### Myeloproliferative Neoplasms (MPNs): Diagnosis, Treatment and Side Effects Management

#### Transcript

<table>
<thead>
<tr>
<th>Question</th>
<th>Slide Name &amp; Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) The major mutation responsible for activating myeloproliferative neoplasms is:</td>
<td>JAK2 V617F Mutation discovery in MPNs: ‘the other BCR-ABL’ Slide 7</td>
</tr>
<tr>
<td>a) JAK2</td>
<td></td>
</tr>
<tr>
<td>b) BCR-ABL</td>
<td></td>
</tr>
<tr>
<td>c) P53</td>
<td></td>
</tr>
<tr>
<td>d) BRCA1</td>
<td></td>
</tr>
<tr>
<td>2) Risk stratification in myelofibrosis includes:</td>
<td>Risk Stratification in Myelofibrosis Slide 22</td>
</tr>
<tr>
<td>a) Age</td>
<td></td>
</tr>
<tr>
<td>b) Constitutional symptoms</td>
<td></td>
</tr>
<tr>
<td>c) Infection history</td>
<td></td>
</tr>
<tr>
<td>d) a and b</td>
<td></td>
</tr>
<tr>
<td>e) All of the above</td>
<td></td>
</tr>
<tr>
<td>3) Low risk, asymptomatic myelofibrosis is managed with:</td>
<td>Risk-Adapted Treatment of Myelofibrosis Slide 24</td>
</tr>
<tr>
<td>a) JAK2 inhibitor</td>
<td></td>
</tr>
<tr>
<td>b) Ruxolitinib</td>
<td></td>
</tr>
<tr>
<td>c) Observation</td>
<td></td>
</tr>
<tr>
<td>d) Interferon</td>
<td></td>
</tr>
<tr>
<td>4) Dose adjustments of interferon are required in the setting of:</td>
<td>Interferon From a Pharmacist’s Perspective Slide 26</td>
</tr>
<tr>
<td>a) Pneumonitis</td>
<td></td>
</tr>
<tr>
<td>b) Renal impairment</td>
<td></td>
</tr>
<tr>
<td>c) Fever</td>
<td></td>
</tr>
<tr>
<td>d) Congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>5) Ruxolitinib is dose adjusted for:</td>
<td>Ruxolitinib from a pharmacist’s perspective Slide 33</td>
</tr>
<tr>
<td>a) Renal impairment</td>
<td></td>
</tr>
<tr>
<td>b) Hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>c) Hematologic toxicity</td>
<td></td>
</tr>
<tr>
<td>d) a and c</td>
<td></td>
</tr>
<tr>
<td>e) All of the above</td>
<td></td>
</tr>
<tr>
<td>6) The ECLAP trial demonstrated that thrombotic complications can be reduced in patients with polycythemia vera using:</td>
<td>ECLAP Trial – Results Slide 45</td>
</tr>
<tr>
<td>a) Low molecular weight heparin</td>
<td></td>
</tr>
<tr>
<td>b) Heparin</td>
<td></td>
</tr>
<tr>
<td>c) Warfarin</td>
<td></td>
</tr>
<tr>
<td>d) Aspirin</td>
<td></td>
</tr>
</tbody>
</table>
### Myeloproliferative Neoplasms (MPNs): Diagnosis, Treatment and Side Effects Management

#### Transcript

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7) Unacceptable non-hematologic hydroxyurea toxicity includes:</td>
<td>Definition of HU Resistance/Intolerance Slide 48</td>
</tr>
<tr>
<td>a) Spenomegaly</td>
<td></td>
</tr>
<tr>
<td>b) DVT</td>
<td></td>
</tr>
<tr>
<td>c) Fever</td>
<td></td>
</tr>
<tr>
<td>d) Infection</td>
<td></td>
</tr>
<tr>
<td>8) In patients with polycythemia vera, interferon most commonly results in:</td>
<td>Interferon in the Treatment of PV Slide 49</td>
</tr>
<tr>
<td>a) Complete response</td>
<td></td>
</tr>
<tr>
<td>b) Partial response</td>
<td></td>
</tr>
<tr>
<td>c) Disease stabilization</td>
<td></td>
</tr>
<tr>
<td>d) Disease progression</td>
<td></td>
</tr>
<tr>
<td>9) Polycythemia vera-associated pruritus may be responsive to:</td>
<td>Management of PV-associated pruritus Slide 56</td>
</tr>
<tr>
<td>a) Phlebotomy</td>
<td></td>
</tr>
<tr>
<td>b) Cytoreductive therapy</td>
<td></td>
</tr>
<tr>
<td>c) Selective serotonin reuptake inhibitors</td>
<td></td>
</tr>
<tr>
<td>d) Topical steroids</td>
<td></td>
</tr>
<tr>
<td>10) When treating essential thrombocythemia with interferon, you can expect:</td>
<td>Interferon in the Treatment of ET Slide 66</td>
</tr>
<tr>
<td>a) The same results as using interferon in polycythemia vera</td>
<td></td>
</tr>
<tr>
<td>b) Higher complete response rate than seen in polycythemia vera</td>
<td></td>
</tr>
<tr>
<td>c) Higher partial response rate than seen in polycythemia vera</td>
<td></td>
</tr>
<tr>
<td>d) Lower disease stabilization rate than seen in polycythemia vera</td>
<td></td>
</tr>
<tr>
<td>11) The most common hematologic toxicity of interferon in essential thrombocythemia is:</td>
<td>Interferon Tolerability in ET Slide 67</td>
</tr>
<tr>
<td>a) Anemia</td>
<td></td>
</tr>
<tr>
<td>b) Neutropenia</td>
<td></td>
</tr>
<tr>
<td>c) Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>d) All of the above</td>
<td></td>
</tr>
</tbody>
</table>

### Nursing Considerations in treating patients with Myeloproliferative Neoplasms (MPNs)

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>12) Therapeutic phlebotomy removes approximately:</td>
<td>Therapeutic phlebotomy Slide 79</td>
</tr>
<tr>
<td>a) 30 cc of blood</td>
<td>Learning objective: Describe strategies to manage treatment side effects as well as potential long-term and late effects of treatments for MPNs</td>
</tr>
<tr>
<td>b) 150 cc of blood</td>
<td></td>
</tr>
<tr>
<td>c) 300 cc of blood</td>
<td></td>
</tr>
<tr>
<td>d) 450 cc of blood</td>
<td></td>
</tr>
</tbody>
</table>
13) Hydroxyurea is used as a cytoreductive therapy. HCP’s should monitor the patients for:
   a) Increased BUN and creatinine
   b) Skin rash, pigmentation changes, nail changes
   c) Shortness of breath and dizziness
   d) Increased abdominal girth

14) Treatment for Splenomegaly in patients with myeloproliferative neoplasms includes:
   a) Hydroxyurea, aspirin and liquid diet
   b) Eat small, frequent meals as tolerated
   c) Hydroxyurea, interferon and ruxolitinib
   d) b and c
Myeloproliferative Neoplasms (MPNs): Diagnosis, Treatment and Side Effects Management

Transcript

SLIDE 1: Myeloproliferative Neoplasms (MPN): Diagnosis, Treatment and Side Effects Management

Lauren Berger: Hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), thank you for sharing your time with us for this continuing education program on myeloproliferative neoplasms diagnosis, treatment, and side effect management.

SLIDE 2: Welcome and Introductions

- Describe the types of myeloproliferative neoplasms, including myelofibrosis, polycythemia vera, and essential thrombocythemia
- Identify tests used to diagnose disease and monitor treatment
- Explain the overarching goals of treatment for the various types of myeloproliferative neoplasms.
- Explain approved and emerging treatment options for all myeloproliferative neoplasms, including stem cell transplantation, and the role of clinical trials.
- Describe strategies to manage treatment side effects as well as potential long-term and late effects of treatments.

We're fortunate to have as our presenters Dr. Michael Mauro, one of the nation’s leading experts in myeloproliferative neoplasms, Dr. Troy Horvat, a clinical oncology pharmacist and Ms. Marisa Hine, a Nurse Practitioner. We appreciate their dedication and their commitment to caring for patients living with blood cancers.

