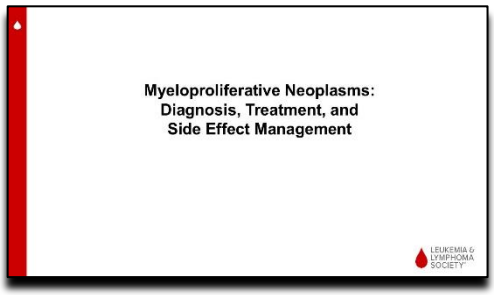
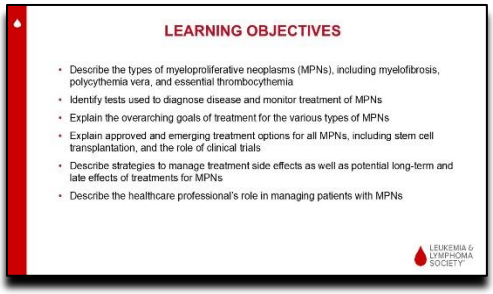


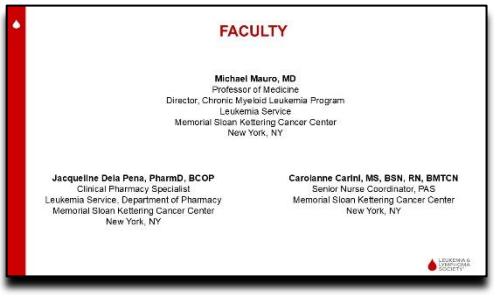
Slide 1: Myeloproliferative Neoplasms: Diagnosis, Treatment, and Side Effects Management

Lauren Berger, MPH: Hello everyone. On behalf of The Leukemia & Lymphoma Society thank you for sharing your time with us for this continuing education program on Myeloproliferative Neoplasms: Diagnosis, Treatment, and Side Effect Management.



Slide 2: Learning Objectives

The learning objectives for this program are listed on this slide.



Slide 3: Faculty

We're fortunate to have as our presenters, Dr. Michael Mauro, a leading expert in MPNs and his colleagues, Dr. Jacqueline Dela Pena a Clinical Pharmacy Specialist and Nurse Carolanne Carini, Senior Nurse Coordinator.

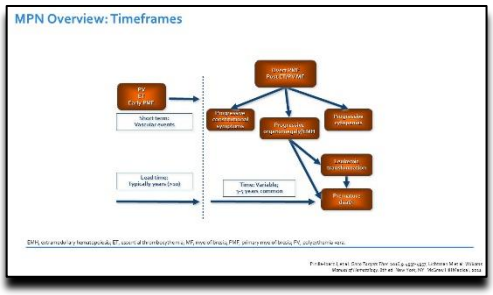
Dr. Mauro is Professor of Medicine, Director, Chronic Myeloid Leukemia Program, Leukemia Service, at Memorial Sloan Kettering Cancer Center in New York City.

Dr. Jacqueline Dela Pena, is a Clinical Pharmacy Specialist, Leukemia Service, Department of Pharmacy, at Memorial Sloan Kettering Cancer Center in New York City.

Nurse Carini is a Senior Nurse Coordinator, Patient Access Service, at Memorial Sloan Kettering Cancer Center, in New York City. We appreciate their dedication and their commitment to caring for patients living with blood cancer.

I am now pleased to turn the program over to Dr. Mauro.

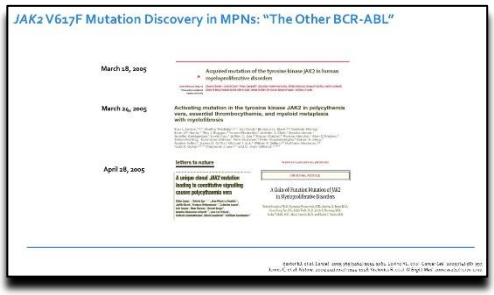
Michael Mauro, MD: Well, thank you, Lauren, and thank you to the LLS for having us present to you today on myeloproliferative neoplasms, a broad topic, but we'll go through diagnosis, treatment, and side effect management. And, again, I'm Michael Mauro from Memorial Sloan Kettering and our Leukemia Service. And I'm joined by Jackie Dela Pena, one of our Clinical Pharmacy Specialists on service; and we'll share the presentation. So, let's get started these are truly chronic diseases.



Slide 4: MPN Overview: Timeframes

So, myeloproliferative diseases can come generally later in life but can present differently. On the left, if you look at the more indolent myeloproliferative conditions – polycythemia vera and ET; we use the term early myelofibrosis – our concerns really in the short term are vascular events, perhaps symptom management, and then we obviously are thinking long term longitudinally. But we often have lead time, and these are truly chronic diseases. Overt primary myelofibrosis or PMF and myelofibrosis that evolves from thrombocytosis or polycythemia can be much more of a serious and shorter time frame condition, and it can lead to many different problems we need to tackle. Again, we're still managing symptoms, but we often are seeing systemic manifestations – organomegaly, extramedullary hematopoiesis, effects on the bone marrow clearly with cytopenias being a major issue, and we'll get into how therapies have really advanced to help allow us to treat while working around cytopenias.

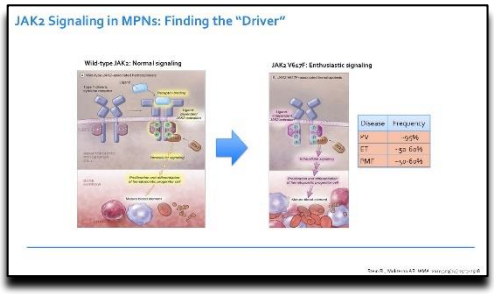
And, of course, our biggest concern is leukemic transformation; and you'll see that we've gotten a lot smarter about how to risk stratify and look into the molecular landscape and the basis of MPNs to understand that. Of course, we're trying to minimize early morbidity/mortality from myelofibrosis. So again, this is a shorter time frame, and we often have just a bit of time. So, this is clearly a spectrum of chronic and more acute disease and requires finesse to manage.



Slide 5: *JAK2* V617F Mutation Discovery in MPNs: "The Other BCR-ABL"

We really gained a lot of traction and a lot of ability to treat MPNs better with the discovery of the conical mutation, the *JAK2* V617F.

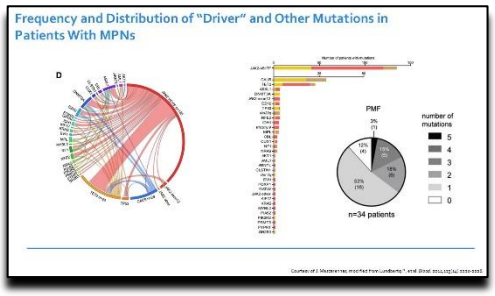
So, this really was groundbreaking, in many of these diseases we're talking about today, because it can be present in really all types. That we understood that a driver mutation, essentially a switch, if you will, that's turned on molecularly, can be the basis of this family of diseases, was quickly recognized as being targetable. Interestingly, it was described in one of our colleague's labs at MSK — Dr. Ross Levine, as is cited in the middle citation — as well as other groups around the world; and this, again, really gave us a leg up on the disease biology and disease pathogenesis and the potential for treatment.



Slide 6: JAK2 Signaling in MPNs: Finding the "Driver"

What I'm talking about here again with this switch connotation is that, on the left, the wild type JAK2 is a normal enzyme present in hematopoietic progenitors that are involved in hematopoiesis, so blood production. And it's often a central kinase, if you will, an enzyme that is a master switch. It normally requires a ligand or something to turn it on, a signal input to activate to regulate processes and so.

On the right, if you had a so-called enthusiastic signaling, you'd have ligand-independent signaling or the switch turns itself on or doesn't need an input or a stimulus. And that can clearly lead to an overactive state and quite an overactive one. And you see that the frequency of a JAK2 mutation extremely prevalent in PV and is half or more of patients with both ET and primary myelofibrosis. So, this is a key central driver.many more mutations.



Slide 7: Frequency and Distribution of "Driver" and Other Mutations in Patients with MPNs

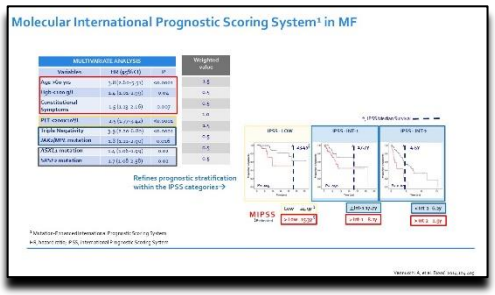
However, that's not the only thing that happens molecularly. This is a complicated slide, but these ribbon maps, as you see on the left; and then, of course, the plots on the right show you the frequency of additional mutations as seen, for example, in the right in primary myelofibrosis where we often can see not just one but, three, four, five, and sometimes

We, of course, are looking for the central driver mutation, such as this *JAK2* V617F, which is the top one on the right figure. And there are secondary driver mutations which are quite prevalent, including calreticulin or *CALR*, a mutation that acts much like *JAK2* called, in the thrombopoietin receptor called MPL515 or *MPL* mutation. And there are other mutations in the myeloid genetic spectrum that are known to be key actors or key players in myeloproliferative disease and are fairly prevalent and are contributing to risk. And the left, what a ribbon figure shows you is the co-occurrence of mutations and the commonality.

So, you see the big broad red band in the middle of that circle, that's telling us that *JAK2* is often seen with a mutation in another gene called ten-eleven translocation-2 or *TET2*. How that relates to disease biology isn't exactly clear, but I think we've really unraveled the story of clonal hematopoiesis and the aging of the bone marrow and how mutations can build on each other and lead to further genetic instability and disease pathogenesis.

Not all of these mutations are targetable, although some of them are, and such as the IDH family mutations, *IDH1* and *2*. So, we're working on this; but I think the understanding is improving, although it's not complete. The commonality of these mutations is clearly

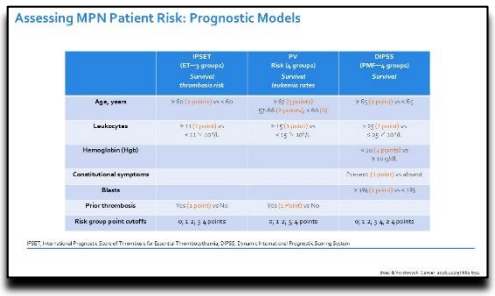
known. The prognostic significance is known, and that's what I'm going to talk about in a moment as well symptom.



Slide 8: Molecular International Prognostic Scoring System[1] in Myelofibrosis

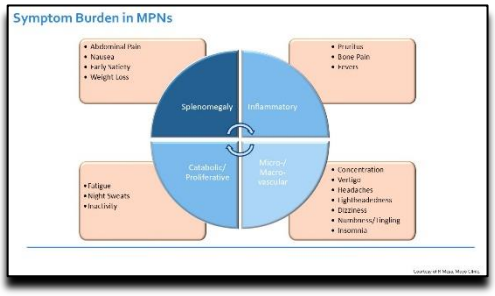
So, as we've looked at how to stratify the risk of these diseases, we know that certain factors have consistently affected the outcome; for example, myelofibrosis, the age of the patient, is anemia a problem or not, are they having strong constitutional symptoms? And these can be weighted differently. Thrombocytopenia is often a more impactful sign or But the mutations, as you can see in a molecular version of this growing system, also can be weighed; and patients without a driver mutation, interestingly — and that's a bit of a paradox — but to explain it, what it means is we don't understand exactly what's driving the biology of that MPN. That may mean the pathogenesis may be more complex and may not be as amenable to our standard therapies, so that way is actually even heavier on the presence of a *JAK2* mutation and the secondary mutations, with some particularly prominent ones such as *ASXL1* and epigenetic regulated mutation noted in this risk score.

So, to look down to this, if you look at a patient with myelofibrosis, you can predict where they are in their disease based on the things that are happening with them. But you also can have a bit of a crystal ball and look into the molecular studies, which are fairly easily obtained, and understand, for example, how quickly they might have further myelofibrosis manifestations, what is their risk of transformational leukemia, and also how long they might manage myelofibrosis without significant input, significant treatment response, or maybe even decision-making regarding allogeneic stem cell transplant. You can see the difference in this in using the prior International Prognostic Scoring System. The two are compared on the figure on the right of this slide here.



Slide 9: Assessing MPN Patient Risk: Prognostic Models

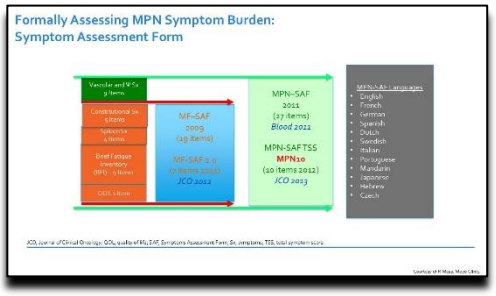
So, we have these fairly complicated risk models, but if you look across the disease spectrum — ET, PV, and primary myelofibrosis — there are some commonalities in risk models for each of the diseases, all three of the major MPNs. Age is a common factor. A rising white count is a common factor. Anemia a major factor in myelofibrosis, as are constitutional symptoms. In the more indolent MPNs — ET and PV thrombosis — the presence of a prior thrombosis is a major, and has a major impact on risk. And this is how we decide our therapies. So, I hope this clarifies things a bit and with regard to risk stratification.



Slide 10: Symptom Burden in MPNs

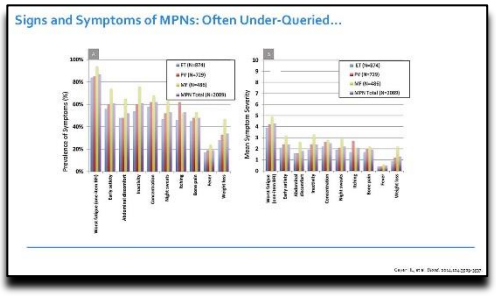
Let's talk about the patients and what they're dealing with a bit more; and these diseases across the board can cause a variety of different signs and symptoms. In the center we have sort of the, the broad categories of spleen enlargement and changes in the abdominal organs which can lead to abdominal pain, nausea, and weight loss. The catabolic or proliferative symptoms, as we might call them, things that are probably a little bit less often quantified and interrogated; things like fatigue, inactivity, change in lifestyle, or night sweats, which also might be probably categorized as very inflammatory symptoms, leading to itching, bone pain, fevers, and so on.

Microvascular symptoms, of course, are the actual pathologic changes in the vascular system; but the manifestations can be pretty broad and somewhat elusive to pin down when you talk to patients. But, they often complain of issues of concentration, headaches, dizziness, neurologic symptoms, sort of in a broad sense, numbness and tingling, insomnia, and sort of a general sense of unwellness which is needing better clarification.



Slide 11: Formally Assessing MPN Symptom Burden: Symptom Assessment Form

So, a symptom assessment burden tool that was developed quite nicely a number of years ago, and really was validated, and is a great tool to use in the clinic to look at these various categories of symptoms and inventory them, come up with a score — it gives you a dynamic sense of how someone's disease may be evolving, how they may be responding to treatment. They're available. They're recommended by the National Comprehensive Cancer Network guidelines; and they're, of course, available in multiple languages. So, I'd suggest using these as a way to follow patients, probably for no other reason than one of the primary endpoints of treatment is often symptom improvement.



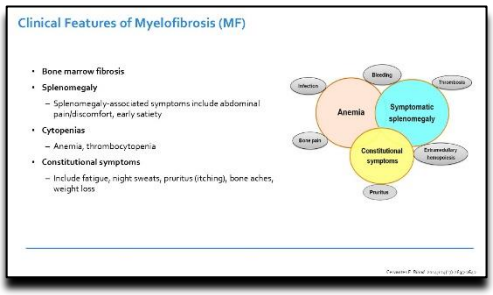
Slide 12: Signs and Symptoms of MPNs: Often Under-Queried…

So, what type of symptoms do patients face? And, again, we've talked about the categories. This just gives a sense for frequency and prevalence. But then, often under-queried, you can see that the prevalence of symptoms is not too different if you look at the different diseases. That's the way these figures are crafted. ET, PV, and MF. Some are a bit more prominent. The fatigue, abdominal discomfort, inactivity may be a bit more prevalent in myelofibrosis where it seems like itching and other symptoms may be more prevalent, for example, in PV. But they are fairly ubiquitous. Many of them in near half or

more than half of all of the disease types; and the severity can vary as you look at the different disease types.

