAK2 gene, which has two sides. So, in the disease called myelofibrosis, this signaling pathway is increased and hyperactive, which signals to our DNA that increase the production, increase the survival, increase the proliferation. And the commonest gene mutation, the JAK2 V617F changes this change, makes an alteration in this gene that even without any stimulus it becomes overactive and continues to tell the cell and the DNA increase the proliferation. Similarly, the second common gene mutation is the calreticulin or CALR mutation. This, again, this mutated CALR tells this JAK-STAT pathway to increase the proliferation of the cell. And the third mutation is something called MPL, which is this receptor called thrombopoietin receptor, which again, in its altered mutated form, tells the cell and the chromosomes increase the proliferation. So, this is not normal proliferation, this is hyperactive increased proliferation and increased inflammation. So, JAK inhibitors, inhibit this hyperactivity. So, they're active not only in JAK2 V617F of mutated patients, they're also active in CALR mutated patients. They're also active in MPL mutated patients because they're not actually affecting the gene, they're affecting this increased hyperactive pathway and helps patients with myelofibrosis, irrespective of JAK mutation, are helped with JAK inhibitors if they have enlarged spleen or if they have constitutional symptoms like fever, night sweats, psoriasis, weight loss from myelofibrosis.

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Jak inhibitors

- JAK-STAT signaling pathway is instrumental in causing this disease
- Inhibiting JAK leads to decrease in spleen size and the inflammation related symptoms
- JAK is needed for normal blood cell production, thus inhibiting JAK can also lead to decrease blood cells
- JAK inhibitors do not cure Myelofibrosis, they help in managing disease symptoms and spleen size
- 4 JAK inhibitors are currently approved by FDA

So, JAK-STAT inhibitors. JAK-STAT signaling pathway is instrumental in causing this disease. Hence, JAK inhibitors are active in this disease. Increasing the activity of this JAK-STAT pathway leads to decrease in spleen size and decrease in inflammation related symptoms, or the constitutional symptoms we talked about. JAK is needed for normal blood cell production. Thus, inhibiting JAK can also lead to decrease in blood cells which is one of the major side effects of these drugs. JAK inhibitors do not cure myelofibrosis unfortunately, they just help in managing disease symptoms and spleen size. And as we mentioned, four JAK inhibitors are currently approved by FDA in the United States.

Jak inhibitor: Ruxolitinib

- Brand name : Jakafi®
- First JAK inhibitor approved for use
- Decreased spleen size and symptoms
- Can cause decrease in blood counts
- Available in different dosages from 5 mg twice daily to 25 mg twice daily
- Dose is dependent on baseline blood counts
- Individuals can gain weight on this drug

The first JAK inhibitor which was approved and studied is named ruxolitinib. It's brand name is Jakafi® US, and it decreases spleen size and it decreases symptoms like fatigue, fevers, night sweats and weight loss. But it can cause decrease in blood counts as it also affects the normal blood cell production. This is available in different dosages from 5 mg twice daily to 25 mg twice daily. The dose is dependent on patients baseline blood counts and sometimes physicians' comfort for different doses, as higher doses can cause sometimes severe decrease in blood counts. The other side effect which sometimes has been noticed, is that individuals can gain weight on this drug, which is good for patients suffering with myelofibrosis weight loss, but sometimes the weight gain can be more than what is needed. This affects a leptin related metabolism pathway and thus, affect the weight gain.

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COMFORT Trial

- Ruxolitinib: JAK-1 and 2 inhibitor used in randomized trial in symptomatic MF patients
- At 24 weeks, 42% patients had decrease in spleen size compared to 0.7% in placebo
- 46 % had symptom reduction
- Responses irrespective of JAK mutation status
- Main adverse event: Decreased cell counts
- Led to the FDA approval in Nov 2011 in symptomatic patients with intermediate to high risk MF

Verstovsek et al. NEJM 2012

The comfort trial is one of the pivotal trials which was studied in myelofibrosis patient with this drug, ruxolitinib and what was found that 42% of these patients at approximately six months had decreased in spleen size compared to 0.7% in placebo, which is basically just a sugar pill, and 46% had symptom reduction. And as we mentioned before, these drugs work irrespective of JAK mutation status because they inhibit the JAK-STAT pathway and not the gene causing the mutation. Main adverse event or the main side effect is decrease in blood cells, and this trial led to the approval of this drug in November 2011 in symptomatic patients with myelofibrosis.