SLIDE 3: Faculty

Dr. Mauro is the leader of the Myeloproliferative Neoplasms Program and Clinical Director of the Leukemia Service at Memorial Sloan Kettering Cancer Center. Dr. Horvat is a Clinical Pharmacy Specialist in the Leukemia Service in the Department of Pharmacy at Memorial Sloan Kettering Cancer Center, and Ms. Hine is a Nurse Practitioner in the Leukemia Service at Memorial Sloan Kettering Cancer Center, in New York. Special thanks to Dr. Mauro, Dr. Horvat and Ms. Hine for volunteering their time and expertise with us.

SLIDE 4: Myeloproliferative Neoplasms: Diagnosis, Treatment, and Side Effect Management

Dr. Mauro and Dr. Horvat, I am now pleased to turn the program over to you. Dr. Michael Mauro: Thank you, and thank you to the LLS and to Walgreens for having this program on myeloproliferative neoplasms.
SLIDE 5: Learning Objectives

Our objectives today are numerous.

- Describe the types of myeloproliferative neoplasms (MPNs), including myelofibrosis (MF), polycythemia vera (PV), and essential thrombocythemia (ET).
- Identify tests used to diagnose disease and monitor treatment of MPNs.
- Explain the overarching goals of treatment for the various types of MPNs.
- Explain approved and emerging treatment options for all MPNs, including stem cell transplant and the role of clinical trials.
- Describe strategies to manage treatment side effects as well as potential long-term and late effects of treatments for MPNs.

SLIDE 6: MPN Overview: Timeframes

So, let’s get started. If you think about MPNs as an overall type of condition or diagnosis, there is definitely more of a chronic or an early stage of several of the MPNs and the possible evolution of these diseases. And, in this figure, you can see on the left how there’s a long lead time for patients initially diagnosed with polycythemia, essential thrombocythemia\(^1\) and early myelofibrosis\(^2\). The risks for those patients are more modest and we mainly focus on vascular events. Patients can have progression of polycythemia and thrombocytosis to myelofibrosis or can present with myelofibrosis, and these situations are more complicated. We’re often addressing progressive constitutional symptoms. We’re watching for organomegaly and extramedullary hematopoiesis, abbreviated EMH, or progressive cytopenias.

Probably the biggest risk of these diseases overall, for all of these conditions, actually, but relatively greater or less depending on the type, is leukemic transformation. Of course, this is a high-risk situation, which can lead to early death. And this more rapid moving phase or more complicated phase of MPNs has a shorter timeframe of just a few years. Hopefully, we can change this algorithm and these timeframes to make these diseases much more treatable and long-term successes greater.

SLIDE 7: JAK2 V617F Mutation discovery in MPNs: ‘the other BCR-ABL’

One tremendous advance in this field came about ten years ago with the discovery of the molecular basis of MPNs. And that is discovery of the JAK2 point mutation called V617F. I like to refer to it as the other BCR-ABL. BCR-ABL was a specific mutation identified in the other major myeloproliferative disorder called CML (chronic myeloid leukemia), which we’re not speaking about today.

---

\(^1\) Thrombocytosis is synonymous with essential thrombocythemia in this circumstance.

\(^2\) The presentation focuses on primary myelofibrosis and does not focus on acquired myelofibrosis.
But, multiple laboratories--the headlines, if you will, which are listed here--simultaneously arrived at the notion that there was a single molecular driver that was common to the MPNs that we’re discussing today. And this work came in a very rapid fashion, and it really changed the way we view these diseases and open up the door for a pathway for novel treatment.

**SLIDE 8: JAK2 Signaling in MPNs: Finding the ‘Driver’**

JAK2 signaling in MPNs, again, is referred to as a driving mutation or something that is essential to the disease. In essence, this diagram you’re seeing shows what happens when a point mutation can alter a kinase or an enzyme that’s highly regulated. And, in this case, it’s something that’s related to blood production, in general, erythropoiesis as well as myelopoiesis to a degree. And, in the normal state, an enzyme like a wild-type JAK2, as you see on the left, binds and a receptor, agonist, is bound, and there’s dimerization or activation of the enzyme, and a pathway is activated.

One the right, you can see that an abnormal version of this enzyme may be activated without a ligand or without a normal signal, and can cause auto-activation, and this enzyme is now not regulated. This enzyme, this JAK2 enzyme, in its altered form, is highly prevalent in myeloproliferative disorders. And you can see the frequency is greater than 95% in polycythemia and accounts for a good proportion of patients with ET and PMF.

**SLIDE 9: Frequency and Distribution of ‘Driver’ and Other Mutations in Patients with MPNs**

In addition to JAK2, this opened up the molecular research in MPNs. And we now know that there are a number of cooperating or additional mutations that are observed. And, to the right of this figure, you can see that again, if a broad number of patients are screened, a very high number will have a JAK2 mutation. For those who don’t have a JAK2 mutation, a number of other driver mutations have been identified, the newest of which is called CALR, or calreticulin.

And then, there’s a long list of what I would call cooperating or additional mutations that can either come simultaneously with JAK2, may precede JAK2, and certainly are under careful scrutiny to see how they cooperate and how they contribute to the diseases, that we know as myeloproliferative disorders, their risk, their progression, particularly, their risk of progression to leukemia.

And it’s clearly a fact that many patients with myeloproliferative disorders have multiple mutations. The inset figure on the right, you can see that, in myelofibrosis, for example, many patients have more than one mutation. Some have as many as four or five. And the figure on the left is a very intricate way to look at the association between mutations. The width of the bands in the figure is showing how often these mutations are paired together, and the arc shows the frequency that you see these paired together. So, a lot is known about cooperating mutations and additional mutations in MPNs.
SLIDE 10: Molecular International Prognostic Scoring System in Myelofibrosis

So much so, that in this next figure, you can see that this information is being integrated into the way we view a patient’s prognosis and outcome with, for example, myelofibrosis. This data set here, although not fully integrated into our thinking and our algorithms, shows that if you take the usual International Prognostic Scoring System, or IPSS, and add in the presence or absence of certain key mutations, you can actually better clarify and understand which patients may be at higher risk using something called MIPSS, or Molecular International Prognostic Scoring System. So, I think we need to stay tuned as we learn more about molecular drivers beyond the large ones that have been discovered, and clearly, have led to therapeutics that can cooperate and help us understand how patients’ prognosis may look, and how their response to therapy may be, and most importantly, what their risk of leukemia may be.

SLIDE 11: Assessing MPN Patient Risk: Prognostic Models

That being said, we have some very well established prognostic models and MPNs, which are outlined on this table. I’ll leave this here for your reference, and we’re going to get to each disease and its specific prognostic modeling as we go through them. But, you can see that both ET, PV, and myelofibrosis or PMF have commonalities in some of the predictors of prognosis - the patient’s age, the white blood cell count with the main thinking being that the higher the white count, the greater the thrombotic risk, and to a degree, the greater the complexity of the disease or the status of the disease.

Anemia is an unfortunate finding and a complication, mainly, of myelofibrosis and its prognostic constitutional symptoms contribute as well - circulating blasts in the blood, and for the more indolent MPNs like ET and PV, thrombosis, prior to the known diagnosis or early in diagnosis, is a poor prognostic marker. And we can definitely learn a lot more about our patients’ needs and treatment and how to best handle them by accurate prognostic modeling.

SLIDE 12: Symptom Burden in MPNs

Beyond the science of MPNs, a lot of attention has been paid and should be paid to patient symptoms, as these conditions are unique and they can cause a number of different subjective symptoms. This figure just describes a few of the things that MPN patients complain of and suffer with because of certain biologic mechanisms such as splenomegaly triggering early satiety or getting full easy, weight loss, nausea, abdominal pain. These conditions often trigger a catabolic state. Patients have chronic fatigue, night sweats, inflammatory pathways such as pruritus and bone pain, and of course, a number of vascular symptoms both micro and macrovascular symptoms.