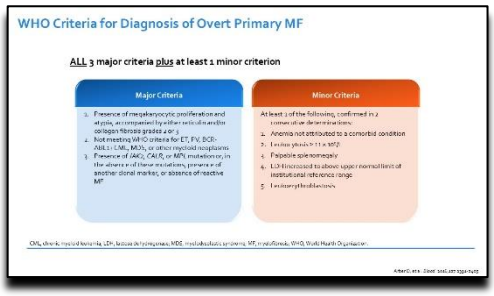
Slide 13: Myelofibrosis

So, if we drill down in each disease type.



Slide 14: Clinical Features of Myelofibrosis (MF)

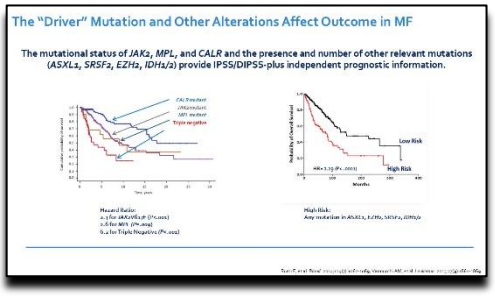
And we're getting to some discussion of treatment; again, we're saying this a few different ways, but the clinical features here: what are we trying to treat? We're trying to manage the imbalanced blood counts, the symptomatic splenomegaly, and the constitutional symptoms, all resulting from an overactive marrow, marrow fibrosis, inflammation, and effect on the vascular system. So, this is our challenge.



Slide 15: WHO Criteria for Diagnosis of Overt Primary MF

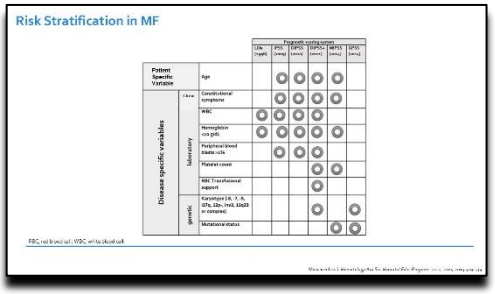
Of course, we want to be clear about characterizing the disease, so just a moment to look at the World Health Organization criteria for PMF. We want to, obviously, examine the marrow looking for classic megakaryocytic changes and significant fibrosis, either moderate or severe, Grade 2 or 3. We want to make sure we're not seeing overlap or question of another of the classic MPNs, be it Ph-positive or Ph-negative. And we want to look for one of these mutations which are, the conical mutation, *JAK2* or *CALR*, *MPL*. And really because they do make the diagnosis and, if they're absent — which is an entity I've described as actually being a higher risk form of myelofibrosis — to look for other clonal markers. So, sequencing the marrow in the blood for myelo mutations has become increasingly important. And, of course, ruling out reactive myelofibrosis from some other diagnosis.

So, you want all three of those major criteria, and then on the right, one of the minor criteria which it's really outputs, anemia, higher white counts, splenomegaly, increase in LDH, or the term leukoerythroblastosis, which is peripherization of the marrow where the immature forms are present in the peripheral blood.



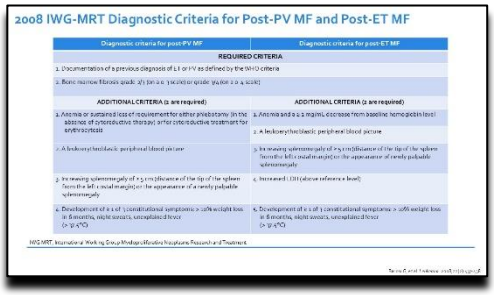
Slide 16: The "Driver" Mutation and Other Alterations Affect Outcome in MF

We talked about the difference in risk score based on mutations. So, this gives us an idea about the outcome; and we see differently disease biology, the difference depending on the mutation. What the figure on the left shows you is that a patient with myelofibrosis who is driven by a calreticulin mutation may have a very different long-term outlook than a patient who doesn't have any of the myeloid driver mutations and sort of on average would be the patients who have a *JAK2* or an *MPL* mutation with regards to long-term outlook. And if you sort of digest it down on the right to the secondary mutations, do you have any of the high-risk mutations, yes or no? And it puts you in high- or low-risk categories, has also a significant impact. So again, we're getting a lot smarter; and we really do have some degree of a crystal ball for patients with myelofibrosis and how they may behave over time.



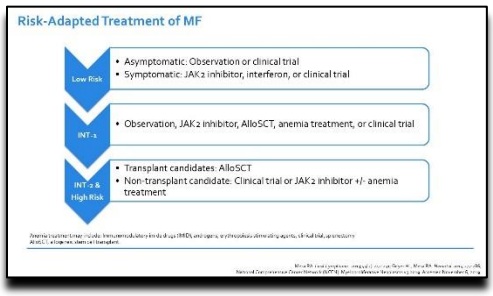
Slide 17: Risk Stratification in MF

The risk models have evolved, and this just shows you from left to right over two decades how we've incorporated, ironically in the beginning, as many things as we possibly could when we had the Dynamic International Prognostic Scoring System, plus or DIPSS-plus; and now we're really drilling down and, even in more current models such as the Molecular Prognostic Scoring System — the Molecular Scoring System, MIPSS70 as it's called for patients under 70 — the mutational profile really makes a difference.



Slide 18: 2008 IWG-MRT Diagnostic Criteria for Post-PV MF and Post-ET MF

Turning to the criteria for post-PV MF and Post-ET MF, not fairly complicated; but, of course, an antecedent diagnosis of thrombocytosis or PV and significant bone marrow fibrosis. And this is essentially an evolving story where you've either lost the phlebotomy requirement and developed anemia; or, in ET, you are now anemic and have clear evidence of myelofibrosis by leukoerythroblastic blood picture, where you're seeing immature forms in the peripheral blood and splenomegaly. These are the hallmarks of myelofibrosis. And we know a fraction of patients in each PV and ET evolved to myelofibrosis with time. We often have constitutional symptoms, and this warrants pivoting from treating these patients for PV and ET and now treating them for myelofibrosis.

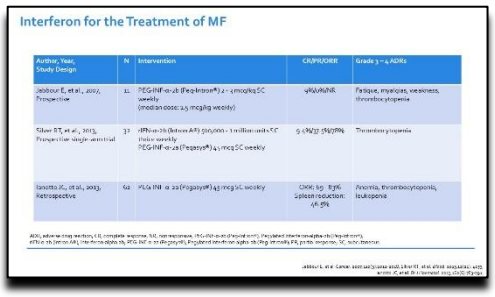


Slide 19: Risk-Adapted Treatment of MF

We take a risk-adapted approach. We've gone through, I think, pretty systematically how we look at risk. A low-risk patient may not have these symptoms, may not have a lot of output and manifestations. They may be able to be observed for a period of time. You clearly want to have done the homework and done the sequencing and queried the disease entirely.

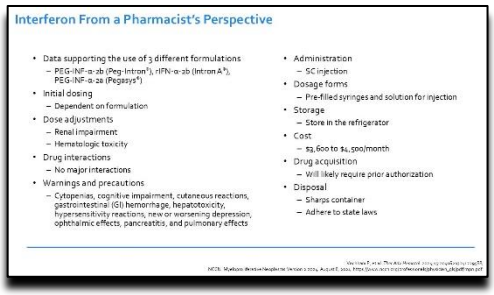
Many patients have either older age symptoms or enough manifestations of the disease to treat. We have a beautiful palette of therapies which my colleague's going to walk through us for in a moment, the JAK2 or JAK/STAT pathway inhibitors. Allogeneic transplant is certainly a discussion in a relevant patient of suitable age, perhaps of higher risk, and often with some sense of how JAK inhibitor therapy is going or not.

We always are either anticipating or needing to manage anemia, because it's a common denominator in myelofibrosis; and, of course, clinical trials are important. And we have high-risk patients who either have extreme manifestations early on. They will benefit from stabilization treatment, but they may warrant from early discussion of allogeneic transplant prior to transformation to leukemia. This is probably the most important message to drive home here. Many myelofibrosis patients develop accelerated phase or blastic phase where an AML picture is not in their best interest. So, I'll turn it over here to Jackie to walk us through treatment as it's evolved in myelofibrosis.



Slide 20: Interferon for the Treatment of MF

Jacqueline Dela Pena, PharmD, BCOP: Hi, everyone, and my name is Jackie. Thank you, Dr. Mauro. I am one of the Clinical Pharmacy Specialists here at Memorial Sloan Kettering. I do want to go over the treatments for myelofibrosis. The first one we have here is interferon. This is back in 2007.They used the pegylated version of interferon. Now, looking at the response rates, it can be seen as low as 9% or even 9.6% with Silver and colleagues in 2013. So, in the era of JAK inhibitors as consideration of maybe interferon, it may have been, been lost in terms of the treatment algorithm. And there's another important point to consider, as well as the side effects with interferon, especially for seeing very limited efficacy with this medication.



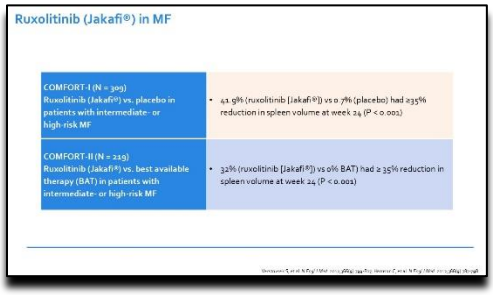
Slide 21: Interferon From a Pharmacist's Perspective

From a pharmacist perspective, it's important to note the different formulations. So, initially, there was the nonpegylated version, which has been discontinued. We only have the pegylated versions available. Here, we have Pegasys® (pegylated interferon alfa-2a). I'll talk later about Besremi® (ropeginterferon). The difference with the nonpegylated interferon is it required more frequent administration, daily or every other day, while the pegylated ones that we have available now are administered either once a week or every two weeks. This is more patient friendly, of course.

In practice, the initial starting dose is low, and we would titrate up based on response and tolerability. However, the dose is adjusted for renal impairment and, of course, hematological toxicity.

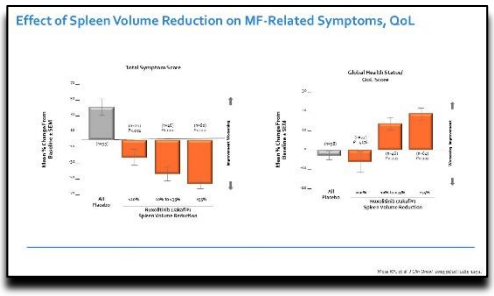
There is no major drug-drug interactions, but major side effects do include cytopenias or new and worsening depression, which is an important thing to note and to weigh risks and benefits when deciding to use this medication. Another important thing to consider is: it is self-injecting, so ensure that your patient is a candidate for this and that they're okay with injecting this at home. I know here in our clinic, we do have nurses that help with providing education regarding administration, and it does come in prefilled syringes as well. So be mindful of the dose when instructing patients on what dose they are and how to properly raise the drug.

In terms of access, this will likely need a prior authorization from the insurance, so ensure that that is done in a timely manner, so the patient's able to get the medication.



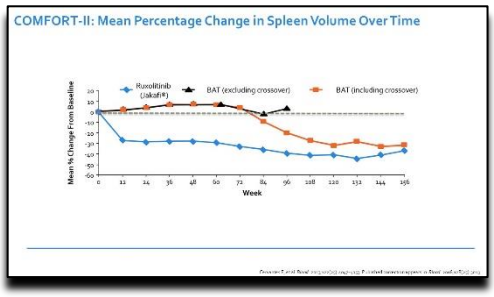
Slide 22: Ruxolitinib (Jakafi®) in MF

Moving onto ruxolitinib (Jakafi®), though this is the first JAK inhibitor approved for myelofibrosis, this is based on results from our COMFORT-I and COMFORT-II trial. The COMFORT-I comparing ruxolitinib (Jakafi®) versus placebo in intermediate or high-risk myelofibrosis. And then in COMFORT-II, this compared ruxolitinib (Jakafi®) versus best available therapy, again in patients with intermediate or high-risk myelofibrosis. We do see a significant amount of patients in these trials get some benefit with ruxolitinib (Jakafi®), which is why it got approved.



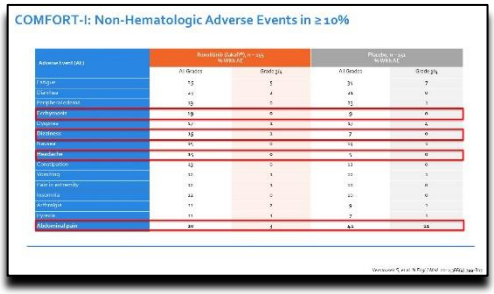
Slide 23: Effect of Spleen Volume Reduction on MF-Related Symptoms, QoL

Looking at these two figures here, we see the effect of spleen volume reduction. Now, that is something that you can see on the left. And then improvement in quality-of-life scores with ruxolitinib (Jakafi®). So, you see in those orange bars, it's significantly better with ruxolitinib (Jakafi®) versus placebo. So, this is really one of the hallmark trials that led to its approval, and we see that the importance of inhibiting the JAK/STAT pathway for myelofibrosis.



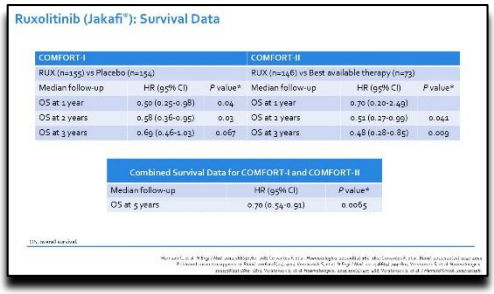
Slide 24: COMFORT-II: Mean Percentage Change in Spleen Volume Over Time

Now this figure shows, in the COMFORT-II trial, it demonstrated the changes over time in terms of spleen volume reduction. We see that the responses are sustained with ruxolitinib (Jakafi®), and you even see a significant improvement in the crossover arm as well, and that's indicated in the orange line.



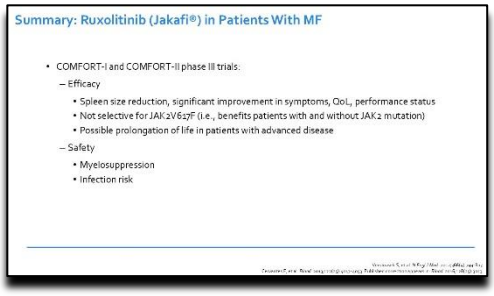
Slide 25: COMFORT-I: Non-Hematologic Adverse Events in ≥10%

Overall, patients on ruxolitinib (Jakafi®) in the COMFORT-I trial felt better compared to placebo, as we can see with the results in the previous slide. But in regards to side effect profile, we did see higher rates of ecchymosis, dizziness, and headaches with ruxolitinib (Jakafi®); but we do not see increased ratesof abdominal pain. Looking all the way at the bottom, I see increased rates in the placebo arm. So overall, these patients did find improvement in their symptom scores and even in their disease burden.



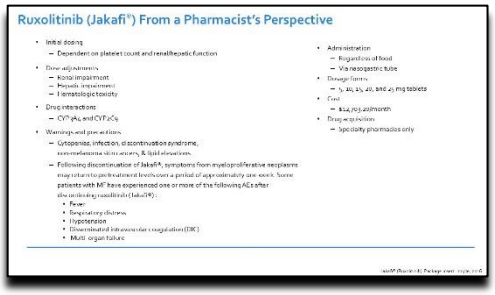
Slide 26: Ruxolitinib (Jakafi®): Survival Data

Another notable finding with the COMFORT-I and COMFORT-II trials is the survival benefit that we can see with ruxolitinib (Jakafi®) as the data matures.These trials also allowed crossover to the ruxolitinib (Jakafi®) arm. So, seeing the overall survival benefit data in that context makes it even more remarkable. These results with ruxolitinib (Jakafi®) has really highlighted again that importance of inhibiting the JAK/STAT pathway in this disease state and likely was the reason why we now have more novel JAK inhibitors that are coming out.



Slide 27: Summary: Ruxolitinib (Jakafi®) in Patients with Myelofibrosis

So, in summary, the COMFORT-I and COMFORT-II trials demonstrated ruxolitinib's (Jakafi®) place in therapy for our integrative and high-risk myelofibrosis patients who are symptomatic. We see a reduction in spleen volume. This leads to maybe improved quality of life scores. Also something to note is that a JAK mutation would not necessarily be required to see benefit with ruxolitinib (Jakafi®).



Slide 28: Ruxolitinib (Jakafi®) From a Pharmacist's Perspective

From a pharmacist's perspective, the initial dose of Jakafi® or ruxolitinib is dependent on their platelet count. Preferably, we start at the full dose of 20 milligrams twice a day; but it's important to follow the patient's blood counts and adjust the dose as needed. Now there are specific guidelines in the package insert on what to do when these platelets drop and when to resume and on what dose, so, I highly recommend you take a look at the package insert for those guidelines.