Jak Inhibitor: Fedratinib

- Brand name: Inrebic®
- Approved for adult patients with intermediate-2 or high-risk myelofibrosis (MF) who have platelet counts $\geq 50K/\mu L$.
- Black Box warning for a very small risk for Wernicke's encephalopathy. Patients are checked for Vitamin B1 deficiency and treated with Vitamin B1 to avoid this rare complication
- Nausea, vomiting and diarrhea can happen which can be easily treated
- Dose is 400 mg once daily

The second drug which was approved for myelofibrosis is fedratinib and its brand name in US is in Inrebic®. It is approved for myelofibrosis patients who have platelet counts over 50,000. There's a black box warning attached to this drug because there's a very small risk for something called Wernicke encephalopathy. Patients have to be checked for vitamin B1 deficiency and treated with vitamin B1 to avoid this rare complication. Some other side effects are nausea, vomiting, diarrhea, which can happen with this drug, but can also be easily treated and generally the starting dose is 400 mg once daily.

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Jak inhibitor: Pacritinib

- Brand name: Vonjo®
- Approved for intermediate or high-risk primary or secondary myelofibrosis and who have platelet (blood clotting cells) levels below 50K/ μ L.
- Common side effects include diarrhea, low blood counts, nausea, bleeding and peripheral edema.
- Dose is 200 mg twice daily

The third JAK inhibitor to be approved is pacritinib or brand name Vonjo® in US. This is approved for intermediate high-risk myelofibrosis, for patients who have platelet counts below 50,000. So the other drugs, the Jakafi or the fedratinib, they are very difficult to use in patients platelet counts below 50,000. But this drug was found to be safe and effective in these patients with such low platelet counts. The normal platelet count is over 150 for most of people. Common side effects include diarrhea, low blood counts, nausea, bleeding and peripheral edema. The usual starting dose is 200 mg twice daily.

Jak inhibitor: Momelotinib

- Brand name: OJJAARA
- Approved for treatment of intermediate or high-risk myelofibrosis with anemia (low red blood count or hemoglobin).
- Increased risk of infections, low blood counts, liver toxicity, nausea, diarrhea
- Dose is 200 mg orally once daily

And the fourth FDA approved JAK inhibitor is called momelitinib, of the brand name Ojjaara. This is approved for treatment of intimidated high-risk myelofibrosis with patients with anemia, which is low red blood cell count or low hemoglobin. Again, there's increased risk of infections, low blood counts, some liver toxicity, nausea and diarrhea. But overall, well tolerated drug and usual starting dose is 200 mg orally once daily.

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Toxicity of Jak inhibitors

- Decreased blood counts as Jak signaling is essential for hematopoiesis(normal blood cell production)
- Infections like zoster, TB reactivation
- Small increased risk of other malignancies
- Major risk of cytokine storm, rebound splenomegaly with abrupt cessation of Jak inhibitor in myelofibrosis. Recommendation is to either switch to alternate Jak inhibitor or taper slowly with steroids and close monitoring

These drugs called JAK inhibitors, they do have certain toxicities that we need to be aware of. As we mentioned, JAK-STAT pathways important for normal blood cell production. Hence, inhibiting this pathway can also lead to decrease of normal blood counts, and thus, we have to worry about decrease in blood counts when we are on these drugs. This increased risk of infections, including increased risk of reactivation of something called zoster, which is shingles, or TB, or hepatitis B. There's very small increased risk of other malignancies like non-melanoma skin cancers, and very, very rare risk of increased lymphomas. The other thing which we need to know is that we cannot abruptly stop these JAK inhibitors. If a patient with myelofibrosis in a JAK inhibitor, there's a major risk of cytokine storm, what we call, is this rebound increase of spleen with abrupt interruption of these JAK inhibitor. What happens is if we suddenly stop JAK inhibitor, these inflammatory enzymes, proteins, they suddenly increase in our body and the spleen size can suddenly increase. So, the recommendation is to always start or stop this JAK inhibitor therapy in conjunction with your physician and either try to switch to alternate JAK inhibitor, or try to taper these doses slowly, or sometimes with the help of steroids, and close monitoring is always needed when someone is stopping JAK inhibitor in myelofibrosis.