3 Macrovascular complications would be myocardial infarction, stroke, or pulmonary embolus and microvascular complications such as headache, dizziness, paresthesia, livedo reticularis, erythromelalgia, and visual changes.
SLIDE 13: Formally Assessing MPN Symptom Burden
In order to better quantify and understand these symptoms, tools have been developed and have evolved to help us see where patients are at baseline and track them with therapy. A symptom assessment form for myelofibrosis has now been in use for more than six years, and was a bit simpler early on, and has evolved to include vascular and psychological symptoms, which many patients suffer with. And these are now well-validated tools that have been translated into multiple languages and have actually been incorporated into guidelines.

SLIDE 14: Signs and Symptoms of MPNs- Often Under-queried...
Why they’re so important is because the prevalence of these symptoms is quite high. These figures here look at a large number of MPN patients, over 2,000 that were queried using some of these tools in their validation process. And you can see the prevalence of things like severe fatigue, early satiety, abdominal pain, and the fact that they’re seen across the MPNs. So, asking about these symptoms and quantifying them really helped us understand what patients’ needs are, and of course, response to therapy.

SLIDE 15: MPN Symptom Assessment: Incorporated into NCCN (National Comprehensive Cancer Network®) Guidelines
The recently born and published NCCN guidelines for myeloproliferative neoplasms introduced just in the last few months has directed us to use symptom assessment scoring at presentation or at diagnosis with this form which is shown on this slide here, which is a bit broader,

SLIDE 16: MPN Symptom Assessment: Incorporated into NCCN Guidelines
and with ongoing monitoring of symptoms a shorter form, a ten-item form, to help us track response to therapy and evolution of patient symptoms and disease. So, these are very important tools that we need to become familiar with.

SLIDE 17: Myelofibrosis
So, let’s talk about each of the MPNs in turn.

SLIDE 18: Clinical Features of Myelofibrosis
Focusing on myelofibrosis, we’ve already covered a number of these issues. But, this is a diagnosis characterized mainly by the fibrotic change in the bone

---

4 Areas of symptom assessment in this tool include fatigue focusing on the impact of fatigue on activity, mood, mobility, relationships and enjoyment of life. In addition, other symptoms assessed are early satiety, pain, headaches, changes in concentration since MPN diagnosis, neuropathy, insomnia, depression, sexual dysfunction, cough, itching, fever, weight loss and overall quality-of-life.

5 Psychiatric symptoms such as: decreased enjoyment in relationships and life, insomnia, depression, and sexual dysfunction.
marrow and the multiple consequences it leads to systemically. One major consequence is splenomegaly, enlargement of the spleen, because of fibrosis in the marrow and extra extramedullary or hematopoiesis outside of the bone marrow. And splenomegaly associated symptoms are broad and are well described in this figure. Cytopenias, as a result of scarring and replacement of healthy areas in the marrow where blood can grow, are clearly an issue with anemia, and thrombocytopenia, and number of constitutional symptoms.

**SLIDE 19: WHO Criteria for Diagnosis of Overt Primary Myelofibrosis**

The World Health Organization criteria for diagnosing overt primary myelofibrosis--and that's an important point because, for example, many patients can present with selective blood abnormalities such as increased white count, increased platelet count, and it may be very difficult to understand what exactly their diagnosis is. Is it early thrombocytosis, for example, or early essential thrombocytopenia? Or is it pre-fibrotic myelofibrosis? So, the criteria have been well established and have been scrutinized and changed over time to help us accurately characterize and diagnose patients to help us treat them better.

So, the major criteria for primary myelofibrosis, many of which are morphologic, which is megakaryocytic proliferation and atypia in the bone marrow accompanied by reticulin/collagen fibrosis of a higher grade. As well, we need to exclude other conditions like BCR-ABL positive CML, dysplasia, and the other MPNs.

And, as I started the talk off with, molecular drivers have really been a huge help to us in making the diagnosis because a lot of this is separating primary versus secondary or reactive conditions and characterize, somewhat further, what type of MPN it might be. Some of the minor criteria are listed to the right, are obviously less specific, but can help make the diagnosis in this disease, myelofibrosis.

**SLIDE 20: NCCN Guidelines for MPNs: Fibrosis Scoring**

The pathologists are crucial in looking at our diagnostic bone marrows and treatment effects, in particular, with the question of fibrosis and myelofibrosis, particularly, is subject to fibrosis scoring. So, again, the pathologists need to carefully examine and stain the bone marrow to help us make this diagnosis, judge the degree of fibrosis, and track it with treatment. And this is especially important as even specific therapies may come online which are directed against fibrosis itself with anti-fibrotic therapies under development.

**SLIDE 21: The ‘Driver’ Mutation and Other Alterations Affect Outcome in MF**

As we eluded to earlier, the main driver mutations, such as JAK2 or this calreticulin recently identified, or other variance, which probably activate the same JAK2 pathway such as MPL515 or other iterations of the JAK2 such as exon 12 have different prognoses and have different effects on the disease. You can see that patients who don’t have a driving mutation actually may have a more complicated disease, and unfortunately, a shortened survival. They may have a similar disease biologically, but the

---

6 Come online - Approved by the Federal Drug Administration (FDA) for use outside of clinical trials.
molecular underpinnings, and in turn, potentially, the risk of progression or the risk of complications may be greater.

On the right, we see the addition of secondary molecular changes and their effect on overall survival or prognosis. And it’s clear that select secondary drivers or select secondary findings can have a clear impact such as ASXL1 and others listed, and unfortunately, leading to a shortened overall survival, and perhaps, allowing us to alter our treatment strategies and lower this risk or mitigate this risk.

**SLIDE 22: Risk Stratification in Myelofibrosis**
When we think about the different prognostic models for myelofibrosis, they’ve clearly evolved. Some are very complicated and include many different elements. I would say the evolution is leaning more and more towards a molecular or a genetic basis, and this figure, I think, supports that. But, these are all predictive and prognostic for myelofibrosis. And the current NCCN guidelines point us towards the Dynamic International Prognostic Scoring System or the Dynamic International Prognostic Scoring System Plus, which adds genetic information on top of previously established elements in the DIPSS score.

I did mention that myelofibrosis can be a primary or secondary condition, and there are clear criteria, which are listed here, for patients who have started with polycythemia or thrombocytosis and have evolved to myelofibrosis. And, again, for the sake of time, I won’t go through the details, but it’s clear that, pathologically and clinically, we need to understand the evolution of these patients and how myelofibrosis may be a result of an antecedent polycythemia or thrombocytosis diagnosis.

**SLIDE 24: Risk-Adapted Treatment of Myelofibrosis**
I’m going to turn it over to Troy at this point to begin to speak about treatment for myelofibrosis.

**Dr. Troy Z. Horvat:** Thanks, Dr. Mauro. So, once we have a diagnosis established, the next logical question is how should we treat these patients? And the first important step is to categorize them based on their risk factors.

Based on their risk factors, patients are categorized into low risk, intermediate 1 risk, intermediate 2, and high risk. And based off of those risk statuses, that’s where we derive our treatment strategies from. So, for low-risk patients that are asymptomatic, observation may be appropriate. However, most of our patients do present symptomatically, and at that point, the choice of therapy would be a JAK inhibitor, interferon, or a clinical trial. For our intermediate-1 patients or our intermediate-2 and high-risk patients, JAK inhibitor, or allotransplant (allogeneic transplant – the stem cells come from a healthy person/donor), or clinical trial would be in the standards of care.

---

7 In this circumstance, thrombocytosis is synonymous with essential thrombocythemia.
SLIDE 25: Interferon for the Treatment of Myelofibrosis

So, the first treatment that I’d like to start off talking about is interferon for our lower-risk patients. And, really, there’s three major studies that I wanted to talk about today. The first was done by Jabbour and colleagues in 2007, and they looked at pegylated interferon α-2β. They gave this in a weekly fashion, and their response rates are shown on the screen. But, what’s important is that 9% of patients achieved a CR (complete response). The grade 3 and 4 notable toxicities were fatigue, myalgias, weakness, and thrombocytopenia.

The next study, which was done by Silver and colleagues in 2013, looked at two different types of interferons. One was the recombinant form that’s given thrice weekly. And the second option that they gave in this trial was pegylated interferon α-2α given weekly. And here, we see similar rates of complete response, 9.4%, but an overall response rate of 78%, which is impressive. And the major grade 3 or grade 4 toxicity here was thrombocytopenia.