Now, the dose adjustments are required for patients with renal and hepatic impairment, as well as the hematological toxicity that, as I noted earlier. It's also a major CYP3A4 substrate, so be mindful for any drug interactions and screen for them at initiation. It's important to counsel our patients, to let them know that there could be drug interactions, and to notify their doctor or pharmacist if it's okay to take it with ruxolitinib (Jakafi®).

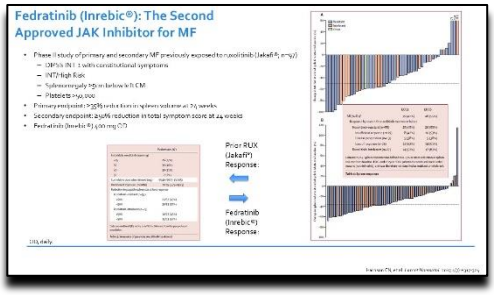
A big counseling point is the importance of not abruptly stopping this medication. These patients can undergo withdrawal or discontinuation syndrome, or, rather, symptoms may significantly worsen or their spleen gets larger when off ruxolitinib (Jakafi®) or, worse case is they may need to be hospitalized for their symptoms. So, it's really important that this is discussed with patients on initiation and that they are on top of their refills when they're running low on ruxolitinib (Jakafi®) supply. If it does need to be discontinued, often we taper it down or we use steroids like prednisone as a temporizing measure.

In terms of administration, it can be administered with or without food, preferably same time each day, twice a day. And it does come in various tablet sizes, so another counseling point for our patients is to review what their current dose is and when adjustments need to be made.

In terms of access, a prescription will likely need to be sent to a specialty pharmacy that carries this medication. It is still expensive, about $12,000 a month, and it will likely need a prior authorization and get approval from the insurance. Again, very important that these prior auth approvals or renewals are done in a timely manner, so our patients don't miss

any doses or they're at risk for withdrawal. And, Dr. Mauro, was there anything you would like to add with ruxolitinib (Jakafi®) at this point?

Dr. Mauro: That's a fantastic overview, no. Thank you very much.



Slide 29: Fedratinib (Inrebic®): The Second Approved JAK Inhibitor for MF

Dr. Dela Pena: Now, moving on with fedratinib (Inrebic®). This is the second agent. This was approved in 2019 based on the JAKARTA trials. These are patients with higher risk disease and symptoms require treatment, similar to our COMFORT-I and COMFORT-II trials.

This slide shows the results from the Phase II study, and these patients did receive prior ruxolitinib (Jakafi®) therapy. Overall, we can see that patients who are intolerant or resistant to ruxolitinib (Jakafi®) still had responses. In regards to reduction in spleen size, of note, a majority of these patients had less than 40 milligrams total daily dose of ruxolitinib (Jakafi®). Again, what I said earlier, we would prefer if patients get at least 20 milligrams twice a day or 40 milligrams total daily dose. But in this trial, majority of patients had less than that with ruxolitinib (Jakafi®).

The waterfall plot on the right here notes improvement in symptom scores with fedratinib (Inrebic®), with sometimes even showing greater than a 50% improvement in their scores.

Now, the table in the middle notes responses at three months and six months. We see numerically higher responses at the six-month mark with fedratinib (Inrebic®), and the waterfall plot at the bottom is a visual of the spleen reduction, again, noting some good response rate, even for those that have received ruxolitinib (Jakafi®) in the past.
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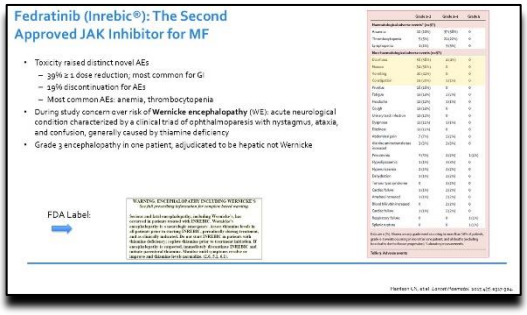
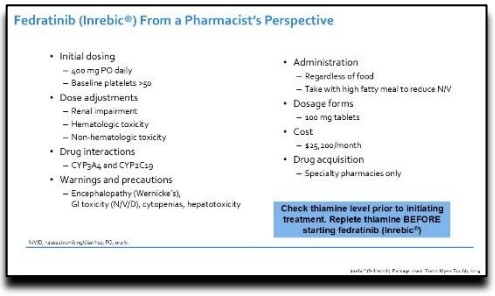


Slide 30: Fedratinib (Inrebic®): The Second Approved JAK Inhibitor for MF

In terms of our safety data, there's a good amount of patients that did require a dose reduction — and even discontinuation altogether — due to side effects and attributing to these side effects, and that includes GI side effects and cytopenias. There's also a big concern for possible neurotoxicity, such as Wernicke's encephalopathy, and it does have a warning label on



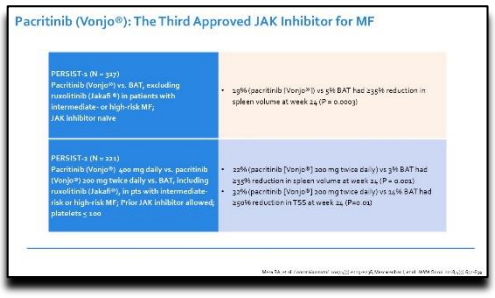
Slide 31: Fedratinib (Inrebic®) From a Pharmacist's Perspective

From a pharmacist perspective here with fedratinib (Inrebic®), the initial dose is at 400 milligrams daily. Baseline platelets must be above 50,000. And unlike ruxolitinib (Jakafi®), there are really no dose adjustments based on that initial platelet count aside of the platelets being greater than 50. There are renal dose adjustments, so the dose should be reduced by 50% if their creatinine clearance is less than 30. And the dose should be adjusted based on hem toxicities as well as other nonhem toxicities, and those are outlined in the package insert as well.

Similar to ruxolitinib (Jakafi®), this is a major CYP3A4 substrate, but fedratinib (Inrebic®) is also a moderate CYP2C19, CYP2D6, and actually a CYP3A4 inhibitor. So, a drug screen of you at the initiation of fedratinib (Inrebic®) is very important, ensuring that other medications are also dosed appropriately.

Now, regarding their neurotoxicity, including or in the case of encephalopathy, it is important that we get a thiamine level prior to treatment initiation. And if these thiamine levels are low, the thiamine should be repeated prior to starting fedratinib (Inrebic®).

And in regards to administration, it can be taken with or without food. However, taking it with a meal may reduce those GI side effects, such as nausea and vomiting. As I noted in the trials, these GI symptoms can lead to dose reductions, can be seen maybe even the first two weeks of treatment. Initiations though, an important counseling point for our patients that are starting out. In terms of access, it must be sent to, again, a specialty pharmacy. It's fairly costly, about twice as much as ruxolitinib (Jakafi®) and, again, will likely need a prior authorization. That'll be a common theme that you'll see with our JAK inhibitors.



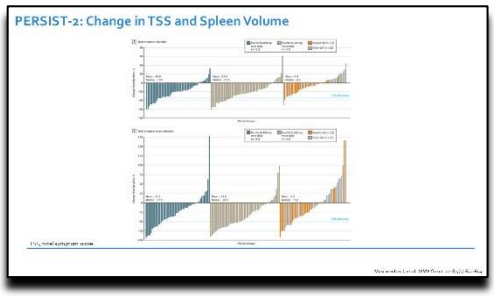
Slide 32: Pacritinib (Vonjo®): The Third Approved JAK Inhibitor for MF

Moving on to pacritinib (Vonjo®), one of the newer ones and the third approved JAK inhibitor for myelofibrosis. Now in 2022, FDA granted accelerated approval to pacritinib (Vonjo®) for patients with an immediate or high-risk myelofibrosis with a platelet count less than 50. Now, the trialsoutlined in this table demonstrate its efficacy in that specific patient population. Here we have PERSIST-1 at the top. These patients were JAK inhibitor-naïve, so they did not get ruxolitinib (Jakafi®) before, did not receive fedratinib (Inrebic®) before, and they were randomized to receive either pacritinib (Vonjo®) or best available therapy.

Now, we can see that 19% of these patients did have a spleen reduction or at least great,

35% or greater at week 24 compared to 5% in the other arm. These patients who were in the best available therapy group were allowed to cross over.

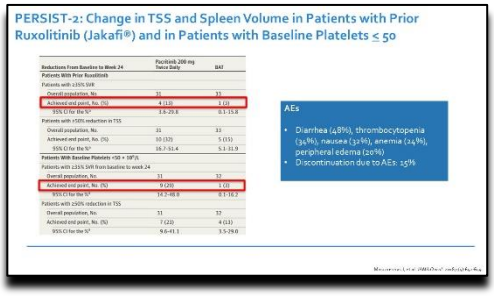
In the PERSIST-2 trial, these patients were included. They had JAK inhibitors in the past, or at least if they had JAK inhibitor use in the past, they were allowed in the trial. We also see similar responses in spleen volume reduction and also an improvement in symptom scores. Patients, again, in the best available therapy arm were allowed to cross over after week 24, or if they had any progression in their splenomegaly. However, if we look back or if we remember from our ruxolitinib (Jakafi®) study, which is COMFORT-I and II and even with fedratinib (Inrebic®), their response rates here with the pacritinib (Vonjo®) studies in terms of spleen volume reduction, the ruxolitinib (Jakafi®) and fedratinib (Inrebic®) studies showed better responses. But, of course, we don't have head-to-head trials at this time; so we can't really say one may be better than the other. But just something to note.



Slide 33: PERSIST-2: Change in TSS and Spleen Volume

Now, we have a lot of waterfall plots. It does show a great visualization for changes in spleen sizes and symptom scores in the PERSIST-2 trial. At the top, we see changes in spleen sizes; and then at the bottom, we see the changes in symptom scores. We see the responses with the 400 milligram daily dose and the 200 twice-a-day dose of pacritinib (Vonjo®). We can also see responses compared to the best available therapy arm all the way to the right. And, of note, most of these patients were actually on ruxolitinib (Jakafi®).

We also have to keep in mind that the patients in PERSIST-2 trial had platelets less than 100, so it's possible that patients that received ruxolitinib (Jakafi®), at least in the best available therapy arm, may have received lower doses because of their low platelets. And thus, response rates may have been lower in this trial. And unlike the data that we showed with ruxolitinib (Jakafi®), pacritinib (Vonjo®) did not demonstrate overall survival benefit.

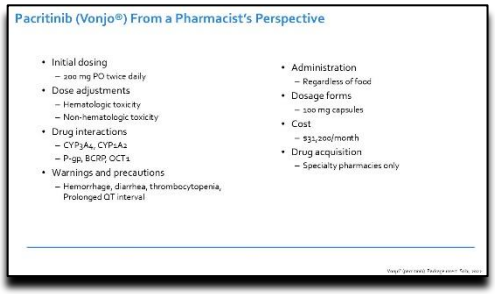


Slide 34: PERSIST-2: Change in TSS and Spleen Volume in Patients with Prior Ruxolitinib (Jakafi®) and in Patients with Baseline Platelets < 50

I also wanted to highlight the results in patients with prior ruxolitinib (Jakafi®) therapy and those with baseline platelets less than 50. So, patients with baseline platelets less than 350 would not have been eligible for ruxolitinib (Jakafi®) or fedratinib (Inrebic®). At the top, you see a small number of patients that achieve that primary endpoint, spleen reduction for patients that had received ruxolitinib (Jakafi®) in the past. And at the bottom, now these are patients with baseline platelets less than 50. And you see almost a third of

them achieved that primary endpoint of spleen reduction, indicating some good response with pacritinib (Vonjo®).

Major side effects I have listed on the right here, with the most common, which is, which is GI toxicity. That includes diarrhea. Other side effects are cytopenias and even peripheral edema can be seen with pacritinib (Vonjo®). Looking at the trial, about 15% of these patients discontinued pacritinib (Vonjo®) therapy because of these side effects.



Slide 35: Pacritinib (Vonjo®) From a Pharmacist's Perspective

From a pharmacist perspective; so, the initial dose of pacritinib (Vonjo®) is 200 milligrams twice a day, so the 400 milligram daily dose that we saw in trials is not FDA approved. It wasn't as well tolerated as the 200 twice-a-day regimen, which is why the 200 twice- a-day regimen is what is the initial dose for pacritinib (Vonjo®).

Now, there are dose adjustments based on hematological and nonhematological toxicities. Again, these are outlined in the package insert. And these also include recommendations for patients with new onset diarrhea because that is one of the very common side effects for pacritinib (Vonjo®). It states things such as initiating antidiarrheal medications like loperamide (Imodium A-D®), encouraging oral fluid intake. It really depends on the grade of GI toxicity and what the recommendations are. These patients should have maybe even Imodium® or generic loperamide (Imodium A-D®) on hand when starting pacritinib (Vonjo®).

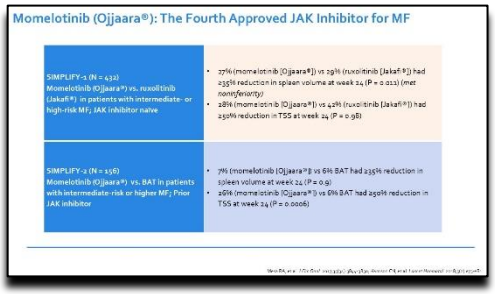
Now, it does have drug interactions which are other JAK inhibitors. It's a CYP3A4 substrate. That's a common theme with these medications. Important to avoid moderate and strong CYP3A4 inhibitors with pacritinib (Vonjo®). That's actually outlined in the package insert. Pacritinib (Vonjo®) is also a CYP1A2, P-gp, BCRP, and OCT1 inhibitor. So do note that other medications that they're taking at the time that they start therapy with pacritinib (Vonjo®), especially if those medications are sensitive substrates. Other warnings include prolonged QT interval with pacritinib (Vonjo®). Very important to get a baseline EKG prior to starting therapy. And to continue monitoring as clinically indicated. So, for adding another agent that we know is QT prolonging, maybe at that time, it's important to consider monitoring that even closer.

Similar to ruxolitinib (Jakafi®) and fedratinib (Inrebic®), prescription must be sent to the specialty pharmacy. High chance that a prior authorization is required by the insurance, and pacritinib (Vonjo®) is actually more expensive when you compare it with rux [ruxolitinib (Jakafi®)] and fedratinib (Inrebic®). This one is almost $32,000 a month, so keep that in mind. It's very important that we get those prior authorizations through.

And Dr. Mauro, is there anything else you would like to add with pacritinib (Vonjo®)?

Dr. Mauro: Yes. Maybe for thinking about now a few of the drugs together, I think one of the comments I meant to make about ruxolitinib (Jakafi®), is do not delay initiation of treatment. I think just a word to the practitioners to think about it early based on what you mentioned about the survival advantage. But to recognize the challenges of dosing and cytopenias and to not have trepidation that we have alternatives. You're seeing the alternative of fedratinib (Inrebic®). It's just a second medication in the class with perhaps good salvageability and now really the ability to treat patients with cytopenias. And the other thing, just a practical thing I was thinking of, is toxicity and adverse effects. Some of the need to check cholesterol levels, need to warn patients to have dermatologic screening for this question of, are we seeing more sun damage-related skin cancers diagnosed that sometimes could be more either symptomatic or risk-based? So, just some nuts and bolts, but fantastic overview. And I think we probably have just a little bit more to cover, so I'll let you continue.

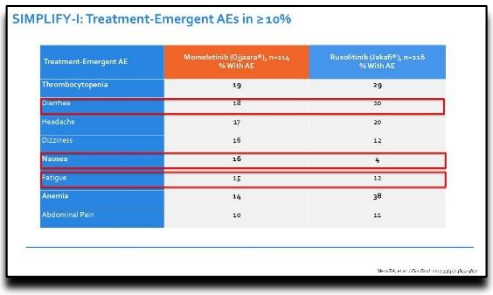
Dr. Dela Pena: Okay, yeah, that's a really good point because some of these newer medications — the newer, novel JAK inhibitors that are coming out — and we may not have all of the safety data just yet. So maybe more to come.