Clinical trials

- Clinical trial participation is always encouraged
- Many clinical trials are very promising
- Different inhibitors other than JAK inhibitors are in development for use by themselves or in conjunction with JAK inhibitors
- Antibodies/ vaccines against JAK and CALR are also being developed
- Find the clinical trials available to you in myelofibrosis, please use the website: clinicaltrials.gov.
<https://clinicaltrials.gov/search?cond=Myelofibrosis>

Clinical trials are always encouraged. We have made so much promising results in this field of myelofibrosis with clinical trials and research. None of these drugs which are available today would have been possible without the participation of thousands of patients with myelofibrosis in these drug trials. There are different inhibitors other than JAK inhibitors which are in development either by themselves or in conjunction with JAK inhibitors. There're exciting antibodies or vaccine trials which are soon going to be available against JAK protein or CALR protein. And I would encourage everyone to look up a clinical trial in myelofibrosis by using the website clinicaltrials.gov and searching for the

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geographical area for the disease or for what stage you are to see if you will be eligible for a clinical trial.

Bone marrow transplant

- Allogeneic stem cell transplantation is the only curative treatment for this disease. This involves the use of stem cells from someone other than the patient. The donated stem cells can come from either a person related or not related to the patient.
- Before beginning an allogenic SCT, the patient receives a conditioning treatment that consists of either chemotherapy or radiation or both.
- Infections, stem cell rejection and graft versus host disease are some of the complications of the transplant
- Candidates for this procedure are carefully chosen by a team of doctors as the procedure can be very risky

Bone marrow transplant is the only curative treatment for this disease and this is an allogenic bone marrow transplant. Allo means from someone else. This involves the use of stem cells from someone other than the patient. The donated stem cells come, can come from either a person related to the patient or not related to the patient. Before beginning an allogenic stem cell transplant, the patient receives a conditioning treatment that consists of either chemotherapy or radiation, or both, and then the stem cells are given. This is a risky procedure. There is a high risk of infections, stem cell rejection, and something called graft-versus-host disease which can be very complicated. Candidates for this procedure is very— are very carefully chosen by a team of doctors, including oncologists and bone marrow transplant specialists, as this procedure can be risky. But as I said, this is the only curative treatment, so we try our best if the patient is eligible for bone marrow transplant that we try our best to get that for them.

Supportive Care

- Diet: Healthy diet rich in fruits, vegetables, whole grains, fish, oils, and nuts is recommended.
- Physical activity: discussion with doctor and as well tolerated
- Rest: Adequate rest and sleep to manage fatigue
- Decrease infection risk: Hand washing, staying current on vaccines, avoid sick contacts, wearing face masks in certain situations
- Mental Health and Emotional Support

What supportive care can be helpful in myelofibrosis? We encourage patients to eat a healthy diet rich in fruits, vegetables, whole grains, fish, oils and nuts. Physical activity should be discussed with your doctor. Patients suffering with anemia and fatigue could have difficulty doing physical activity or vigorous exercise regimen. It should be done as well tolerated and as discussed with your physician. We do recommend adequate rest and sleep to manage fatigue and for better overall health. For decreasing infection risk, we recommend frequent hand washing, staying current on vaccines, avoiding sick context of very large crowds depending on the white blood cell count, and wearing face masks in certain situations. I cannot stress enough, the importance of mental health and emotional support. This

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could be in the form of your friend, this could be in the form of your family, or your therapist, or the whole support of your doctor's office, for various support groups, or any, or someone else suffering from the same disease. Please, please, take care of your mental health and get as much emotional support as possible if you're living with this disease.

Resources

- <https://www.LLS.org/MPN>
- <https://www.mpnresearchfoundation.org/patient-caregiver-resources>
- Patient support groups: local, internet and social media
- Resources at cancer centers

The different resources available. The Leukemia & Lymphoma Society has different resources available on their website. There are patient caregiver resources, MPN Research Foundations, there are support groups available locally, available on Internet through various social media websites, and there are many resources available at cancer centers. Please ask your physician, your treating team, about the different resources available to you if you're living with this disease.



And I want to thank you for your attention and I would welcome any questions or answers.

Questions & Answers

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Elissa Baldwin: Thank you, Doctor Goel, for your very informative presentation. It is now time for the question-and-answer portion of our program. These are the most commonly asked questions that have come into our LLS Information Specialists and online Community.