Lastly, Ianotto and colleagues looked at PEG-interferon α-2α given weekly and showed similar results in terms of overall response rates, and they also showed that there was a 46.5% reduction in splenomegaly. Again, the grade 3 and 4 toxicities were consistent with the previous two trials.

SLIDE 26: Interferon From A Pharmacist’s Perspective

I think, from a pharmacist’s perspective, there’s many things to think about when starting a patient on interferon. First of all, there’s three different formulations that have been shown, in the literature, to have activity in myelofibrosis. And it’s important as both the verifying and dispensing pharmacists to know which interferon is being prescribed. Going along with that, the initial dosing of interferon depends on the formulation. So, typically, our standard would be to use a pegylated form, which is once weekly dosing, versus a recombinant form, which requires thrice-weekly dosing. Important dose adjustments are shown on the screen for a severe renal or hematologic toxicity.

There’s no major drug interactions, and I think one of the biggest important things to take away from this slide are the warnings and precautions that that patient should be counseled on. The first are cytopenias. Patients can, as we saw, develop grade 3 or grade 4 hematologic toxicities, so this needs to be closely monitored. The other major toxicities or warnings are listed there, but one thing that’s an important consideration is new or worsening depression. Patients should be screened before starting and during treatment for any mood changes.

The other important thing on this slide—two more important things. The first is that this drug is not approved, FDA approved, for any MPN, so it will require, likely, a prior authorization. So, prescribers should be prepared for that. And then, secondly, the disposal is a very important counseling point for pharmacists to educate their patients on how to properly dispose of these.

And different states have different laws, so I’ll refer you to your own state guidelines for the proper disposal.
Switching gears a little bit, I want to move on and talk about ruxolitinib (Jakafi®), which would be a standard treatment for our symptomatic patient or our higher risk patients. And the two landmark trials that I'm going to discuss are the COMFORT-I and COMFORT-II trials, which were presented and published, actually, in the same issue of New England Journal of Medicine in 2012.

The COMFORT-I trial was done here in the U.S. while the COMFORT-II trial was done in Europe, and basically, they both compared ruxolitinib, which is a JAK2 inhibitor, to either placebo or best available therapy in the COMFORT-II trial. They were both done in intermediate or high-risk myelofibrosis patients, and the primary objective in both trials was a greater than 35% reduction in spleen size with secondary objectives being safety and survival.

So, the primary objective here was reduction in spleen size. And what we see is a 41.9% reduction in spleen size with ruxolitinib versus virtually none with placebo. And, in the COMFORT-II trial, a 32% reduction in spleen size versus zero with best available therapy.

So, going along with the reduction in spleen size, what we see here are patients’ quality-of-life reported outcomes. So, how it’s divided is by the best result in terms of spleen volume reduction. So, in patients that had the best spleen size reduction, greater than 35%, those patients reported a much better quality-of-life and total symptom score than those on placebo or those patients with less than a 10% reduction in spleen size.

What we see here, on this graphic, is the mean percentage change in spleen over time, and this is from the COMFORT-II trial. And what we see in blue are those patients that were initially treated with ruxolitinib; in orange, the best available therapy that were allowed to crossover to ruxolitinib; and in the black, we see the best available therapy arm. And, again, this diagram clearly demonstrates that ruxolitinib was great and better than the best available therapy at reducing the spleen size.

When we think about ruxolitinib, it’s generally well tolerated. And what we’ll see in the first three highlighted boxes are the increase in ecchymosis (bruising), dizziness, and headache. Those are the major side effects that increase with ruxolitinib. And what we’ll notice with the last red box is the abdominal pain that actually decrease compared to placebo. So, a very well tolerated, active agent for our patients with symptomatic, or intermediate, or high-risk myelofibrosis.

When we look at the survival data, there’s now follow up published out to three years, and at the three-year mark, what we’re seeing is an improvement in overall survival that borderlines on statistical significance in the COMFORT-I.
trial, and is statistically significant in the COMFORT-II trial. So, not only are patients feeling better and their symptoms are improving, their spleens are shrinking, but the patients are also having extended survival with ruxolitinib therapy.

**SLIDE 32: Summary: Ruxolitinib in Patients with Myelofibrosis**

So, in summary, in terms of efficacy, the COMFORT-I and COMFORT-II trials both showed that ruxolitinib was effective in shrinking spleens, improving quality-of-life and symptoms. It's nonselective for the mutated JAK form, so it benefits patients both with and without JAK2 mutations. And, in terms of safety, there is a risk for myelosuppression and infection, particularly, a low incidence of opportunistic infections.

**SLIDE 33: Ruxolitinib from a Pharmacist’s Perspective**

When I think about this from a pharmacist’s perspective, the initial dosing of ruxolitinib is dependent upon the patient’s platelet count, and also, the renal and hepatic function. So, these are lab parameters that need to be checked before starting a patient on ruxolitinib. While on therapy, patient’s doses should be adjusted if there’s any hematologic toxicity.

A big issue with ruxolitinib is that it’s metabolized by CYP3A4 and 2C9, so numerous drug interactions here. Most notably, “azole” antifungals, particularly fluconazole, can increase ruxolitinib up to 300%. The warnings and precautions are listed there, and patient counseling should be made on these points as well.

Importantly, from an administration standpoint, the drug can be given with or without food. And, in the case of intubation, it can be given via NG (nasogastric) tube. There’s numerous dosage forms of the drug, and what we like to do is start patients on the five-milligram dosage form until we’ve established a stable dose. So, that allows for dose adjustments in five-milligram increments.

And then, the last important point here is that the drug’s only available through specialty pharmacies. And so it’s not a drug that you can pick up the same day that the prescription goes in. And, therefore, patients should be counseled on the process in which drug acquisition of ruxolitinib is acquired.

**SLIDE 34: Patient Case: BP**

So, now that we’ve talked about the standard treatments for myelofibrosis, I want to use a patient case example to sort of reinforce what we’ve talked about. I’m going to introduce our patients BP, who’s a 60-year-old male with no major past medical history. And he presents to the clinic with fatigue, pruritus, abdominal discomfort, and a 15-pound weight loss. On physical exam, he’s found to have splenomegaly, and on laboratory findings, he’s found to have an increased white blood cell count with peripheral blasts, a decreased hemoglobin, and he’s slightly thrombocytopenic. Additionally, he has an elevated LDH to 1,000. This prompted a bone marrow biopsy, which showed atypical megakaryocytes and proliferation with grade 3 fibrosis. His cytogenetics were normal, and on diagnostic molecular pathology, he was found to have a JAK2 V617F mutation.
SLIDE 35: Patient Case: BP
So, our first question is, based on the patient’s presentation, does he meet the criteria for primary myelofibrosis? And the answer is yes. And I’ve starred here and brought back the WHO criteria for both the major criteria and minor criteria, and our patient clearly meets the required major criteria.

SLIDE 36: BP’s Risk Status
The second question for you is what’s the IPSS risk status of the patient? And, when we think back to the patient, he had constitutional symptoms, he was anemic, he had an elevated white count above $25 \times 10^9$, and he had peripheral blasts greater than 1%. And all of these factors puts him into the high-risk category.

SLIDE 37: Treatment Options for BP
Next, based on this, his high-risk status, what would be the best treatment option? And, as we reviewed on previous slides, the best treatment option for our patient would be ruxolitinib, choice C, or allogeneic stem cell transplant if the patient is amenable to that.

SLIDE 38: Treatment for BP
And our patient, unfortunately, he opted against going to transplant. He was worried about the potential side effects. And, as such, his hematologist wanted to prescribe ruxolitinib. And he comes to you as the pharmacist and asks you to help him with the dosing. So, there’s two important considerations that I think about. In terms of the dosing consideration, like we said, you have to look at the platelet count, the patient’s renal function, and his hepatic function. And, based on these parameters and the FDA labeling for myelofibrosis, the patient's dose would be 15 milligrams by mouth twice a day.