Slide 36: Momelotinib (Ojjaara®): The Fourth Approved JAK Inhibitor for MF

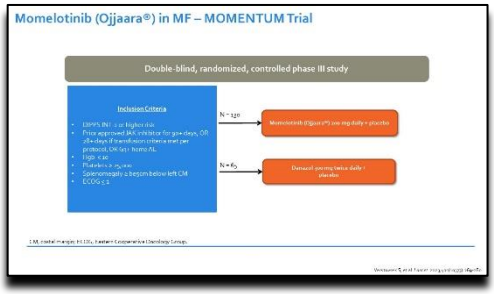
Now, our next JAK inhibitor, we have the fourth approved JAK inhibitor for myelofibrosis. We have momelotinib (Ojjaara®). We have the SIMPLIFY-1 and -2 trials, so demonstrating clinical activity against some of the hallmark features of myelofibrosis, such as splenomegaly. So, it's SIMPLIFY-1. We had patients randomized either to momelotinib (Ojjaara®) or ruxolitinib (Jakafi®). It did meet its noninferiority in terms of spleen reduction, but these patients were also JAK inhibitor-naïve.

In SIMPLIFY-2, so these patients received prior JAK inhibitor. They were randomized to either momelotinib (Ojjaara®) or best available therapy, which was mainly ruxolitinib (Jakafi®). These patients had similar rates of spleen reduction as well, but what's investigations, investigators didn't note with both of these studies is that we saw improvements in the rates of transfusion independence by week 24 with momelotinib (Ojjaara®).



Slide 37: SIMPLIFY-I: Treatment-Emergent AEs in ≥ 10%

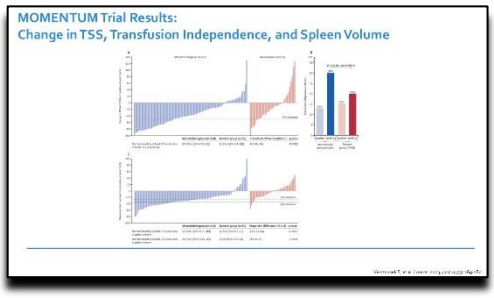
So, this table shows emerging adverse events in that SIMPLIFY-1 trial. So, again, these patients were JAK inhibitor-naïve and are randomized to either momelotinib (Ojjaara®) or ruxolitinib (Jakafi®). We did see higher rates of nausea with momelotinib (Ojjaara®), but fewer rates of thrombocytopenia and anemia, which is encouraging because that's one of the issues that we do have with ruxolitinib (Jakafi®).



Slide 38: Momelotinib (Ojjaara®) in MF – MOMENTUM Trial

So, this is the MOMENTUM trial. It's one of the hallmark trials that led to its approval, momelotinib's (Ojjaara®) approval in 2023, so a fairly new medication. It included patients with intermediate and higher-risk myelofibrosis, similar to our other trials. These patients were anemic, with a hemoglobin less than 10. And it allowed patients higher exposure to other JAK inhibitors, so really capturing the patient population here, patients that have received JAK inhibitors in the past and that may be having issues with cytopenias.

Of note, patients with platelet counts even as low as 25 or 26 here were included in the trial. These patients were randomized to either receive momelotinib (Ojjaara®) or danazol (Danocrine®).

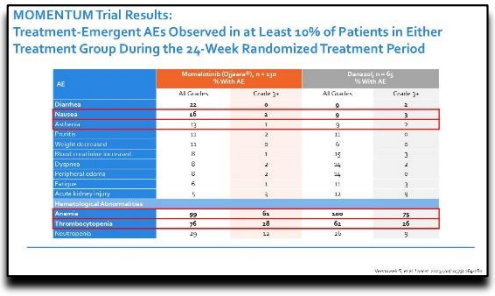


Slide 39: MOMENTUM Trial Results: Change in TSS, Transfusion Independence, and Spleen Volume

We have two waterfall plots that show changes again in symptom score and spleen volume with momelotinib (Ojjaara®) and danazol (Danocrine®). We can see that there were some responses seen with momelotinib (Ojjaara®), like we saw in the SIMPLIFY trials in the table earlier. On the right we see changes in rates of transfusion independence. Additionally, 30% of patients in the momelotinib (Ojjaara®) are actually achieved transfusion independence, which is great, versus 20% of those in the danazol (Danocrine®) arm. And these translated to a noninferiority treatment difference of 14%. So, overall, these results solidified momelotinib's (Ojjaara®) role for patients with myelofibrosis and anemia.

I believe it's hypothesized that it's the role of inhibiting activin A receptor type 1, or ACVR1, helps with improving anemia, unlike our other JAK inhibitors. And unlike ruxolitinib

(Jakafi®), the SIMPLIFY and MOMENTUM trials did not demonstrate an overall survival benefit. But do note that a crossover was allowed at week 24 with the MOMENTUM trial.



Slide 40: MOMENTUM Trial Results: Treatment-Emergent AEs Observed in at Least 10% of Patients in Either Treatment Group During the 24-Week Randomized Treatment Period

The most common side effects were diarrhea and nausea. Most reported serious adverse event were infections, something we can see with some of our other JAK inhibitors. Otherwise, well tolerated.

I want to point out the hem toxicity that's shown in the trial. Now, these were based on lab values during that 24-week period, regardless of whether there was a change in baseline. So, all of the patients in the trial had a hemoglobin less than 10, so it should be noted that there was an increase in hemoglobin concentrations in patients that received momelotinib (Ojjaara®) because we did see transfusion independence as one of the selling point for momelotinib (Ojjaara®).

Slide 41: Momelotinib (Ojjaara®) from a Pharmacist's Perspective

Now, looking at momelotinib (Ojjaara®) from a pharmacist perspective, the starting dose is 200 milligrams daily. There are dose adjustments required for severe hepatic impairment. None for renal impairment or mild-to-moderate hepatic impairment. Now, it's based on the Child-Pugh Criteria. Other adjustments are based on toxicity, such as hepatotoxicity or thrombocytopenia, and these are all outlined in the package insert.

It's an OATP 1B1/B3 substrate. So, for patients that are taking these inhibitors, monitor for increased side effects to momelotinib (Ojjaara®), such as diarrhea, nausea, or vomiting. And like the others, this one's actually not a CYP3A4 substrate, so that's a difference from our other JAK inhibitors. Momelotinib (Ojjaara®) is also a BCRP inhibitor, so monitor for any drug interactions again with patient's current medication list. It can be taken with or without food once a day, preferably around the same time each day. And it has the same monthly cost as pacritinib (Vonjo®) at around $32,000 a month; and only specialty pharmacies carry it, like the other JAK inhibitors. So, a prior auth is, is likely needed to, to initiate therapy.

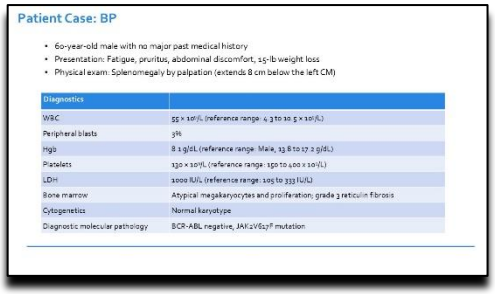
Anything else that you would like to add, Dr. Mauro, especially what you see in clinical practice? I know this is one of our newer, newer medications for myelofibrosis.

Dr. Mauro: Yes. I think you've highlighted the fact that — so this agent, through the FDA

approval, came authorization for patients newly diagnosed with anemia and with anemia after ruxolitinib (Jakafi®), so we might be looking at this as our first therapy, as anemia's pretty common. And as you alluded to, I think these drugs are common in their targets but maybe different in their onset and intensity of action.

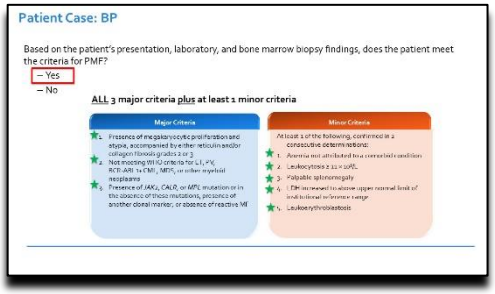
We give full doses of momelotinib (Ojjaara®) to patients who have anemia. We give full doses of pacritinib (Vonjo®) to patients who have thrombocytopenia. But they may act at different rates, and I think we've seen some patients where they may have had taken a bit more time to have the anti-inflammatory effect. So, we've taken caution in transitioning patients from one JAK inhibitor to the other. I would say that ruxolitinib (Jakafi®) is a more fast-acting and drug at relevant doses than, than momelotinib Ojjaara®); but I think it's nice to have a breadth of options, and it probably just takes some time and experience and familiarity with patients to know how to use them all properly.

Dr. Dela Pena: Yeah, we're, definitely are now in the era where there's more treatment options with these JAK inhibitors and switching from one over the other, I think time will tell on what's the most appropriate way to do that. I think that's still a question that needs be answered.



Slide 42: Patient Case: BP

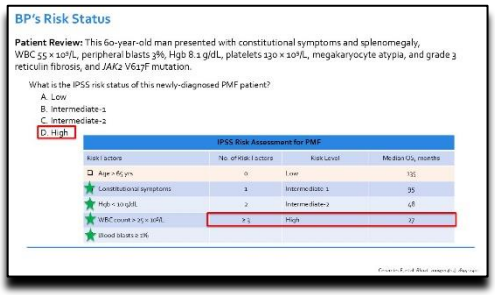
Dr. Mauro: So, thank you, Jackie, that was tremendously comprehensive; and, a good springboard would be to talk about a case. So, here is a patient, BP, a 60-year-old male without any major past medical history, but presenting with the typical spectrum of MPN symptoms – fatigue, pruritus, abdominal discomfort, and a 15-pound weight loss. We know that he's got splenomegaly, so when we look at the details and from a hematologic perspective, the white count's elevated with circulating blasts. He's anemic fairly significantly for a male, has moderate thrombocytopenia, elevated LDH, and a marrow testing shows that atypical megakaryocytic proliferation picture and Grade 3 fibrosis cytogenetics are normal. And molecular testing shows the absence of BCR-ABL, which would be a hallmark of CML with a conical *JAK2* V617F mutation.



Slide 43: Patient Case: BP

So, based on this patient's presentation and laboratory and bone marrow biopsy findings, does he meet the criteria for a primary myelofibrosis? And the answer would be yes. And, but perhaps and, more importantly, why? As we alluded to earlier, this patient has all of the features and symptoms. As we can look on the right and output from the myeloproliferative disease if you will: has anemia; has some degree of thrombocytopenia; has leukocytosis, clearly; and splenomegaly; and an

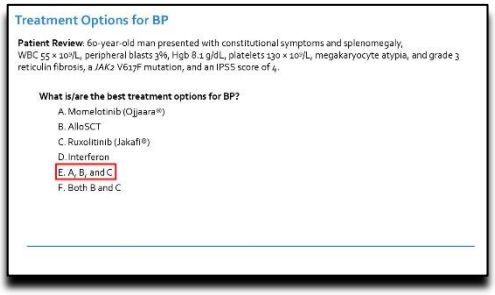
elevated LDH. So, he has all of the criteria, but bone marrow findings are consistent with fibrosis and megakaryocytic changes. We don't see a fit for another MPN, and he has the presence of the *JAK2* mutation, so clearly this is a patient in need of treatment.



Slide 44: BP's Risk Status

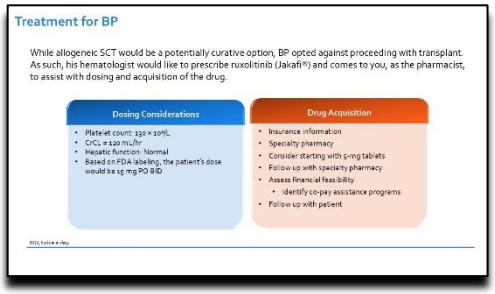
So, how do we risk-stratify the patient? Again, that's just a review of his presenting features on the top. How do we classify him by the International Prognostic Score, the Prognostic Scoring System, which again was just looking at basic principles; and you can see that based on his white count being very high, he has anemia, has constitutional symptoms, doesn't meet the advanced age criteria, or any other high-risk features, but does have circulating blasts. So, in summary, he has a high-risk presentation.

And you can see the difference in overall survival. Someone who has a low-risk presentation is likely to have this MPN for some time. Whereas this patient may have a predicted survival of much shorter duration and, again, this is without significant treatment or significant intervention. And, so, I think we have to act quickly on these patients who present such as this gentleman.



Slide 45: Treatment Options for BP

What could we treat him with? So, we've just reviewed in beautiful summary all of our treatment options. So what treatment options would we have? Such a patient, would momelotinib (Ojjaara®) be suitable? Allogeneic transplant? Would ruxolitinib (Jakafi®) be suitable? Interferon perhaps, or some combinations, and the answer in this case would be that Ojjaara® or momelotinib would be suitable, given his anemia presentation. We could consider him early for allogeneic transplantation based on a high-risk presentation, probably with a notation that JAK inhibitor therapy would be reasonable to begin with. And ruxolitinib (Jakafi®) is still labeled for this patient, because he has still a preserved platelet count, and the dosing is generally based on the platelets — as Jackie nicely summarized for us. Interferon would be a challenge, and, again, I know there's definitely been research in interferon, but the data is a little weaker. And I think clinical benefit from JAK inhibitors would be much stronger.



Slide 46: Treatment for BP

I primed the witness here to say that a transplant might have been curative. He opted to proceed with nontransplant therapy, and we want to talk about the dosing. So, here's where I bring up Jackie and ask about the dosing of Jakafi® (ruxolitinib) based on the patient's blood count. So, we do know that there's some degree of thrombocytopenia; and he has a preserved creatinine clearance and normal liver function, so we're going to choose a dosage of 15 milligrams, BID. Do you, agree?

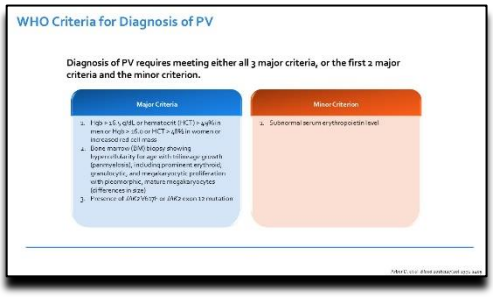
Dr. Dela Pena: Yeah.

Dr. Mauro: Thank you. I chose wisely.

So the problem is, I think, that many of these patients may have now manifestations on treatment of what could be disease biology and drug toxicity, both, so we want to start at the proper dose and, of course, monitor carefully. And Jackie nicely covered some of the challenges of drug acquisition, including prior authorization, specialty pharmacy. Consider starting the 5 milligram tablets because of the dosing flexibility and may need to dose reduce quite quickly. And, if it's possible, you may want to add that flexibility for the patient. Think about copay assistance programs, as Jackie had mentioned. A lot of the drugs are quite expensive from the standpoint of wholesale acquisition costs and maybe even with higher copays to patients. And, of course, we're going to follow these patients closely.

Slide 47: Polycythemia Vera

So, let's turn to polycythemia vera.



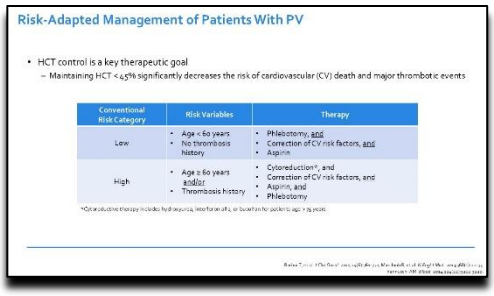
Slide 48: WHO Criteria for Diagnosis of PV

Which has some overlap, but as we talked about with PMF, the criteria for PV is shown here; and I think it's important to know that one of the most important things that I highlight is that the hemoglobin levels of 16 or 16.5 for men and women, or the recognition of an increased red cell mass, which requires somewhat complex testing leads to the fact that polycythemia may be masked or not immediately apparent based on blood counts or may be attributed to some other finding, dehydration or some, some other secondary cause.

A bone marrow's a very definitive way to diagnose polycythemia as it shows classic changes, such as panmyelosis increased all of the marrow lines, myeloid, erythroid, and megakaryocytic with typical changes in the cells, cellular forms. And as we mentioned earlier, the *JAK2* conical V617F mutation is highly prevalent in this disease, although you can see other variants.

Lastly, the serum erythropoietin level, which I always describe to patients as essentially a thermostat. If it's subnormal, that's the autonomous over, overactivity of the bone marrow in proliferative disease. Driving erythroid overproduction in excess is telling, the body's saying, "We don't need extra blood," and the bone marrow's saying, "We're going to continue to produce," so a subnormal erythropoietin level is a minor criteria.

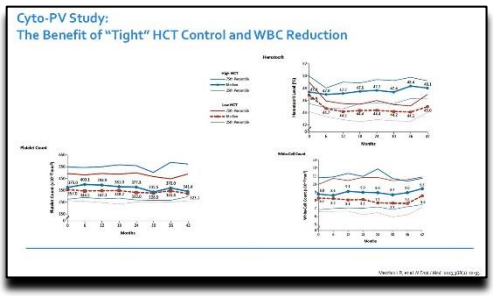
What we've learned in more recent days, which ironically brings us back to historical and conventional testing, is that a bone marrow is often very important, and we don't want to underrecognize and we want to pursue diagnostics in patients who have some elevation in hemoglobin, hematocrit, or other signs or symptoms of polycythemia.