We'll get started. So, our first question.

Should I find an oncologist who specializes in myelofibrosis, and how would I find a specialist?

Dr. Swati Goel: Yes, that's a great question. So, the answer would be since it's a rare disease and it's not something that every oncologist is comfortable treating, if you are able to, please find a specialist who specializes in myelofibrosis. But having said that, I can appreciate that not everybody has the resources and not everybody can travel to a myelofibrosis specialist. So, even if you're not able to be treated by a myelofibrosis specialist, you should not worry. I would encourage you to read about the different resources available to you as mentioned on LLS and other websites, so that you're up to date yourself and you can ask the right questions. We as doctors are always learning. We learn from our patients mostly. We learn what patients tell us what are the side effects of the drugs.

So, even if your doctor is not specializing in myelofibrosis, please encourage them by asking questions, by being a part of the team for your own caregiving. So, please, definitely seek out information from the different resources available to you and try to get the best treatment available.

Elissa Baldwin: So as a follow-up to that. **So, if a patient lives, say, several hours from a specialist or a major cancer center, would they be able to work with their own oncologist and then also be working with a specialist as well to have coordinated care?**

Dr. Swati Goel: Yes. That is an excellent solution for people who live miles away from a comprehensive cancer center that they can go to a myelofibrosis specialist for or a second opinion, and their own oncologist can work in conjunction with the myelofibrosis specialist. So, an individual living with myelofibrosis can see the myelofibrosis specialist once a year or even twice a year, and their own oncologist who lives close to them can work in conjunction. We often treat patients this way because some of our patients again lives hours and hours away, and it's not feasible for them to come see us every month or every other month. So, we try to work closely with their local oncologists. And I would say, that has been one of the very rewarding situations in our medical career because that makes us a part of the team, with the other doctor included as well. And also, with video appointments, you can also seek the care of myelofibrosis specialist, as I said, once or twice a year, even with video appointments that you don't need to travel, you know, hours and waste time and resources. So definitely, there are many options available, even if you don't live close to a myelofibrosis specialist in a comprehensive cancer center.

Elissa Baldwin: Great. That's great advice, particularly about the video appointments.

Now, our next question.

My doctor is recommending a transplant, but says, I need a caregiver. I live alone and it would be challenging to find one. Would I still be able to have a transplant?

Dr. Swati Goel: Yes. Bone marrow transplant, I would not lie, is a tough and risky procedure. But if you don't have a caregiver, that doesn't mean that you won't be able to have a transplant. With the philanthropy and with donations, we have several resources, several organizations which help people in this exact situation, with the living situation, with the caregiver situation. So, I would encourage you to seek help from your cancer center social worker. Again, going online with different resources, as we mentioned, and try to seek help from these organizations who work for this exact reason, to help people

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go through their cancer treatment, and help people go through transplant if they don't have caregivers who can support them every minute of this journey.

Elissa Baldwin: Okay. Now, earlier in the presentation, you mentioned good foods that would be recommended to the patient. **Now, in addition to a healthy diet, are there supplements that would be helpful?**

Dr. Swati Goel: Generally speaking, our food, our natural foods have all the supplements we need. So, there's no special supplements that I would recommend. If you're able to eat kinds of food, again, fresh fruits and vegetables, nuts, you know, different, different fish if available, or if you're able to, you don't need extra supplements. So, food can be helpful in decreasing inflammation. I would not say that food would be the reason that, you know, your cancer gets cured or your cancer gets into remission as such. But it does help in reducing inflammation to some extent and also helps you feel better, good food helps you feel better. But the supplements have never been proven to help in this disease, and I would just recommend eating a good, nutritious diet.

Elissa Baldwin: Okay, now our next question.

If I'm having side effects from treatment, would my doctor be able to help ease them?

Yes, that is an excellent question. These medications can often cause side effects like nausea, vomiting, and diarrhea. We have excellent drugs available to help with these side effects. We have drugs that help with vomiting, with nausea, with diarrhea. So, please seek help and ask your doctor, and tell your doctor that you're having these side effects, and they should be able to help you with most of these side effects.

Elissa Baldwin: Great. Now our next question.

You mentioned this a little bit earlier, but what are the chances of my myelofibrosis turning into another cancer, such as leukemia?