In terms of drug acquisition, as a clinical pharmacist assisting the hematologist in clinic, things that we always need to get are the patient’s insurance information. We need to identify a specialty pharmacy. As I stated, we consider starting with the five-milligram tablets so we can adjust based on potential hematologic toxicities. Then, we like to follow up with a specialty pharmacy to ensure that there’s no issues that we can help them with. We also have to assess the financial feasibility because the drug’s quite expensive. And, if there are financial issues, we like to identify copay assistance programs for the patients. And then, lastly, you need to follow up with the patient to ensure that they’ve received the drug and that they’re tolerating the drug adequately.

SLIDE 39: Polycythemia Vera
So, now that we’ve gone through a nice patient case of myelofibrosis, I’m going to turn it back over to Dr. Mauro to discuss polycythemia vera.

Dr. Michael Mauro: Well, thank you, Dr. Horvat, for that great review of therapies for MF and the case. So, moving on to polycythemia vera,
Myeloproliferative Neoplasms (MPNs): Diagnosis, Treatment and Side Effects Management

SLIDE 40: WHO Criteria for Diagnosis of PV

and thinking again back to the classic World Health Organization diagnostic criteria, I have to say that this is the diagnostic criteria that’s been the most in flux. And, suffice it to say that the criteria have changed in order to capture more patients who probably have what was called masked polycythemia, where they didn’t necessarily have a very abnormal blood count. You can see that the criteria include a hematocrit greater than 48% for women and 49% for men. And those are actually within the normal range.

So, the hemoglobin values are a bit more telling, generally, above 16 or 16 and a half. And that's just part of the story. As I mentioned earlier, the presence of a JAK2 mutation, either the V617F or the exon 12 mutation, really tell us that what we think may be an erythrocytosis, which is where we basically start with in making a diagnosis of polycythemia vera, is malignant, is due to a myeloproliferative disorder, is primary and not secondary. And the third piece of the puzzle, of course, would be a bone marrow biopsy showing the hypercellularity across the board with prominent, generally, erythroid changes, but again, panmyelosis, as we say, and as well megakaryocytic changes typical in MPNs.

Some other things have fallen into a less important criteria. The erythropoietin level can be indicative of a primary condition as it’s suppressed in true polycythemia vera. But, a low normal value may not be as helpful as previously stated. And the role of the erythropoietin level in making a diagnosis of PV has diminished somewhat. As well, erythroid independent colony formation is a very challenging test and was something done in the past in order to help make this diagnosis.

SLIDE 41: Risk-Adapted Management of Patients with PV

The management of patients with PV is fairly straightforward, and it's contingent upon some very basic facts. First, of course, this is an excess erythrocyte burden with incumbent risk of thrombosis, vascular symptoms both macro and micro, and our main goal is lowering the hematocrit. Maintaining a hematocrit below 45% as an overall target is acceptable. And the addition of cytoreductive therapy, in addition to phlebotomy and aspirin, which is really indicated in nearly any patient, is contingent upon some risk stratification.

Patients who are older, who already have a history of thrombosis, are probably going to benefit from the addition of cytoreductive therapy in addition to controlling their hematocrit and the use of aspirin whereas patients with lower risk, younger age, no thrombosis, may do well without the addition of cytoreductive therapy. But, of course, each case is unique and these are dynamic questions. But, when they present, these are some of the features that we would use to make the decision about initial therapy. And cytoreductive therapy includes hydroxyurea (Droxia®, Hydrea®), interferon, and much rarely used now, busulfan (Busulfex®, Myleran®), as an alkylating agent with some more risk associated with it.

SLIDE 42: Cyto-PV Study:The Benefit of ‘Tight’ HCT Control and WBC Reduction

There’s a very important study called the Cyto-PV study, which really showed us the benefit of good hematocrit control. Suffice it to say that this study asked...
the question, if your target hematocrit was 45%, if patients had that number all the time, or if they were close to that number, how was their outcome? And these numbers here show the difference in what I would call tight control versus more generalized control. And you can see for hematocrit, if the target is 45%, in the upper right where the hematocrit’s noted, you can see the median is actually above 45%, which may not be optimal for patients, whereas with tight control, it should be at or below. In turn, because these patients were getting more phlebotomy in these two groups in the study, or you’re getting cytoreductive therapy, they often had a lower white count. But that wasn’t much different than the platelet count.

SLIDE 43: Cyto-PV Study: Events
That being said, from this paper published in the New England Journal just a few years ago, you can see that the primary endpoint of all cardiovascular events, and the total cardiovascular events which added superficial venous thrombosis was lower in patients who had better hematocrit control. And these were statically significant with different hazard ratios for patients with so-called high hematocrit or low hematocrit, and that would be 45-50% versus 45% and less. So, our recommendations are 45% or less in all patients. And some even consider 42% in women the therapeutic target; although, this is on a case-by-case basis.

SLIDE 44: ECLAP Trial – Study Design
A second trial really showed us the role of aspirin, and this was the ECLAP trial, which in PV patients, showed us, as a primary endpoint, the ability to reduce vascular occlusive events such as myocardial infarction, stroke, or cardiovascular deaths. The design is shown here. This is a large trial randomizing patients to 100-milligrams, interestingly, of aspirin, which isn’t as widely available as 81 milligrams, but I think we believe them to be equal.

SLIDE 45: ECLAP Trial – Results
And you can see the differences in the relative risks with the aspirin group versus the placebo group. The relative risks being across the board lower for nonfatal vascular occlusive events - death from cardiovascular causes, any cause, and major or minor thrombosis.

There was some difference in bleeding, and certain patients may benefit more than others, so it’s, again, just taken on a case-by-case basis. But, this really is applied in the setting of polycythemia, and also, in patients with thrombocytosis or ET to support the use of aspirin as a mainstay of therapy for patients with MPNs.

SLIDE 46: Summary
Low dose aspirin can really be given to prevent thrombotic complications in patients with PV who have no contraindications. Of course, you’ll want to think about patients who have GI issues to add H2 blockers. And there is the consideration to switch to other antiplatelet drugs if aspirin is not tolerated.

And the important footnote that patients that have very high platelet counts, extreme thrombocytosis, may actually have bleeding risk due to acquired von Willebrand syndrome and...
need to be screened for that. So starting aspirin in patients with very high platelet counts may be more risk than benefit.

**SLIDE 47: Hydroxyurea in PV Management**

I'm going to turn it back to Troy to discuss some further therapies for PV starting with hydroxyurea.

**Dr. Troy Z. Horvat:** Thanks, Dr. Mauro. And the main goal in treating patients with polycythemia vera is controlling their hematocrit and keeping their counts at a low enough level. And one of the hallmark drugs that we use to do that is hydroxyurea. It’s the first-line cytoreductive treatment for these patients because it controls the myeloproliferation. It can reduce splenomegaly, and it can reduce or it may reduce the risk of thrombosis.

Important side effects to note here is that too high of a dose of hydroxyurea can cause myelosuppression. We do see leg ulcers or any skin ulcer, really, for patients that have been on hydroxyurea for a long duration of time. Patients can have hyperpigmentation, fever, alopecia. They are at an increased risk of squamous cell carcinoma, and there is long-standing controversy regarding the risk of activation of PV into an acute myeloid leukemia with the use of hydroxyurea.

**SLIDE 48: Definition of HU Resistance/Intolerance**

So, undoubtedly, if patients get started on hydroxyurea, at some point, they may develop either resistance or intolerance. And it's important to know what the definition of that is. And the full definition is here on the screen, but it's important to note that the main takeaway points is the need for continued phlebotomy despite two grams of hydroxyurea a day, uncontrolled myeloproliferation, failure to reduce splenomegaly after three months, an ANC or platelet count that's less than 1 or less than 100 respectively, and then, any presence of unacceptable non-hematologic toxicities such as leg ulcers or GI symptoms, pneumonitis, or fever at any dose of hydroxyurea.