Slide 49: Risk-Adapted Management of Patients With PV

Much like MF, we talk about risk-adapted management. I had, I mentioned the risk scores and the overlap and how we look at things. A low-risk patient again, in general, is going to be a younger patient without thrombosis. And we may begin with phlebotomy or therapeutic phlebotomy where we're controlling the hematocrit through venesection, through patients essentially doing the equivalent of donating blood, in the background of correcting cardiovascular risk factors and using aspirin as an antiplatelet therapy.

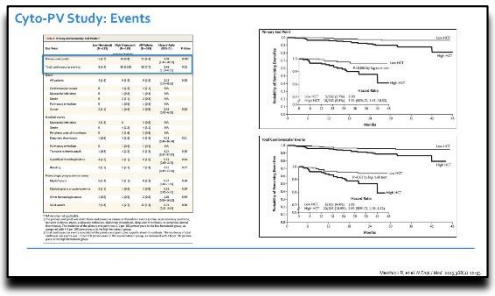
For high-risk patients who are, just have older age and have, therefore, more vascular risk, or who have already had a thrombosis in the setting of PV, we want to control the blood counts more smoothly and more clearly — and not just the hematocrit — with phlebotomy, but also the white blood cell count and potentially the platelets with therapies. We'll talk about that in a moment. We still want to correct the CV risk factors, of course, even more here; and we can use phlebotomy, and we're adding aspirin in all of these patients.



Slide 50: Cyto-PV Study: The Benefit of "Tight" HCT Control and WBC Reduction

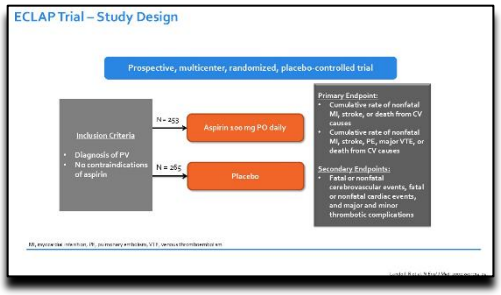
One of the best studies to kind of give you just a clear black and white simple picture in polycythemia is the CYTO-PV study, which really just asks the question: "Is there a difference between controlling patients tightly?", meaning for men and women, not specifying a sex-based hematocrit target of 42 or 45. But just saying, "Keeping everyone below 45 meticulously or allowing some flexibility," which is often more patient friendly someone might say — meaning keeping the hematocrit generally below 45 or between 45 and 50 — does have an impact in outcome. And these are the types of trends we saw in patients.

And you can see the patients with the high hematocrit, if you will. Their platelet count is running higher. Their white blood cell count is generally running higher, and their hematocrit may be not too far above 45, but it is, unfortunately, above 45.



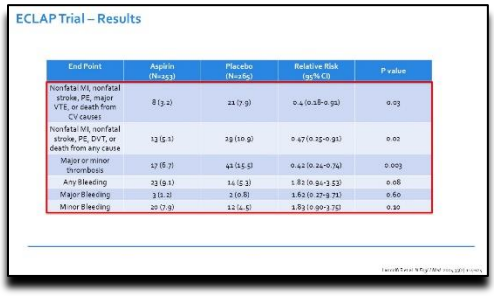
Slide 51: Cyto-PV Study: Events

And what did we see? That there was a clear impact on vascular events. The patients in the high hematocrit group, had more total and cardiovascular events; arterial events in particular were a concern. And I think this taught us a lesson that keeping a strict amount of good target is very important. And again, the trends in the higher white count, higher platelet count on these patients who had less intervention, I think, was also a clue.



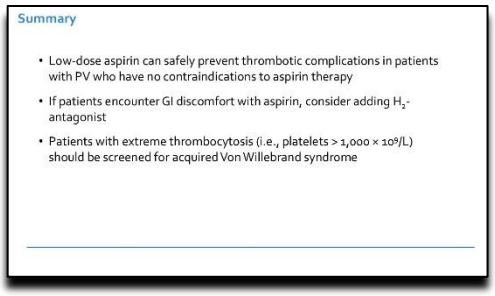
Slide 52: ECLAP Trial – Study Design

And, and the ECLAP study was a study of aspirin and showed clearly the benefit of aspirin in patients with polycythemia vera, because with aspirin — not the American dose if you will of 81 milligram coated aspirin, but 100 milligrams as is used in, across the pond and in other countries versus placebo.



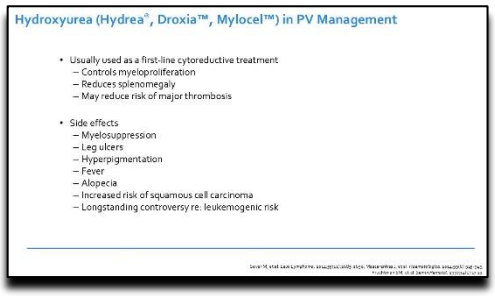
Slide 53: ECLAP Trial – Results

And we saw a clear benefit, but the risk reduction for the kind of events we're trying to avoid across the board, venous and arterial events. There were more bleeding events in the aspirin versus the placebo group, but the benefit outweighed the risk, and we use aspirin in these patients as we do in patients with thrombocytosis.



Slide 54: Summary

So, low-dose aspirin as a preventative measure. It doesn't change the blood counts, but it impacts events and morbidity/mortality. GI complications, of course, can happen; and we want to be on the lookout and manage that. And we want to have the clear footnote that, ironically, aspirin may need to be held in patients who have a very high platelet count, an extreme platelet count over a million, because high platelet count can interfere with von Willebrand's Factor — the high molecular weight von Willebrand's multimers that trigger thrombosis most easily. So patients with high platelet count can have reduced von Willebrand's antigen and function and, therefore, more bleeding risk when their platelets are very high. So, you need to hold their aspirin. It's really the opposite of what you think but is important to know.

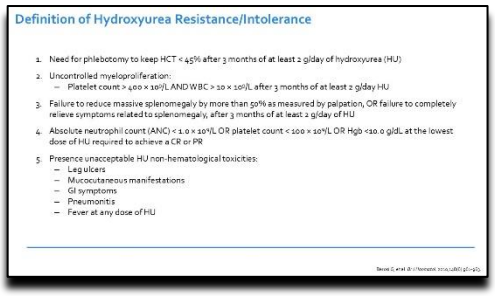


Slide 55: Hydroxyurea (Hydrea®, Droxia™, Mylocel™) in PV Management

So, I'm going to turn it back to Jackie to go through some of the treatment elements in PV which overlap, I think, in some degree with that of MF.

Dr. Dela Pena: So beyond aspirin and phlebotomy, we have hydroxyurea (Hydrea®) as one of our first-line cytoreductive therapies in PV. Obviously, it helps control a patient's blood counts, control myelo-proliferation. It also reduces splenomegaly, and maybe even reduce risk of major thrombosis; again, in addition to having aspirin onboard. Side effects that we commonly see, mucositis, myelosuppression. They are controlling blood counts, so it can bring white blood cells down and hemoglobin and hematocrit, which is what we wanted, or even the platelets.

Skin toxicities such as skin ulcers or leg ulcers, something to counsel our patients on. Unfortunately, some of these toxicities, like the mucositis or the skin ulcers could be dose-limiting toxicities. There's also a question of whether it causes an increased risk of nonmelanoma skin cancer; again, something to consider with hydroxyurea (Hydrea®).

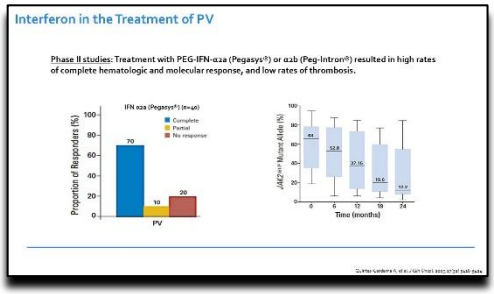


Slide 56: Definition of Hydroxyurea Resistance/Intolerance

Now, in terms of the definition of hydroxyurea (Hydrea®) resistance and intolerance, fairly straightforward. Here we have the criteria, so we have the need for a phlebotomy to keep hematocrit less than 45% after three months or, of at least 2 grams a day of hydroxy or we have uncontrolled myeloproliferations, so looking at the platelet count or looking at white blood

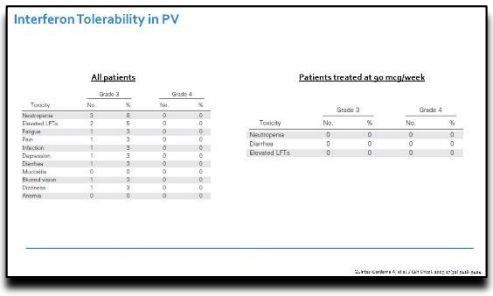
cell counts on a set with at least 2 grams a day of Hydrea® (hydroxyurea). Patients who had really heavy, severe symptom burden — so unable to reduce that, that spleen size — can't control their symptoms, again, with at least 2 grams of Hydrea® (hydroxyurea). Or in the opposite direction, we had patients who are maybe intolerant to hydroxyurea (Hydrea®). Their ANC is low, less than 1. Platelet count less than 100. And that's, with hydroxyurea (Hydrea®), we can't control their hematocrit, hemoglobin because their ANC or platelet counts are low.

Or, like I mentioned earlier, the dose-limiting toxicity, their side effects, these nonhematologic toxicities, mucositis, or skin ulcers. So, what other therapies do we have if these patients can't tolerate hydroxyurea (Hydrea®)?



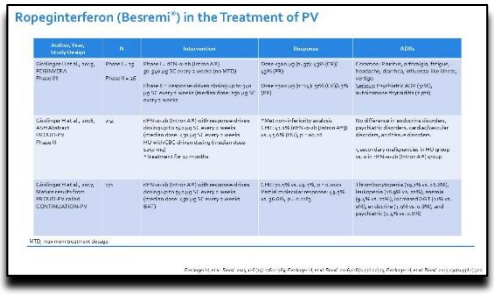
Slide 57: Interferon in the Treatment of PV

And that leads us to interferon. We have these interferon trials. Now, this was an older trial, back actually in 2009. In terms of responses, we can see, meet to target hematocrits and control blood counts in all patients with polycythemia, whether it's phlebotomy or hydroxyurea (Hydrea®) or combination. But interferon can do it as well. It's intriguing. Interferon may be directly led to molecular responses, as we can see on the right. It's projecting the (*JAK2*) mutant allele percentage. So that's the time plot showing the allele frequency with interferon and that reduction with the JAK2 clones. This can be seen in ET as well, not just PV. So, continued studies comparing this in hydroxyurea (Hydrea®), and I will be going over more with the pegylated version for, for PV that was through, so more for that.



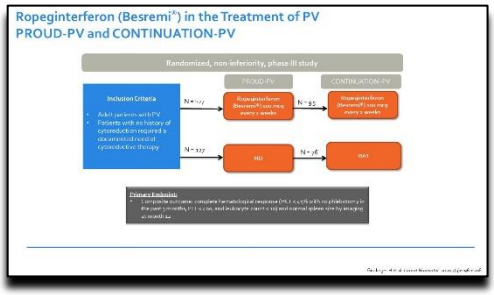
Slide 58: Interferon Tolerability in PV

Just going to breeze over the tolerability of interferon because we did discuss it earlier; so with the neurological side effects, we'll need to consider such a good question or anxiety. Liver function abnormality, so you can see interferon as well as cytopenias. So, we want to be careful at minimizing these side effects but also ensuring that we get efficacy with interferon.



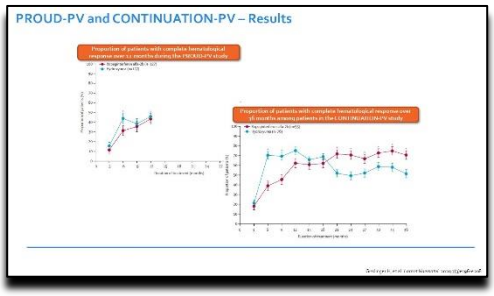
Slide 59: Ropeginterferon (Besremi®) in the Treatment of PV

Now, I do want to spend more time with Besremi® (ropeginterferon) for treatment of polycythemia vera. We discussed other interferon agents with myelofibrosis, so I want to, again, introduce this other pegylated interferon preparation. This was approved in 2021 for patients with PV. We have this table that summarizes the earlier data with Besremi® (ropeginterferon), noting that increased doses of this pegylated interferon version, or Besremi® (ropeginterferon), had numerically better responses and tolerable. They also noted decrease in that *JAK2* allelic burden by about 1.2% each month. And this led to the PROUD-PV and CONTINUATION-PV studies that I do want to review closer since it did lead to its approval.



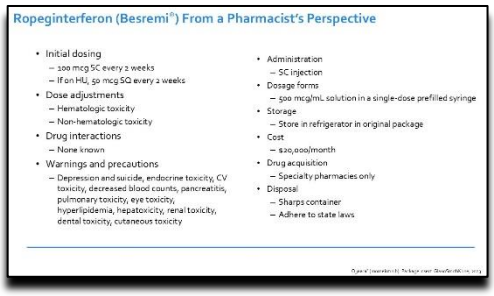
Slide 60: Ropeginterferon (Besremi®) in the Treatment of PV PROUD-PV and CONTINUATION-PV

Now the PROUD-PV was a Phase III noninferiority trial, included a patient's PV with no history of cytoreductive treatment. They were randomized through PV. They're good, Besremi® (ropeginterferon) every two weeks or hydroxyurea (Hydrea®). So, after one year, these patients could opt to enter the extension trial — part of that trial — or the CONTINUATION-PV. So we can see the more mature data. With the PROUD-PV trial, the primary endpoint was, again, noninferiority of Besremi® (ropeginterferon) versus hydroxyurea (Hydrea®). This is in regards to complete hematological response with a normal spleen size at 12 months.



Slide 61: PROUD-PV and CONTINUATION-PV – Results

The graph below shows the final results of the PROUD-PV study, at least on the left-hand side, month 12. And then we also have the interim results at 36 months with the CONTINUATION-PV study, and that study is still ongoing, so still more to come. But at 12 months, we do see responses to be similar between hydroxyurea (Hydrea®) and Besremi® (ropeginterferon), indeed the PROUD-PV trial. So, it did meet its noninferiority endpoint, but with the CONTINUATION-PV trial, we see that these responses improved over time with Besremi® (ropeginterferon).

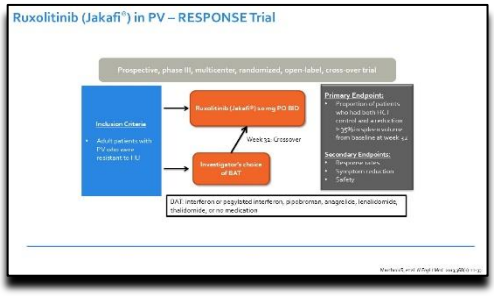


Slide 62: Ropeginterferon (Besremi®) From a Pharmacist's Perspective

Now the initial dose is 100 micrograms subQ; again, similar to our other pegylated interferon version which is Pegasys® (pegylated interferon alfa-2a). This one is given or administered every two weeks, and the dose is actually lower if the patient is already on hydroxyurea (Hydrea®). The dose is titrated and outlined in the package insert. But the dose is typically increased by 50 micrograms every two weeks. Again, ours tolerated up to a maximum of 500 micrograms every two weeks.

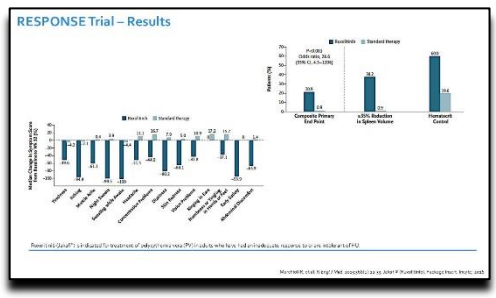
There are actually ongoing studies at this time to evaluate a more accelerated dosing scheme, so maybe more to come on that. And in terms of the side effect profile, similar to the other pegylated interferon medication, which is Pegasys® (pegylated interferon alfa-2a). Do note that it is contraindicated for patients with existing or a history of severe psychiatric disorders. Again, something to keep in mind when deciding on therapy between Besremi® (ropeginterferon) or hydroxyurea (Hydrea®).