Dr. Swati Goel: About 15% to 20% of the patients with myelofibrosis can transition to a more aggressive cancer called acute myeloid leukemia. So, some of the things that we worry about is suddenly if the blood cells become even less in number, or suddenly the white blood cells become very much in number, or the patient is feeling severe bone pains, or severe infections which were not there. So, change in clinical symptoms, clinical signs, or blood work, abrupt changes can sometimes be signs and symptoms of this disease changing into acute myeloid leukemia.

Elissa Baldwin: Now, our next question.

I'm worried about the financial aspect of cancer. Is there someone in the hospital system, like a social worker, who would be able to assist me?

Dr. Swati Goel: Yes, we have multiple resources in form of social workers, forms of pharmacy liaisons that help people whose insurance is not able to cover this drug or whose copay is amount of thousands of dollars per month that help us navigate this. Also, these companies which produce these various drugs have something called Patient Care Assistance Programs, which help patients cover their copays or give the drug free of charge if the patient doesn't have insurance. So, we do have different resources to help people overcome financial toxicity. I'm not saying that we are always able to make the drugs available free of cost, but please seek out help. Please tell your doctor and their team that you're having this financial toxicity from this treatment, and we try our best to help you.

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Elissa Baldwin: That's very good advice to make sure that you're talking to your treatment team if you are having financial difficulties. And, for our viewers, we will have information at the end with our financial resources that LLS provides.

And now our final question of the program. **How do I know if my myelofibrosis is progressing? Are there certain signs or symptoms I should be looking out for?**

Dr. Swati Goel: There are certain things like feeling more pain in the belly, which could indicate that your spleen is enlarging, having bone pains and this is not joint pains from arthritis. This is something different. You feel that your bones are hurting from inside. There could be fevers from no infection—from no obvious reason, just fevers, having night sweat that you have to change your clothes at night. That your bed sheets are soaked, or your pillowcases are soaked. There could be changes in your blood counts. You are requiring more transfusions or you're requiring more support to maintain blood counts at the same level of drugs you were at. And then again, seeking, telling, these things to your doctor so that they can run appropriate tests would definitely help us decide whether your disease is changing to a more severe form of myelofibrosis or something more complicated, like acute myeloid leukemia.

Elissa Baldwin: Thank you so much, Doctor Goel, for sharing your expertise with us and for your continued dedication to cancer patients.

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LLS EDUCATION & SUPPORT RESOURCES

HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials.

-  **Call: (800) 955-4572**
Monday to Friday, 9 a.m. to 9 p.m. ET
-  **Chat live online: www.LLS.org/InformationSpecialists**
Monday to Friday, 10 a.m. to 7 p.m. ET
-  **Email: www.LLS.org/ContactUs**
All email messages are answered within one business day.



PERSONALIZED NUTRITION CONSULTATIONS

Ask to a registered dietitian about nutrition and diet.

NUTRITION CONSULTATIONS

Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.

www.llsnutrition.org



CLINICAL TRIAL SUPPORT CENTER

Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.

www.LLS.org/Navigation




If we were not able to answer any questions you may have had during this program, please contact an Information Specialist at The Leukemia & Lymphoma Society at 1 (800) 955-4572 from 09:00 a.m. to 09:00 p.m. Eastern Time, or reach us at LLS.org/ContactUs.


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Online Chats
Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit www.LLS.org/Chat




Education Videos
Community of blood cancer patients, survivors and caregivers supporting each other and giving trusted information and resources, please visit www.LLS.org/EducationVideos




Patient Podcast
The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit www.TheBloodline.org




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The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancer: www.LLS.org/Finances



To order free materials: www.LLS.org/Booklets



Please take a moment to view the resources that LLS has available to you, online chats, educational videos, podcasts, financial resources, booklets, and more.

THANK YOU

Please fill out Program Evaluation at
LLS.org/MF_eval







We have one goal: A world without cancers

We also encourage you to please complete the program evaluation which can be found at LLS.org/MF_eval or by scanning the QR code on your screen with your smartphone. Completing this evaluation will help us to continue to provide the engaging and informative programming that would benefit you the most.

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Doctor Goel, thank you again for volunteering your time with us today. And on behalf of The Leukemia & Lymphoma Society, thank you all for watching this program.

Take good care.