**SLIDE 49: Interferon in the Treatment of PV**

In the case of patients who are either intolerant or resistant to hydroxyurea, interferon has been used to treat patient with polycythemia vera. And what's shown here is a phase 2 study that looked at interferon α-2a or 2b, the pegylated forms of interferon. And what's shown here are the proportions of responders. In blue, we see a 70% complete response with a 10% partial response. So, an overall response rate of 80%. And what's more interesting and maybe more important is the reduction in the JAK2 allele burden over time. So, at baseline, the median was 64% down to 12% at two years, so really interesting aside.

**SLIDE 50: Interferon Tolerability in PV**

When we think about tolerability in these PV patients, it's interesting. In the study design, they used much higher doses, and they saw much higher grade 3 toxicities in terms of neutropenia, LFTs (liver function tests)—, patients had blurred vision, and even, depression. But, when they reduced the dose down to 90 micrograms per week of the pegylated interferon, what they saw is virtually no grade 3 or grade 4 toxicities. So, going forward in our practice, we tend to use this lower dosing strategy at either 45, as a starting point, and then, escalating up to 90 if tolerated.
SLIDE 51: Ruxolitinib in PV – RESPONSE Trial

Now, if a patient is either resistant or intolerant to hydroxyurea, and they’re not a candidate for interferon, or they failed interferon, what’s left for them, now, is ruxolitinib. And that’s based on the response trial that was published in New England Journal of Medicine in 2013. And this was a phase 3 multicentered trial that compared ruxolitinib versus best available therapy in adult patients with PV. And the trial did allow for crossover at week 32. And the primary endpoint of the trial was both a composite endpoint of a reduction in spleen size and control of hematocrit with secondary endpoints being response rates, symptom reduction, and safety.

SLIDE 52: Response Trial – Results

And what’s shown in the top right of the slide are the composite endpoint as a primary endpoint, and also, the two endpoints as separate endpoints. And what we see is an overall response with ruxolitinib 20% of the composite endpoint and virtually zero with standard therapy. And what's even more impressive is that both the hematocrit control at 60% and the spleen reduction at 38%, which are both far superior to standard therapy.

What’s shown in the bottom left of the slide are the symptom analysis of these patients. And what we see with these negative numbers are improvement in symptoms. So, the patients on ruxolitinib across the board reported better symptomatic control than those on standard therapy. And, in some cases, those symptoms completely dissipated.

SLIDE 53: RESPONSE Trial – Safety Results

When we think about safety, the major grade 3 and grade 4 toxicities were cytopenias, most notably thrombocytopenia. There was an increased risk of herpes zoster infection in the ruxolitinib group at 6.4%. And there was a decrease in thrombotic events with ruxolitinib compared to standard therapy.

SLIDE 54: Treatment Summary

So, in summary, patients with PV, their modifications of their cardiovascular risk factors should be made including the use of low-dose aspirin. Patients should be phlebotomized with a target hematocrit less than 45%. They should, like I said, be on antiplatelet therapy with our choice being low-dose aspirin if they’re able to tolerate that. And then, first line, they should receive cytoreductive therapy, and if not able to tolerate that or if they’re resistant to hydroxyurea, patients should be started on ruxolitinib.

SLIDE 55: PV-associated Pruritus

One of the main symptoms that patients with PV complain of is pruritus, and the differential diagnosis of PV-associated pruritus is PV associated pruritus, idiopathic pruritus, aquagenic pruritus (AP), or aquagenic pruritus of the elderly. And this is a busy slide, but the take-home point is that patients with PV usually have no family history of pruritus. It’s an equal male to female gender, and it usually follows contact with water at any temperature. And the rest of the information on the slide is there for your information.
SLIDE 56: Management of PV-associated pruritus

Importantly is how we treat these patients that have pruritus. And what’s been shown is that interferon, and ruxolitinib, and SSRIs (selective serotonin reuptake inhibitor) are typically effective at treating this. And there’s mixed results with antihistamines; although, antihistamines really have a favorable side effect profile, and maybe, a reasonable choice to start with. And typically, cytoreductive therapy alone, or phlebotomy alone, are ineffective at treating pruritus.

SLIDE 57: Patient Case: SO

So, now that we’ve gone through the overview and treatment strategies of PV, I want to introduce a patient case. This is a 66-year-old man with a history of a right lower extremity DVT (deep vein thrombosis), who on presentation has fatigue, pruritus, and headaches. And there’s no evidence of splenomegaly on palpation. His diagnostics are shown below but include a hemoglobin of 18.1 and a hematocrit of 54 with a platelet count of 223. On bone marrow biopsy, he is found to have a hypercellular marrow with trilineage hematopoiesis with mature megas, and his cytogenetics were normal, and he does have a JAK2 mutation. An EPO (erythropoietin) level was checked, and this was below the lower limit of normal.

SLIDE 58: Patient Case: BP

So, the first question is does the patient meet criteria for diagnosis of PV? And the answer, of course, is yes. He meets all three of the major and the minor criteria.

SLIDE 59: BP’s Risk Status

Our second question is what is the risk status of this patient with newly diagnosed PV? And the answer here is he is a high-risk patient.

SLIDE 60: Patient Case: BP

The next question for us is what are the best treatment options for BP? And the correct answer here are aspirin and hydroxyurea. He’s previously untreated and he’s high risk, and therefore, deserves aspirin and cytoreductive therapy.

SLIDE 61: Patient Case: BP

However, after being on hydroxyurea for quite some time, he presented to clinic with leg ulcers and increasing hemoglobin and hematocrit and a return of his constitutional symptoms. And the question is what should we do now? And the right answer is consider switching to ruxolitinib. The patient’s obviously intolerant and has side effects from hydroxyurea and should be treated with something else.

SLIDE 62: Essential Thrombocythemia

Now, I’m going to turn it back over to Dr. Mauro to conclude by talking about essential thrombocythemia.

Dr. Michael Mauro: Thanks, Troy. So, we’ve covered MF and PV. Now, let’s talk about ET.
SLIDE 63: Diagnosis of Essential Thrombocythemia
Again, back to the World Health Organization, and when thinking about making diagnosis of essential thrombocythemia, I think it’s important to highlight that this is sometimes difficult to tease apart from what could be an early presentation of myelofibrosis.

So, the bone marrow study is quite important as is the rest of the findings noted here. Of course, the high platelet count’s going to trigger an evaluation. But, reactive thrombocytosis is also quite common. So, this really needs to be teased out. The bone marrow is going to mainly show megakaryocytic abnormalities, and the megakaryocytes have particular pathologic changes. And the degree of reticulin fibers, I think, is quite important to help us understand what could be an early stage of myelofibrosis rather than true essential thrombocythemia.

Of course, they can have criteria for other MPNs or other hematologic disorders, and here, again, the molecular driver is quite helpful. And this is a disease where the calreticulin finding has really added to our armamentarium of understanding the molecular basis, and allowing us to account for a molecular driver, and make the clear diagnosis of a myeloproliferative disease.

So, the diagnosis of ET is probably about as complex as it can get, but it can be made and can be made with a degree of confidence.

SLIDE 64: ET Risk Assessment
Like the other conditions, there are prognostic assessments. And this is also in evolution, and I think, the main prognostic score we use is called IPSET and looks at some basic questions - is the patient of older age, have they had a prior thrombosis, and do they have evidence of an elevated leukocyte count? And it may not seem very important to judge whether the white count is just minimally elevated or not, but it’s really felt that the white count contributes as much to the risk of thrombosis than the disease itself, the inflammatory state that it creates, and perhaps, the platelet count. And we almost pay equal or more attention to the white count than we do to the platelet count.

On the bottom, you can see what is perhaps, the evolution of IPSET, where we incorporate the addition of the presence of a JAK2 mutation or a patient’s cardiovascular risk. And, in patients with high and low risk, based on the older model, you can see that we can now sort out an intermediate or an evolving risk if we add in these features. And this helps us understand, what is the risk of thrombosis per patient year? It’s kind of the most important thing for your patient to know because this is the most indolent of MPNs. And the main threat, although there is risk of evolution to leukemia, and there is risk of evolution to fibrosis, but it is thrombosis.