Again, this is a subQ injection, so education, administration is very important; and it does come in the single-dose prefilled syringe. So, education on the correct dose and how to waste the drug is important as well. In terms of access, it's about $20,000 a month, so it's fairly expensive and it's specialty pharmacy only and likely again requires a prior auth for access.



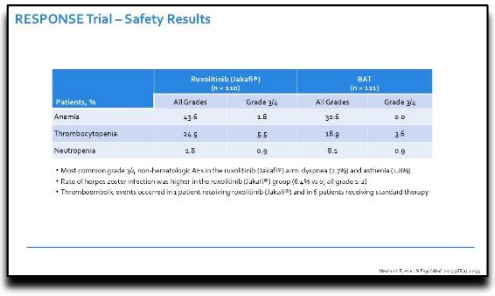
Slide 63: Ruxolitinib (Jakafi®) in PV – RESPONSE Trial

I also want to quickly review ruxolitinib (Jakafi®) as a second-line therapy for patients with PV. Now, this is based on the RESPONSE trial. This is a Phase III study of patients with PV who are resistant to hydroxyurea (Hydrea®). Ruxolitinib (Jakafi®) was compared to best available therapy, and crossover was allowed at week 32. Primary endpoint includes hematic control and spleen size reduction at baseline as well.



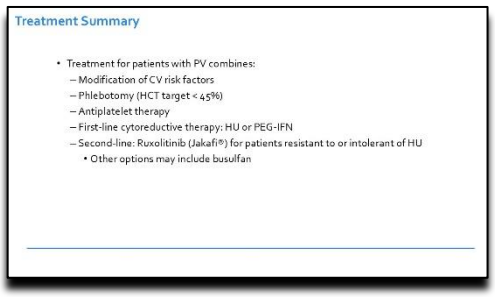
Slide 64: RESPONSE Trial – Results

When compared to best available therapy, ruxolitinib (Jakafi®) did demonstrate and prove responses — so improvement in spleen reduction; and we can also see, it might be hard to read there, but in terms of patient symptoms at the bottom graph, there was improvement in symptom scores with ruxolitinib (Jakafi®). This, as we've noted with the previous trials something to keep in mind.



Slide 65: RESPONSE Trial – Safety Results

Adverse events noted in the RESPONSE trials are similar to the previous ruxolitinib (Jakafi®) studies, cytopenias, anemia, thrombocytopenia, and infections. But I do want to highlight that this is for second-line therapy. These are patients that were resistant to hydroxyurea (Hydrea®). That was the patient population included in the RESPONSE trial, so something to keep in mind.

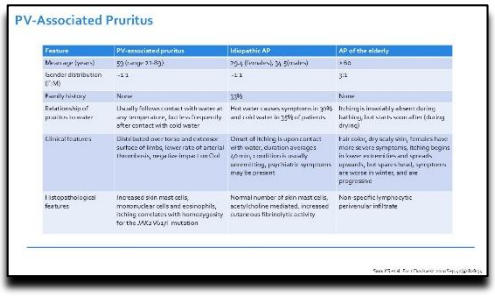


Slide 66: Treatment Summary

In terms of treatment options for PV, so we have that combination to modify cardiovascular risk factors. We have phlebotomy that Dr. Mauro highlighted, targeting that hematocrit's with less than 45%. On antiplatelet therapy with aspirin, 81 milligrams daily, keeping in mind that the patient's platelet counts are about one million to hold that strength. And we have first-line cytoreductive therapies with hydroxyurea (Hydrea®), and we have that new medication that's running as an alternative; and we have second-line therapies with ruxolitinib (Jakafi®), as noted in the RESPONSE trial. Again, these are for patients that are resistant or intolerant of hydroxyurea (Hydrea®). So, we are now getting more and more options for polycythemia vera population, like we are in our myelofibrosis patients. And then if there's anything else that you would like to add, Dr. Mauro.

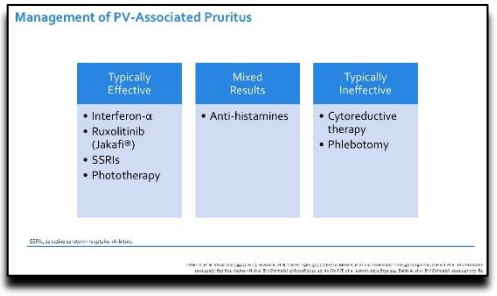
Dr. Mauro: Yeah, that was a great summary. So, speaking about Besremi® (ropeginterferon) and pegylated interferons in general, we continue to do research to try to see if we can understand the risk/reward when it comes to interferon, because patients ask, and we ask the same question. These are chronic diseases, and we want to treat them as best as we can. It's interesting that hydroxyurea (Hydrea®) remains our standard of care for all these years, and we have such good salvage therapy with ruxolitinib (Jakafi®), and we're trying to continue to place interferons; and it's nice to see an approved version, and I think the research will continue. And it's nice to have options, as you mentioned, including other drugs in development, such as drugs that interfere with iron metabolism and the iron uptake and drugs like PTG-300, so thank you.

Dr. Dela Pena: Yeah, definitely more to come and more options and then there's an issue. How do we choose? So, those are some unanswered questions.



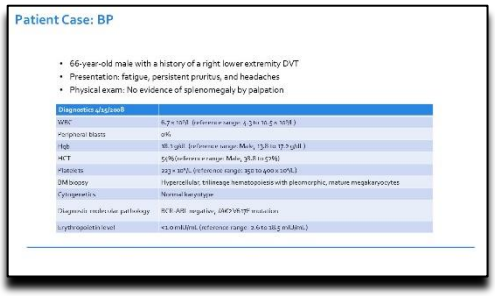
Slide 67: PV-Associated Pruritus

Dr. Mauro: Yes. So, in the clinic, one of the biggest complaints would be pruritus in our resume for patients with PV. There are, sort of, different features of pruritus. Per the classic teaching is about aquagenic pruritus that can be classic in PV, usually at hot water or warmer water, and the distribution can be different. The pathogenesis might be microvascular. It might be related to activated wound due to inflammation and other cells such as mast cells, eosinophils, and other cells. And it's just an interesting and really bothersome complaint. And it often can be a challenge to treat. And amenable to our anti-inflammatories, and I think it's much better treated by our JAK/STAT pathway inhibitors. It's also treated with interferon. It's a little less well-treated with hydroxyurea (Hydrea®), I would say. So, I just wanted to cover that very unique symptom.



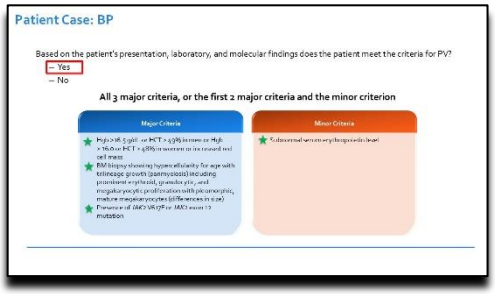
Slide 68: Management of PV-Associated Pruritus

And as I was just speaking about, interferon's effective. Ruxolitinib (Jakafi®) can be effective. And Jackie, I know I often have challenging cases I might ask you about, things like selective serotonin reuptake inhibitors, low doses of drugs being used for depression, and other conditions. Our dermatologists can sometimes help us with phototherapy. Antihistamines are simple and are a easy thing to try. But interestingly, hydroxyurea (Hydrea®), phlebotomy doesn't always change it, so it's something to note and a challenge and something we might look to better treat as we develop even more therapies in this space.



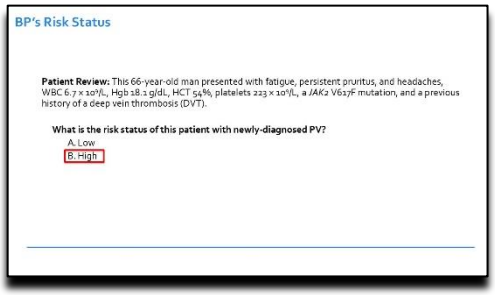
Slide 69: Patient Case: SO

So, we'll turn next to a case. Now, this is another man here in his 60s, SO, with a right lower extremity DVT. So, he has presented with fatigue and pruritus, as we just covered, headaches. No splenomegaly on exam. And when we look at his blood counts, we see that the white count's normal. There's no circulating blasts, but his hemoglobin is well above the normal range for a man. And if you remember back early in the presentation that he meets the WHO criteria of 16.5, 17 or 16 to 16.5 minimal, his hematocrit's also above the normal range. Platelets are normal. His marrow looks different. It's hypercellular and there's megakaryocytic changes. His karyotype's normal, but he carries a V617F *JAK2* mutation, and his erythropoietin level is subnormal.



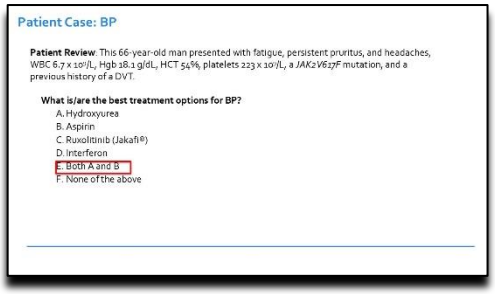
Slide 70: Patient Case: BP

So, here we have a case where we're questioning the criteria of PV and we've hit them all. He has an elevated hematocrit above normal and above WHO criteria. His bone marrow shows atypic megakaryocytic changes, and some, I think, was described as that of panmyelosis where he has increased activity across the cell lines. He has a JAK2 mutation, and his EPO level is subnormal.



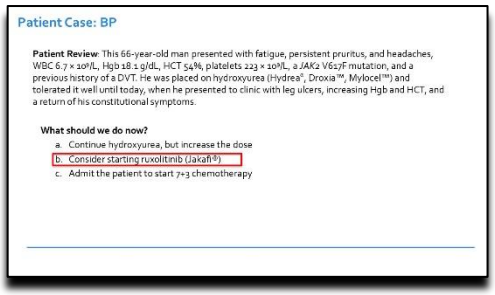
Slide 71: BP's Risk Status

So, how would we risk-stratify this patient? Remember, he's had a DVT, and he's over 60 years of age. Those are the two key factors. His clinical picture wasn't particularly surprising. He had an elevated hematocrit and hemoglobin, but the express of his blood counts weren't worrisome. For example, his white count wasn't higher, which can be an adverse prognostic factor and so on; and his bone marrow didn't have anything beyond PV. But this is a high risk based on age and thrombosis history.



Slide 72: Patient Case: BP

So, how would we treat this? Jackie just gave us this wonderful overview of things we might want to think, more boldly about, such as ruxolitinib (Jakafi®) as an alternative for interferons, whether it's Besremi® (ropeginterferon) or Pegasys® (pegylated interferon alfa-2a). But he needs aspirin and hydroxyurea (Hydrea®) would still be the standard, and I think that was the point I was trying to make earlier is that we seem a little bit stuck in trying to prove the long-term benefits and the merits of interferon, more complicated drug, and what's the risk/reward? So, stay tuned and we'll continue to update perhaps through the LLS and other channels on this hot topic.



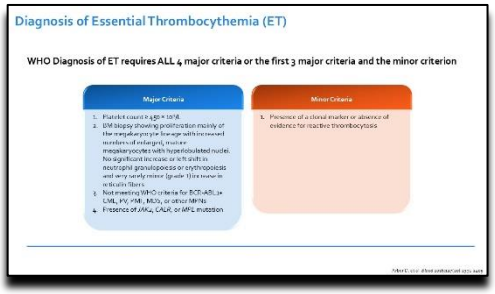
Slide 73: Patient Case: BP

So how about this story continues with this description where if you follow in the middle of the patient review, he's placed on hydroxyurea (Hydrea®) and tolerated it well. Unfortunately, he developed an unusual problem of leg ulceration, and so the surface of the anterior tibia region of the shins can often see ulcers or shin breakdown; and his blood counts aren't well controlled, and his symptoms aren't controlled. That is clearly an inadequate

therapeutic benefit for ruxolitinib (Jakafi®) and an adverse effect which is rare but possible and is very difficult to treat outside of discontinuation. This is a perfect candidate in whom we might start ruxolitinib (Jakafi®) as an alternative to provide hematocrit control, spleen responses Jackie covered, and probably very good symptom control. So that's not an uncommon scenario when it comes to adverse events.

Slide 74: Essential Thrombocythemia

Okay, last but not least, essential thrombocythemia or essential thrombocytosis.

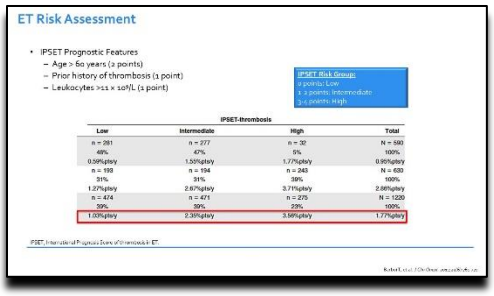


Slide 75: Diagnosis of Essential Thrombocythemia

As I did with the other diseases, we'll talk about the criteria. The one point I'd like to make here is that this disease can be very difficult to sort in comparison to early myelofibrosis. So to walk through it though, an elevated platelet count, of course, is the main feature. The bone marrow is very helpful here, because that's where you really can differentiate myelofibrosis from thrombocytosis. You need to see very little fibrosis or really no fibrosis to call a clinical scenario where you had elevated platelets and some of these other features; ET versus the possibility of prefibrotic myelofibrosis.

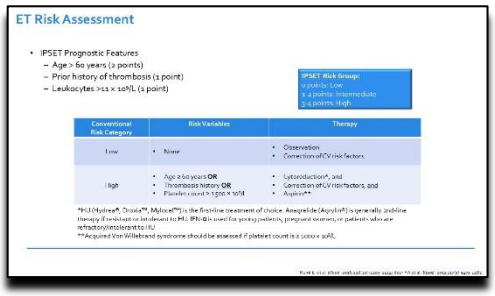
Our pathologists at MSK are often noncommital, I'll say, for good reason, because it's hard to know. They can meet WHO criteria for another MPN. They both generally have a driver mutation. They can have *JAK2*. They can increasingly have the more recently described mutation and a chaperone protein called calreticulin or a similar signaling pathway interruption mutation and gene *MPL*, particularly MPL515 which is also in the JAK/STAT cascade.

Minor criteria would be that presence of another clonal marker and the absence of reactive thrombocytosis; and that's noting that some patients don't have a driver mutation. They may have all the hallmarks of ET, but they don't have a driver mutation and still, this population still exists.



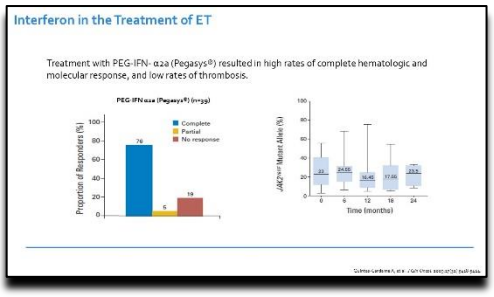
Slide 76: ET Risk Assessment

We risk-stratify these patients by a different model called the IPSET model, which weighs things much like some of the other MPNs, including age, prior thrombosis, and white blood cell count elevation; and it's possible to have further clarification of this model to have very low risk, low risk, intermediate, high. And accordingly, very low-risk patients may not even need aspirin low risk and so on. Patients will be treated, and those with high risk are generally going to be treated more definitively with cytoreductive therapy.



Slide 77: ET Risk Assessment

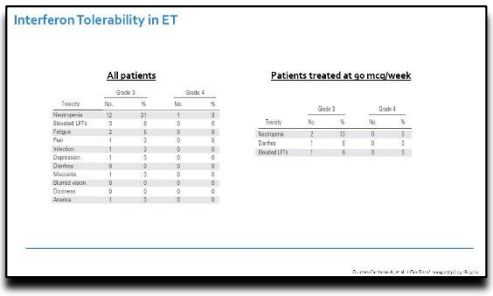
As is outlined here, the low-risk patients, again, some can be observed. Everyone should have their cardiovascular risk assessed and managed. In general, MPN or no. But MPN patients it's even more important. High-risk patients, again, based on age with thrombosis; and also extreme thrombocytosis. If you remember earlier on, we mentioned the possibility of having interference with clotting due to Von Willebrand's protein being pulled out of the blood or limited in its function by extreme thrombocytosis. That's an indication for treatment too. Those patients would benefit from cytoreduction in addition to good living and cardiovascular risk reduction and the addition of aspirin.



Slide 78: Interferon in the Treatment of ET

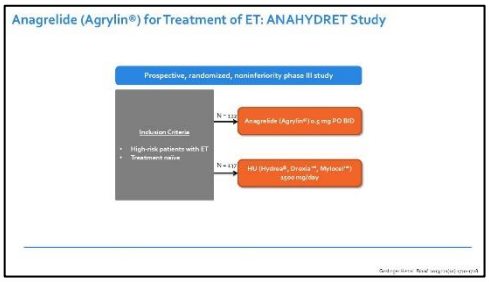
So, let me, once again, turn it over to Jackie to talk about some of the things she's already mentioned and a little bit of how ET is managed.

Dr. Dela Pena: So, similar to PV, we have interferon that could be used for ET. Again, this is one of the older studies back in 2009 that showed a proportion of responders of patients that responded with complete hematologic or molecular response and as well as low rates of fibrosis with interferon. And then we have the graph on the right that showed the responses with the *JAK2* mutant alleles.the ANAHYDRET study.



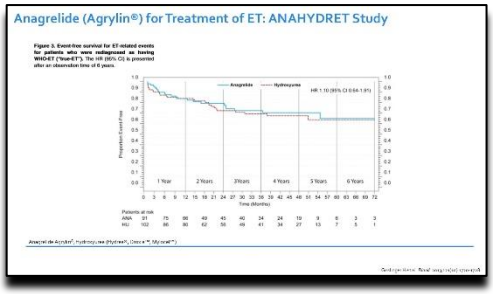
Slide 79: Interferon Tolerability in ET

Just a brief overview of tolerability with interferon. It's similar to the safety profile that I discussed before via the cytopenias, the serious psychiatric side effects or that maybe even some liver toxicity as well. So, these are the side effects that we have to keep in mind when we make decisions on how we choose therapy with interferon or other therapies, such as anagrelide or Agrylin® for treatment of ET. So this is the study.



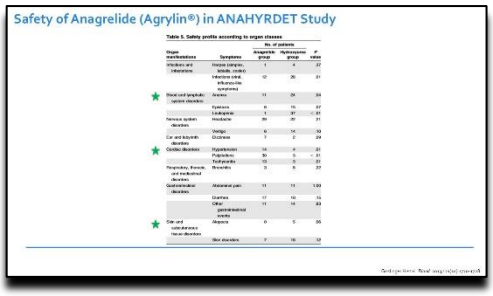
Slide 80: Anagrelide (Agrylin®) for Treatment of ET: ANAHYDRET Study

So, here we have anagrelide or Agrylin® for treatment of ET, or the ANAHYDRET study. This is another option for patients with ET. This is a noninferiority Phase III study. It included patients, high-risk patients with ET, treatment naïve as well. They were randomized to either anagrelide (Agrylin®) or hydroxyurea (Hydrea®), starting at Hydrea® (hydroxyurea) dose, starting at 1,500 milligrams a day, anagrelide (Agrylin®) 0.5 milligrams twice a day. And these doses were titrated based on complete response.



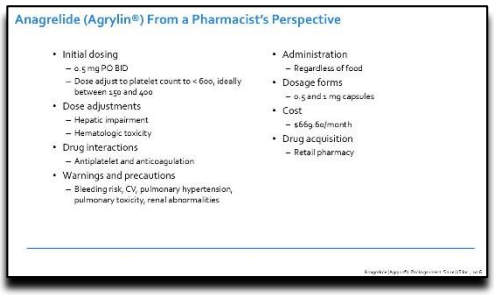
Slide 81: Anagrelide (Agrylin®) for Treatment of ET: ANAHYDRET Study

And overall, the event-free survival between the two cohorts, again, anagrelide (Agrylin®) or hydroxyurea (Hydrea®), were similar, with the blue line, which is showing anagrelide (Agrylin®), and hydroxyurea (Hydrea®), which shows the red line.



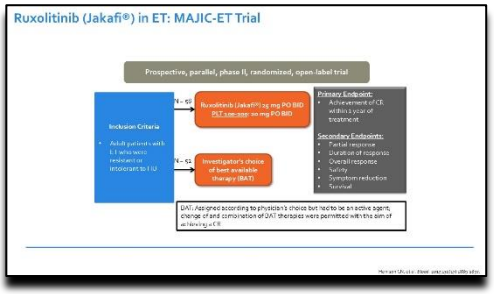
Slide 82: Safety of Anagrelide (Agrylin®) in ANAHYRDET Study

And, really, given similar efficacies and we have to review differences and side effects or the tolerability of both medications. They both had a similar discontinuation rate, but there are higher rates of cardiovascular side effects seen with anagrelide (Agrylin®) over hydroxyurea (Hydrea®). So, I really think it's a risk-adverse benefit to how you decide between hydroxyurea (Hydrea®) and anagrelide (Agrylin®). So, if we really want to minimize those cardiac disorders, the hypertension, again, on any other cardiovascular side effect, anagrelide (Agrylin®) may not be the best option because of the similar efficacy between both medications.



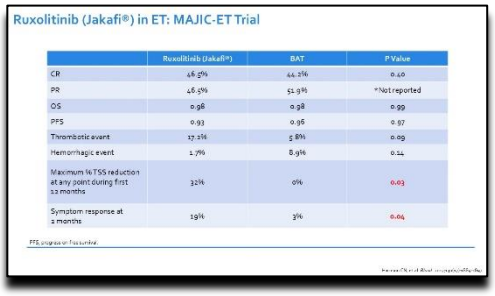
Slide 83: Anagrelide (Agrylin®) From a Pharmacist's Perspective

From a pharmacist standpoint, we have anagrelide (Agrylin®) dose, at least especially looking back at the trial. We had the 0.5 milligrams twice a day dose titrated based on the platelet count. It does come in 0.5 milligrams and 1 milligram capsules, so we have the ability to reduce the number of capsules per day for our patients if they need titrating. And this can be taken with or without food; and in terms of cost, it's a lot lower. I mean it's still fairly expensive but a lot lower than their other medication.



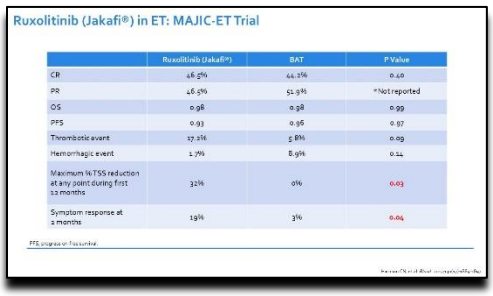
Slide 84: Ruxolitinib (Jakafi®) in ET: MAJIC-ET Trial

Also, ruxolitinib (Jakafi®) for ET. So you're probably wondering where does it come into play for ET? We have the MAJIC-ET trial. So, these patients are resistant, intolerant to hydroxyurea (Hydrea®), so highlighting that this is the second-line option. These patients are randomized either to receive ruxolitinib (Jakafi®) or best available therapy. The primary endpoint was CR at one year of therapy. Now this study intended to really answer the question of where does ruxolitinib (Jakafi®) play a role. But based on the inclusion criteria and that these patients were resistant in terms of hydroxyurea (Hydrea®), it's likely in the second-line setting.



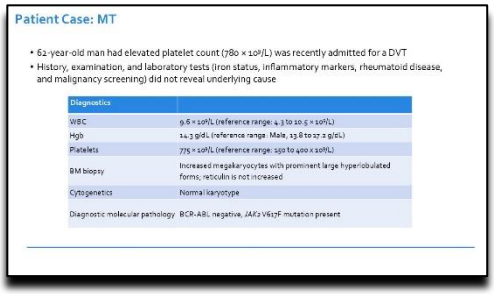
Slide 85: Ruxolitinib (Jakafi®) in ET: MAJIC-ET Trial

There are no differences in response rates, however, if we take a look at the thrombotic event from the chart in the middle, it was higher with, with ruxolitinib (Jakafi®) compared to the best available therapy arm. Hemorrhagic events was actually lower with ruxolitinib (Jakafi®). In terms of symptom score reduction, we did see an improvement with ruxolitinib (Jakafi®). So, this may be where it falls in the line and maybe why you would want to reach for this medication.



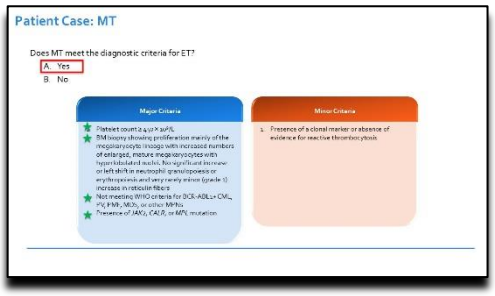
Slide 86: Ruxolitinib (Jakafi®) in ET: MAJIC-ET Trial

For side effects, and surprisingly similar to our other ruxolitinib (Jakafi®) trials we've had: anemia, thrombocytopenia, and that increased infection risk as well.



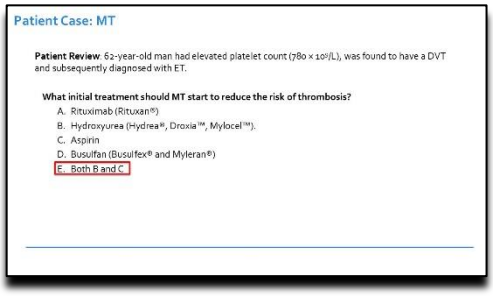
Slide 87: Patient Case: MT

Dr. Mauro: Well, thank you, Jacqueline. Thank you. So, one more case. This is patient MT. Apparently, these are all 60-year-old men that are in the clinic today. So, this is a 62-year-old man. We do have both guys and gals in the clinic with MPNs. Now, we have an elevated platelet count of 780, recently admitted for a DVT. So a broader work-up, was pursued: looking at iron status for the possibility of areactive thrombocytosis, inflammatory markers, and rheumatologic disease; malignancy screening, thinking that sometimes inflammation and thrombosis can be driven by other causes, was performed and was unyielding. So, this gentlemen's blood counts show essentially normal range white count and hemoglobin, elevated platelets, and a bone marrow smartly done showed megakaryocytic atypia with large hyper lobulated cells, so cells with a very atypical features. And importantly, reticulin is not increased, so no fibrosis. Normal karyotype, no BCR-ABL positivity, and the *JAK2* mutation.



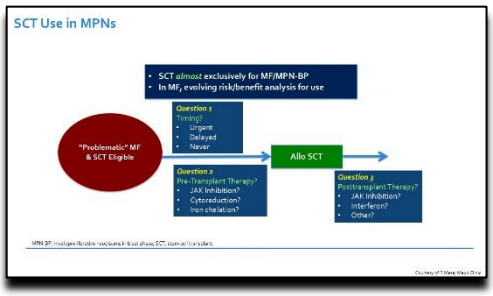
Slide 88: Patient Case: MT

So, does this patient meet criteria for ET? All the cases in our presentation were strong cases of their diseases. Platelet count was elevated. Bone marrow showed the changes that met the criteria for ET and, most importantly, confidently or fairly confidently moved us away from a myelofibrosis diagnosis. So there really wasn't any fibrosis, and the megakaryocytic morphology, as pathologists would tell us, how the megakaryocytes look, what features they have, is more classic for ET versus MF. Doesn't meet criteria for another MPN and has the *JAK2* mutation. Again, we might have a mutation-negative patient with a different clonal marker. Not the case here.



Slide 89: Patient Case: MT

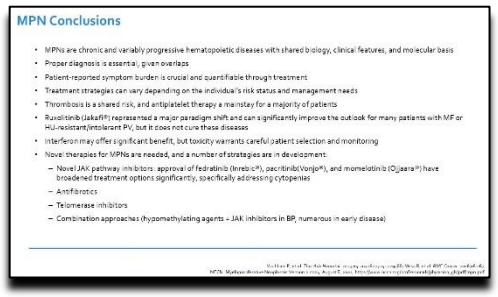
So, what do we do in this gentleman? He, unfortunately, meets criteria for cytoreductive therapy based on the fact that he is greater than 60 years of age and has a DVT in the setting of an MPN. So, rituximab (Jakafi®) is not used in this disease. That's a curveball. Hydroxyurea (Hydrea®), Jacqueline nicely outlined as a possibility. Aspirin is the standard for most patients with ET. Not absolutely all, but the overall majority; and Busulfan's (Busulfex®) a very old alkylator drug which had, unfortunately, more side effects than our current drugs. It really is no longer used. So, both B and C is the correct answer.



Slide 90: Stem Cell Transplant Use in MPNs

So, in the last few moments, we cannot forget about, or autologous stem cell transplant is an active discussion. We often partner and segue into transplant, especially for myelofibrosis. I think most certainly, if eligible for a patient who has a blastic phase of myelofibrosis, and then, of course, as I mentioned at the very beginning, myelofibrosis at very high risk who has perhaps had now as an unbalanced risk/benefit equation when it comes to therapy. They may have significant complications already from the disease and very poor treatment options, or have had poor response to therapy, or may have evolved during therapy with new mutations or progressive splenomegaly or worsening symptoms.

So, it's problematic though. What's the timing of it? Is it something to do early, or where's the line in the sand? I think there's generally often a role to try to improve the disease, but JAK inhibitors and cytoreductive agents can make a major clinical difference. I think an early discussion is warranted; and, of course, our transplant colleagues and I — and us, not just I — all of us in the community, do research into how we can manage the disease potentially afterwards, given the fact that we have targeted therapies. JAK inhibitors are often incorporated into the post-transplant setting to allow for engraftment in GVL (graft-versus-leukemia) while we continue to, to minimize any output, from the disease manifestations.



Slide 91: MPN Conclusions

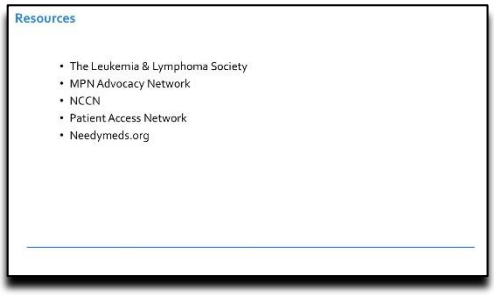
So, in conclusion, and again I want to just have a huge thanks to LLS for sponsoring and allowing us to present and Jackie for yeoman's work to present all the therapeutics. She's a phenomenal pharmacist partner, not only here but in the clinic and in the wards. MPNs are chronic and variable progressive diseases of the hematopoietic system. They share a lot, but you have to carefully parse them out, and we're getting a lot smarter about how to do that and how to care, understand them through molecular testing. So, proper diagnosis is essential.

My favorite thing to teach a young physician of how you work with me in a clinic is if someone walks in the clinic with a *JAK2* mutation and a high platelet count, we have no idea what that is. We need to really sort it because it could be mass polycythemia, thrombocytosis, myelofibrosis at an early stage. It can be any of them.

Patients are at the center of this, so their symptom burden and managing that is crucial and quantifiable with then the symptom assessment tools we develop. Treatment strategies depend on the comorbidity status and their needs. Thrombosis is a shared risk, and antiplatelet therapy is a cornerstone of our treatment. Clearly the JAK inhibitors, the

identification of the mutation and development of now a series of drugs, as Jackie has outlined for us, is a paradigm shift; and the research continues into combinations, which we really haven't had any major conclusions yet. We've had a lot of research, and I think we should stay tuned there. We may have some breakthroughs. Novel agents continue to be explored.

Interferon, a drug that's been with us for decades, offers benefit, is complex. It may offer long-term benefits and molecular response improvements, which is the moniker of some of the single-arm studies which Jackie shared with us. But I think randomized trials have have left us a little bit short, so stay tuned. And novel therapies, of course, I think, as we hopefully covered in this updated talk, really are helping us with multiple JAK2 inhibitors; and there, there's continued research into other targets, antifibrotics, telomerase inhibitors — which are now approved in other disease areas — and combinations that they mentioned.

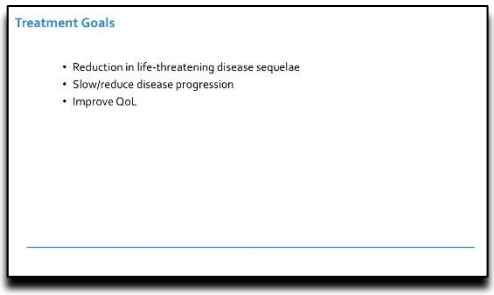


Slide 92: Resources

So, again, resources for patients, of course, with the LLS who have been partners for patients and providers of leukemia for the ages. MPN Advocacy Network is a very good place to look for both clinical trials and experts and patient information. Of course, the National Comprehensive Cancer Network gives us guidelines and has both patient- and provider-facing sites and tools. Patient Access Network and Needymeds.org, which is something Jackie probably knows a bit more about, and other websites which patients can look at for patient assistance programs and support for therapies.