SLIDE 65: ET Risk Assessment
So, the algorithm boils down to this, patients with low risk and without known risk variables may be observed and may not have any therapy necessary, save for the avoidance of bad habits such as smoking and weight gain, correction of hypertension, and treatment of other cardiovascular risk factors. But, as you can see in patients, in turn, you have are older age, thrombosis, or very marked proliferation may need cytoreductive therapy and clearly can benefit from aspirin.
But, the caveat that von Willebrand syndrome acquired from a high platelet count should be ruled out. And here, again, there’s the use of hydroxyurea the mainstay for a cytoreductive agent with the additional option of anagrelide (Agylin®), which has been looked at in comparison to hydroxyurea, and overall, is felt to probably have somewhat greater risk, particularly, cardiovascular risks particularly in the elderly and may not be inferior, but in some studies, may not be as good a risk-benefit ratio compared to hydroxyurea.

**SLIDE 66: Interferon in the Treatment of ET**
I’m going to turn it over to Troy to cover a little bit more treatment including the interferons and treatment of ET.

**Dr. Troy Z. Horvat:** Thanks again, Dr. Mauro. So, what’s shown here is the evaluation of interferon, pegylated interferon alpha 2a in patients with ET. This is a very similar study design as the study that was published regarding PV that we talked about earlier. And what we see are very similar results - complete response rate of 76% with 5% of a partial response for about an overall response rate of 80%. And, again, what’s shown here, nicely, is the reduction in the JAK2 allele burden.

**SLIDE 67: Interferon Tolerability in ET**
When we think about the interferon tolerability, what’s shown here is the same thing that we saw in the PV trial, is that patients were treated at a higher dose. And patients treated at higher doses had greater grade 3 or grade 4 toxicities, and as such, the protocol was amended so that patients started at lower doses and patients had a decrease in the amount of grade 3 toxicities. What’s different between this study and the PV study with interferon is that, even at the reduced dose, there was a 13% risk of neutropenia with interferon.

**SLIDE 68: Patient Case: MT**
So, now that we’ve talked about the treatment pathway in ET, we want to emphasize it through a patient case. So, we have a 62-year-old male who had an elevated platelet count to 780, and he was recently admitted for DVT. His history, exam, and labs did not reveal an underlying cause for the DVT or the thrombocythemia. And his other lab values are shown there. And this warranted a bone marrow biopsy, which showed increased megakaryocytes with prominent large hyperlobulated forms, and the reticulin was not increased. His cytogenetics were normal, and he did have a JAK2 mutation.

**SLIDE 69: Patient Case: MT**
So, the first question is does the patient meet diagnostic criteria for ET? And the answer’s yes. We’ve starred the major criteria that the patient meets by WHO.

**SLIDE 70: Patient Case: MT**
The second question is, now that we know that he has ET, what initial treatment should the patient start to reduce his risk of thrombosis? And the answer here is both B and C - hydroxyurea to reduce his counts and aspirin to act as an anti-platelet agent.
SLIDE 71: Stem Cell Transplant Use in MPNs
And I'm going to turn it back over to Dr. Mauro to finish off the presentation.

Dr. Michael Mauro: Thanks. So, we talked about all the different diseases, and we left out one important question. We know that hematopoietic stem cell transplantation can be useful in myeloproliferative disease. And, on this slide, I think I've highlighted the key questions and the way we approach it. And the stem cell transplant is almost always thought of for patients who develop myelofibrosis given the complexity and the morbidity from that state whether it’s primary, secondary, or either, or of course, patients who have progressed to a more advanced phase, what we call a blast phase, really secondary AML.

In myelofibrosis, said somewhat earlier, there's an evolving risk-benefit analysis for use. And it’s generally relegated only to patients of younger age with low-risk donor options who have significant complications, rather, from the disease. So, problematic myelofibrosis that’s stem cell transplant eligible may be what is the input in addition to patients with advanced phase. And we ask questions such as the timing. Is it urgent? Can it be deferred, maybe never utilized? What about therapy pre-transplant? Should we be using JAK inhibitors extensively or for a period of time to maximize response in order to improve outcomes? What about classic cytoreductive therapy? And, of course, patients who have received transfusions may need and benefit from iron chelation therapy.

Even more intriguing is what do we do post-transplantation? Is there a role for using JAK inhibition as a way to eliminate MRD (minimal residual disease) or to allow for complete remissions? What about interferons to engender or strengthen an allogeneic graft versus disease effect or other therapies? So, stem cell transplantation remains a work in progress but may be reserved, mainly, for patients with advanced forms where we would handle this like AML (acute myeloid leukemia) or patients that have select scenarios, particularly, MF where it’s a younger patient with complex situation and low risk of morbidity.

SLIDE 72: MPN Conclusions
So, to conclude, MPN’s are chronic and variable progressive conditions with a fair bit of shared biology, clinical features, and molecular basis. So, teasing them apart can be a challenge. But, proper diagnosis is essential given these overlaps. Patient-reported symptom burden is crucial, and really, quantifiable to treatment. And we’ve been reminded of that by their inclusion in the NCCN guidelines recently developed. Treatment strategies can vary depending on the individual’s risk status, ranging from observation and no therapy to fairly brisk referral for intensive therapy or even consideration of allogeneic transplant, as I just mentioned, and everything in between.

The thrombosis risk is a shared one, and antiplatelet therapy is a mainstay for the majority of patients. I think I’d like to highlight that ruxolitinib, as my colleague, Dr. Horvat, has very nicely summarized, represents a major paradigm shift and can significantly improve the outcome for many patients with MF or hydroxyurea resistant or intolerant PV, but unfortunately, doesn’t cure these diseases. So, we’re needing to move even beyond that.

Interferon, a historic but important current mode of therapy, offers significant benefits and has not faded at all from our landscape. And, in fact, an important randomized trial is running
comparing interferon to hydroxyurea in higher risk MPN patients around the world—but, as toxicity warrants, careful patient selection and monitoring.

There's a number of novel therapies for MPNs that are in development as they're needed, and the strategies include novel JAK pathway inhibitors, which would have a better risk-benefit ratio, perhaps, less myelosuppression and more of a specific MPN clone effect. Specific antifibrotic therapies—telomerase inhibitors have been studied and shown to be beneficial in these diseases and combination approaches, one example being the use of hypomethylating agents with JAK inhibition in the advanced forms of MPNs and numerous combinations that have been recently studied in earlier phases of MPNs.

SLIDE 73: Resources
So, I want to thank you for your attention and point you to some important resources that physicians, pharmacists, patients, and providers, and loved ones can point to to get more information, more education, and to answer further questions.

SLIDE 74: Nursing Care in the Treatment and Side Effect Management of Myeloproliferative Neoplasms
Lauren Berger: Thank you Dr. Mauro and Dr. Horvatt, I am now pleased to turn the program over to Ms. Marissa Hine.
Marisa Hine:
Hi everyone. I'd like to start by thanking The Leukemia & Lymphoma Society for this opportunity to present today and to share my knowledge and experience in working with patients with myeloproliferative neoplasms.

Today I am going to be discussing nursing care in the treatment and symptom management of MPNs with a special focus on patient and caregiver education.

SLIDE 75: Treatment Goals
As nurses and caregivers, we strive to provide the highest quality of patient-centered care and in order to do so successfully, we first need to establish the mutual treatment goals of both the patient and the provider. When I think about the goals of treatment for MPNs, I consider the following: reduction of life-threatening disease sequelae, specifically, micro and macro vascular occlusive events, for example, myocardial infarction and stroke, reduction of disease progression, specifically the evolution to secondary myelofibrosis or acute leukemia. Reduction of symptom burden; which we will discuss in greater detail in just a few moments, and of course improvement in quality of life.

The last goal may mean something different to each patient, which is why as a care provider we must have individualized care for every patient that we treat. Some questions I like to ask patients are: what do you hope to gain from your treatment? What symptoms are most bothersome? And, can you tell me in your own words what is your understanding of your disease and your current treatment plan? This can help us as clinicians to better grasp the patient's understanding as well his or her personal goals.
SLIDE 76: “It’s not just about the numbers”
In both hematology and in medicine in general, we often focus on numbers to drive our decision-making, but we must also incorporate patients’ subjective symptoms into our plan of care. We need to empower our patients to recognize and report worrisome and bothersome symptoms; it’s not just about the numbers.

SLIDE 77: Microvascular Occlusive Symptoms
When we talk about assessing vascular occlusive symptoms, we must pay close attention to the following symptoms which are a result of impaired blood flow and perfusion. Microvascular occlusive symptoms that these patients may experience include: headaches, dizziness, difficulty concentrating, changes in vision, paresthesias, neuropathy and angina.

SLIDE 78: Macrovascular Occlusive Events and Symptoms
The symptoms of macrovascular occlusive events can be nonspecific. It’s important to note that patients often present with atypical symptoms. In the case of myocardial infarction patient may experience chest pain, pressure or tightness, fatigue, diaphoresis, dyspnea, dizziness, indigestion and nausea. In the case of transient ischemic attack or stroke, slurred speech, difficulty speaking, facial or extremity weakness or numbness, (commonly unilateral), sudden severe headache, dizziness, and loss of balance may occur.

In the case of pulmonary embolus, patients may experience sudden dyspnea, chest pain, rapid heartbeat, palpitations, hemoptysis, diaphoresis and anxiety.

SLIDE 79: Therapeutic Phlebotomy
Now let's focus on the mechanisms of prevention of vascular occlusive events in MPNs. Both Dr. Mauro and Dr. Horvat have already provided a comprehensive summary of the treatment indications for polycythemia vera, essential thrombocytopenia and myelofibrosis.

Now I would like to touch upon some of the most pertinent teaching points for these patients. In polycythemia vera, the hallmark of the disease is excess red blood cell production. As Dr. Mauro discussed earlier, our hematologic target in this population is a hematocrit less than 45%. So what is therapeutic phlebotomy? This is a procedure in which blood is removed from the body in order to reach the target hematocrit. This process is comparable to that of blood donation, typically one unit of blood, or approximately 450 cc's is removed from the body. Patients and caregivers should be aware of potential side effects of therapeutic phlebotomy as well as proper precautions. The more common side effects of phlebotomy are a result of a decrease in blood volume and include dizziness, lightheadedness, and low blood pressure.

Patients should be encouraged to increase oral hydration prior to and following therapeutic phlebotomy. Hydration should be with water. Caffeine and alcohol should be avoided as they may worsen dehydration. Ecchymoses, or bruising, and/or soreness at the needle site may
occur. Patients should keep their bandage on for 3 to 4 hours after the procedure and avoid heavy lifting for at least 24 hours.

**SLIDE 80: Aspirin**
Antiplatelet therapy with low-dose aspirin is used in patients with MPNs to prevent thrombotic complication. As with any pharmaco-therapy we need to monitor patients carefully to ensure that the benefit of the treatment outweighs the risk. In this case the risk of serious hemorrhage versus prevention of vascular occlusion. For example, careful consideration should be given to patients with a history of severe bleeding, intestinal ulcers, chronic alcohol use, concurrent anticoagulation, asthma and renal dysfunction. In patients with extremely high platelet counts, acquired von Willebrand disease may actually place them at a higher risk for bleeding. Antiplatelet therapy is contraindicated in these patients. Patients and caregivers should be educated on monitoring and reporting signs of bleeding.

**SLIDE 81: Hydroxyurea**
Hydroxyurea is used as a cytoreductive agent in patients with MPNs. The goal of hydroxyurea therapy is to keep blood counts at a low enough level to reduce the risk of thrombotic complications. That being said, patients require close monitoring of their blood counts to assess for myelosuppression. In general hydroxyurea is a well-tolerated therapy. Patients, however, should be monitored for potential dermatologic changes generally associated with prolonged therapy including skin rash, pigmentation changes, nail changes and leg ulcers.

**Slide 82: Interferon**
Interferon is used to control erythrocytosis and thrombocytosis and to reduce the risk of thrombotic complications in patients with MPNs. Both alpha interferon and pegylated interferon are administered subcutaneously. Patients or caregivers who are administering these injections should receive subcutaneous injection teaching. A return demonstration should be observed to ensure adequate medication delivery. Local injection site reactions such as mild bruising are common. Potential side effects of interferon include flu-like symptoms fevers, body aches, malaise, nausea, vomiting, mood changes, depression and insomnia. Patients should be monitored closely for toxicity.

**SLIDE 83: Cardiovascular Risk Reduction & Lifestyle Modification**
In addition to disease specific treatment modalities, we must also pay close attention to reduction of cardiovascular risk factors, which can precipitate vascular occlusive events. Patients should be taught to maintain a heart healthy diet with a special emphasis on reducing high sugar and high fat foods. Patients should maintain a healthy weight. The focus here should be on diet and exercise. Thirty minutes of moderate intensity exercise five times a week is recommended. Patients should maintain blood pressure and glycemic control as well as healthy cholesterol levels. The goals here include prevention of target organ damage in patients with hypertension, diabetes, and high cholesterol and of course avoidance of smoking. Smoking cessation program should be offered to all current smokers. A collaborative relationship with patients’ primary care providers and or referrals to cardiology when warranted can be extremely helpful in
optimizing preventive care.

**SLIDE 84: Splenomegaly**

Now let's shift our focus to the common nonvascular symptoms that may affect our patients with MPNs. Splenomegaly is most common in patients with myelofibrosis but can also be a common finding in patients with polycythemia vera and essential thrombocytopenia. In patients with MF the scarring in the bone marrow makes hematopoiesis increasingly difficult and therefore we see an enlarged spleen as a sign of extramedullary hematopoiesis. In patients with PV and ET the increased production of red blood cells leads to increased filtration in the spleen and therefore splenomegaly. Symptoms of splenomegaly may include early satiety, nausea, abdominal fullness and increased abdominal girth. Patients should be encouraged to eat small frequent meals as tolerated. As previously discussed in the pharmaco-therapeutic portion of this program, treatment with hydroxyurea, interferon and ruxolitinib have been shown to reduce spleen size and therefore reduce associated symptoms.

**SLIDE 85: Pruritus**

Pruritus, or generalized itching, is most commonly seen in patients with PV, but can also be seen in patients with ET and MF. The pathophysiology of MPN-associated pruritus is not completely clear, and therefore neither are the corresponding treatments. Pruritus is believed to be related to an increased number as well as functional differences of mast cells in patients with MPNs and therefore an exaggerated response of the inflammatory pathway.

Antihistamines may be effective in the treatment of MPN-associated pruritus. They are generally well tolerated and have few drug interactions. Selective Serotonin Reuptake Inhibitors, (SSRIs) have also been shown to reduce the severity of MPN-associated pruritus. However, these medications carry more potential side effects and drug interactions. Disease treatments with interferon and ruxolitinib have been shown to effectively treat MPN-associated pruritus.

**SLIDE 86: Constitutional Symptoms**

Other constitutional symptoms felt to be related to inflammation in the bone marrow and throughout the body caused by MPNs include nightly sweats low-grade fevers, fatigue, weight loss and bone pain. These symptoms can be extremely distressing to patients and caregivers. These patients often benefit from additional psychosocial support as provided by our nursing team and our team of social workers. Worsening or failure to improve these symptoms should prompt a discussion about initiation or change in therapies.

**SLIDE 87: Conclusion**

In conclusion of our discussion today, I’d like to summarize by stating that the nurse’s role in the monitoring and the treatment of the patient with an MPN should concentrate strongly on symptom assessment, as this can dictate the need for initiation or changes in treatment. Patient and caregiver education should focus on symptom recognition and strategies for cardiovascular risk reduction. Care planning and patient education should be individualized with each patient. Collaboration between physicians, advanced practice providers, both nurse practitioners and physician
assistants, pharmacists, social workers, nurses and our patient is essential to providing the highest quality of care to our patient.

Thank you again to The Leukemia & Lymphoma Society for this opportunity to present and to those providers who have participated in this education program.

**SLIDE 88: Conclusions**

Lauren Berger: Thank you Dr. Mauro, Dr. Horvat and Ms. Hine for your very clear and informative presentations on diagnosis, treatment, and side effects management.

The Leukemia and Lymphoma Society is pleased to offer additional resources for healthcare professionals, patients and caregivers. You can access this information using the Resources Tab.