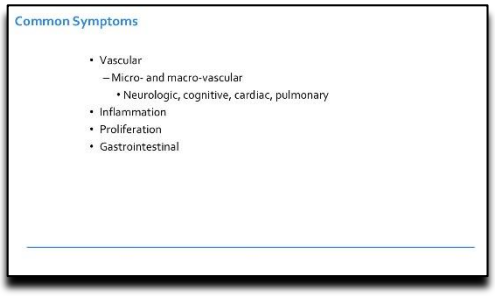
So, with that, I'll say thank you and I'll thank Jackie and let her have the last word.

Dr. Dela Pena: Yeah, thank you, Dr. Mauro. And thank you as well to The Leukemia & Lymphoma Society really for, for having us here.



Slide 93: Treatment Goals

Carolanne Carini, MS, BSN, RN, BMTCN: Treatment goals include reduction in life-threatening disease sequelae, such as blood clots and thrombolic events; reducing or slowing the disease progression; and improving the quality of life by decreasing symptoms and reducing the amount of time patients are at medical appointments; therefore, increasing the amount of time they are with family/friends and doing activities they enjoy.



Slide 94: Common Symptoms

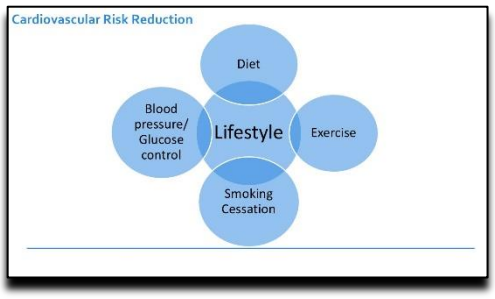
Common symptoms can be broken into, down into several different categories. Vascular symptoms can present as micro- or macro-vascular symptoms. Microvascular symptoms can feel most troubling to patients and may lead to an overall decreased feeling of well-being and decreased quality of life. Microvascular symptoms can be neurologic in nature, such as headaches, dizziness, neuropathy, paresthesias, and changes in vision.

Cognitive deficit such as difficulty concentrating, brain fog, memory loss, and difficulty with word finding are also some common symptoms reported. In addition, microvascular symptoms may be cardiac in nature, such as angina.

Macrovascular symptoms are more imminently life threatening, such as cardiac, which might be myocardial infarct; neurologic, such as TIA or stroke; pulmonary, such as a pulmonary embolism.

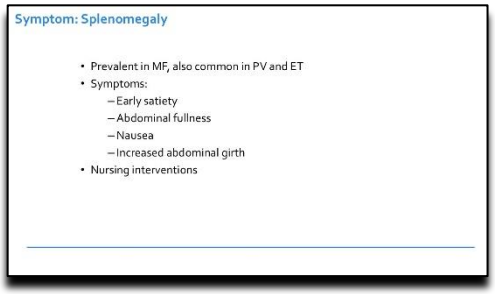
Inflammation symptoms also include pruritus, such as itching, which is most commonly occurring after showering; bone pains; and fevers. Proliferation symptoms, such as fatigue, night sweats, decreased energy, ability to do activities.

Lastly, gastrointestinal symptoms — which are mostly associated with splenomegaly — such as fullness in the stomach and early satiety. GI symptoms can also manifest as nausea and abdominal pain and weight loss.



Slide 95: Cardiovascular Risk Reduction

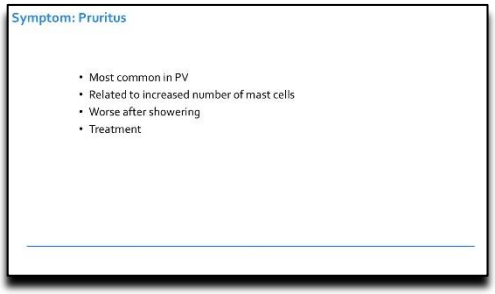
An important aspect of managing life-threatening side effects is by reducing cardiovascular risk. This is, in part, driven by lifestyle modifications such as maintaining a healthy weight and following a heart-healthy diet; doing moderate exercise most days of the week. The American Heart Association recommends 150 minutes of cardiovascular activity each week or 30 minutes a day of exercise five days a week. If a patient smokes, the best thing they can do is enter into a smoking cessation program and stop smoking. For patients with high blood pressure or diabetes, preventing organ damage by maintaining normal blood pressure and blood sugar control is also very important.



Slide 96: Symptom: Splenomegaly

A common symptom patients may present with or report is splenomegaly. Splenomegaly is most prevalent in patients with myelofibrosis, but it is also seen in patients with PV and ET. In myelofibrosis, bone marrow scaring makes hematopoiesis more difficult, which leads to an enlarged spleen. In PV and ET, increased production of red blood cells may lead to the enlarged spleen.

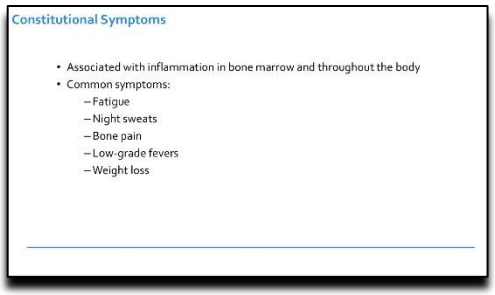
Nursing interventions include educating patients on eating small, frequent meals as tolerated, and, also, a referral to the nutritionist or dietitian may be helpful. Treatment with ruxolitinib may also help the symptom by reducing spleen size. Abdominal ultrasound to check the spleen size may be part of a yearly restaging and assessing efficacy of treatments.



Slide 97: Symptom: Pruritus

Pruritus is the most commonly reported symptom in patients with PV. While the pathophysiology is not completely understood, it is believed to be related to increased number and functional differences in mast cells, which can cause an exaggerated response in the inflammation pathway.

Pruritus tends to be worse after showering and generally starts in the lower extremities. It eventually works its way up to the full body but generally does not affect the patient's head. It seems to be worse in females and those with fair complexions, and is also generally worse in the winter months. Pruritus can be treated with H_2 blockers, antihistamines, or SSRIs. Treatment with interferon and ruxolitinib (Jakafi®) also effectively helps with the symptoms.



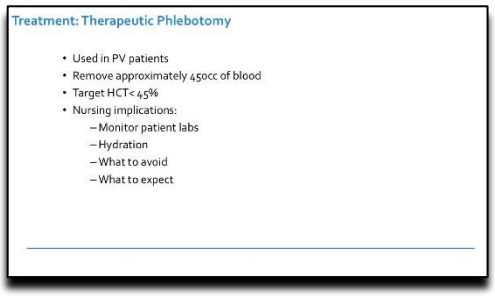
Slide 98: Constitutional Symptoms

Constitutional symptoms are generally associated with inflammation in the bone marrow as well as throughout the body. These symptoms are generally reported as fatigue, night sweats, bone pains, low grade fevers, and weight loss. Fatigue and bone pain are major contributors of decreased quality of life and overall decreased feelings of well-being.

It is important to educate patients on sleep hygiene practices, such as sleeping, going to sleep at the same time each night; setting an alarm to wake up in the morning; sleeping in a

cool, dark, quiet room without distractions. That means avoid reading and watching TV in bed.

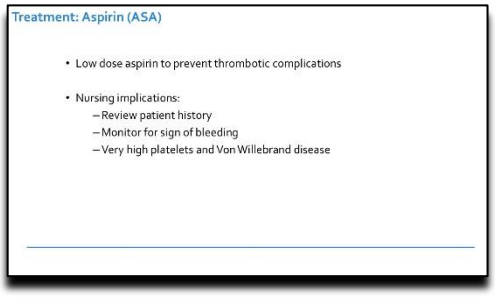
It is also important to educate patients on getting exercise to help combat cancer-related fatigue. Setting a schedule for activities and rest throughout the day can also help patients optimize their energy.



Slide 99: Treatment: Therapeutic Phlebotomy

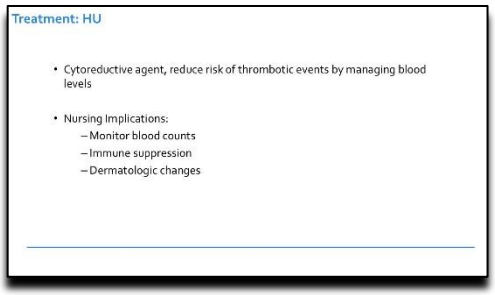
Moving onto some treatment options. Therapeutic phlebotomy is commonly used in patients with polycythemia vera. The target goal is to keep the hematocrit less than 45% for males and less than 42% for females. This is according to the NCCN Guidelines. Patients who undergo therapeutic phlebotomy have approximately 450 cc's of blood removed, which is the equivalent to a unit of blood.

Some nursing implications for patients undergoing this procedure is monitoring the patients' bloodwork, especially their hematocrit levels; encouraging the patients to stay well-hydrated prior to their therapeutic phlebotomy procedure, as well as after the procedure; and to instruct the patients to avoid caffeine and alcohol prior to the procedure. Patients may experience soreness or pain at the needle insertion site, as well as some bruising. Some patients may feel light-headed, and IV hydration may be warranted if, after the phlebotomy is completed.



Slide 100: Treatment: ASA

Low-dose aspirin is commonly used in patients with PV and ET to prevent thrombotic complications. Each patient's personal history should be carefully reviewed to ensure the benefits outweigh the risk. Nursing implications include reviewing the patient's medical history to see if they have a past history of severe bleeding, GI upset, including ulcers, chronic alcohol use, concurrent anticoagulation therapy, asthma, or renal dysfunction. Nurses should monitor and educate patients and caregivers about signs and symptoms of bleeding. It is important to note: patients with very high platelet counts, over a million, should not use aspirin, as they are at an increased risk for bleeding. These patients should have bloodwork done to assess for Von Willebrand's disease.

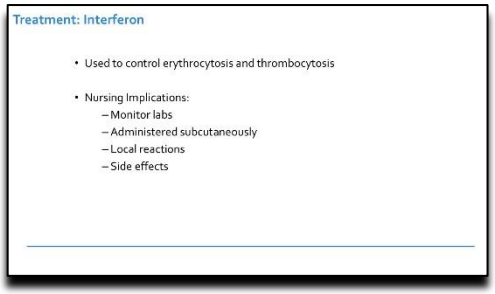


Slide 101: Treatment: Hydroxyurea

Another common treatment is hydroxyurea. It is a pill that patients take at home. It is a cytoreductive agent, and it helps to keep the blood counts at stable levels. Some nursing implications include monitoring blood counts. This medication may decrease or suppress the immune system, so it is important to educate patients and family members to report fevers to their clinical team.

This medication may also cause mouth sores. Generally, these mouth sores resolve on their own, but for some patients, they may require prescription intervention. Skin changes, such as ulcers to the lower extremities, rashes, hyperpigmentation, and alopecia, may also occur with this medication.

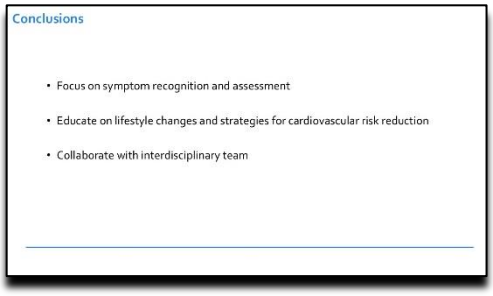
Patients on Hydrea® (hydroxyurea) may have a higher risk to develop squamous cell carcinoma, so they should be encouraged to follow with a dermatologist for yearly screening visits. Hydrea® (hydroxyurea) is started at lower doses and then adjusted according to the lab values. So, it is important to inform the patients that they will have dose adjustments, either higher or lower, throughout the course of their treatment.



Slide 102: Treatment: Interferon

Interferon is a subcutaneous injection used to control high red blood cells and high platelets. The nurse would review regular lab work to monitor for neutropenia, anemia, and low platelet counts. In addition, it is important to monitor liver function tests as well as thyroid function tests. Patients should also be educated to report any signs and symptoms of hyperthyroidism to their clinical team. Subcutaneous teaching will need to be done, and oftentimes this medication is not available in prefilled syringes. So, the nurse will also have to review with the patient and caregivers how to draw up the appropriate dose from the vial. It is important that the patients and caregivers are able to do a teach-back so you can be assured they are giving themselves the correct dose at home.

Local reaction, such as redness or irritation, are also common. Other side effects to monitor include fatigue, generalized weakness, depression, infections due to neutropenia, and sometimes cognitive changes. Always monitor patients closely for toxicities.



Slide 103: Conclusions

So, in conclusion, symptom recognition and assessment is the main focus of the nurse's role in monitoring and providing interventions. It is important for the nurse to be able to assess and recognize subtle symptom complaints. Educate the patient on lifestyle changes to reduce cardiovascular risks as well as help with symptoms they may be experiencing.

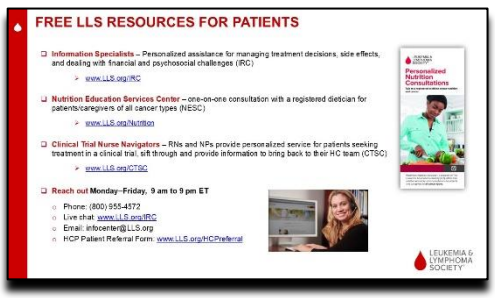
Collaborating with the multidisciplinary team to help patients as needed with the emotional distress, symptom management, and any issues with their prescriptions. Working together with the interdisciplinary team, nurses can help to ensure that patients enjoy an optimized quality of life.

Slide 104: LLS Resources for Healthcare Professionals

Lauren Berger: Thank you, Dr. Mauro, Dr. Dela Pena and Nurse Carini for your presentations, and for your dedication and commitment to caring for patients.

I am now pleased to share free resources from The Leukemia & Lymphoma Society. LLS is the leading source of free blood cancer information, education and support for patients, survivors, families, and healthcare professionals. LLS helps navigate their cancer treatment and ensures they have access to quality affordable and coordinated care.

LLS offers Free CE and CME accredited healthcare professional education including live and recorded webinars, such as this one, accredited in-person education, and a podcast channel for healthcare professionals, where you can listen to interesting discussions on treatment, side-effect management and more. New topics are added every few weeks. I encourage you to access these, as well as videos and fact sheets for HCPs at www.LLS.org/CE and to share these resources with your colleagues.



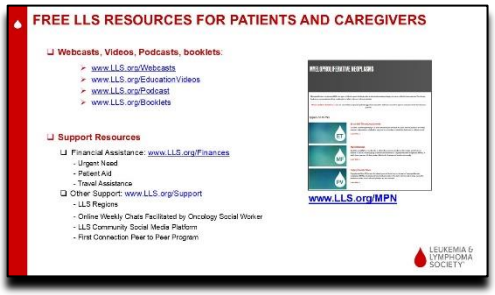
Slide 105: Free LLS Resources for Patients

LLS Information Specialists are highly trained oncology social workers and nurses who provide accurate, up-to-date disease, treatment and support information, including financial. Patients can contact them directly, or you can complete a Referral form. They can also help you order free copies of booklets to give to your patients and caregivers. LLS offers free nutrition consultation with one of our registered dietitians. Contact them using the link or the phone number listed here to refer to a patient.

Our Clinical Trial Support Center Nurse Navigators are Registered Nurses and Nurse Practitioners with expertise in blood cancers. CTSC Nurse Navigators work one on one with patients, via telephone, to provide user friendly information, help find appropriate clinical trials, personally assist them throughout the entire clinical trial process and provide them with information for the patient to bring back to their healthcare professional. They also work directly with healthcare professionals. This is a unique service from LLS. I hope you will consider all of these specialists as an extension of your team.

Slide 106: Here to help: LLS commitment

Here is a brief overview of the Clinical Trial Support Center Process for supporting patients. The goal is not to enroll every patient in a trial, rather to increase opportunities for participation by facilitating informed decision making and minimizing logistical barriers for the patient. They work in collaboration with the patient's healthcare team to decide if a clinical trial is right for them. Ultimately, they educate, support, and empower patients to be active participants in and have control over their treatment decisions.



Slide 107: Free LLS Resources for Patients and Caregivers

LLS offers blood cancer disease specific information and support resources for patients and caregivers, including telephone and web education programs, videos, podcasts and booklets. I encourage you and your colleagues to stay up to date on the availability of LLS' Financial Assistance programs and other resources, using links on these slides.

Slide 108: Free LLS Resources for Your Patients

Through targeted and culturally appropriate programs and services, we are committed to addressing needs of minoritized communities impacted by a blood cancer and those facing barriers to optimal care. Our booklets are available in English and Spanish and our Information Specialists and other specialists, consult with patients in additional languages. I hope this information will be helpful to you as you care for your patients. If you would like more information for yourself or to support your patients on any of the LLS resources, please contact an Information Specialist at 800.955.4572 or www.LLS.org/support

Slide 109: Thank You

Thank you again to our presenters and thank you to everyone listening.