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Myelofibrosis Overview and Pathophysiology

Epidemiology

Michael Grunwald, MD: We have the relatively new 2022 International Consensus Classification, (ICC) and myeloproliferative neoplasms (MPNs) fit into the myeloid neoplasms category. If we broaden the myeloproliferative neoplasm category or focus down on it a bit more, within it we have multiple disease entities, including what have been traditionally called the classical Philadelphia chromosome-negative myeloproliferative neoplasms or polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) which then is broken into 2 categories, prefibrotic or early stage PMF and overt fibrotic stage PMF.

For the epidemiology of myeloproliferative neoplasms, the prevalence of essential thrombocythemia in the United States is about 135,000 individuals. The prevalence of polycythemia vera is 148,000 and the prevalence of myelofibrosis is approximately 13,000. Essential thrombocythemia is more common in females than males. Polycythemia vera is more common in males than females and primary myelofibrosis is approximately as common between the 2 sexes. The median age at diagnosis of ET is 56 years, polycythemia vera 61 years and myelofibrosis 65 years. Myelofibrosis affects primarily an older population.

Pathophysiology and Molecular Targets

Michael Grunwald, MD: For the mutational landscape in MPNs, polycythemia vera patients almost always have a Janus Kinase 2 (JAK2) mutation and usually this is the JAK2 V617F mutation. There is a small subset of patients who have the JAK2 Exon12 mutations and there is a very small subset who do not have a JAK2 mutation. Essential thrombocythemia can be defined by a number of mutations. JAK2 is the most common mutation in essential thrombocythemia, however, it is also relatively common to have mutations in calreticulin (CALR) and myeloproliferative leukemia protein (MPL). There is a group of ET patients who lack mutation in those 3 genes, JAK2, MPL and CALR.

When we look at myelofibrosis, the genetic breakdown is similar to ET. The majority of patients do have a JAK2 mutation and that is usually JAK2 V617F. And then we also see a group of patients who have a CALR mutation, a group of patients who have a MPL mutation and a group of patients who lack mutations in those 3 genes, and those patients frequently are called triple-negative patients.

Patients can have more than 1 mutation. Many patients with primary myelofibrosis will have mutations in 2, 3, 4, sometimes even 5 genes. It is not just JAK2, CALR, and MPL that can lead to prognostic significance or prognostic differences between populations of MPN patients. In addition, there are other genes at play, showing that various mutations can cause adverse prognosis in PV, and this has some overlap with genes that cause adverse prognosis in ET. And then in myelofibrosis, we see a number of genes that can lead to adverse prognostic risk. Among these genes, we see some that are not surprising, including additional sex combs like transcriptional regulator 1 (ASXL1) and tumor protein 53 (TP53).

Myelofibrosis Burden of Disease and Prognostic Scoring System

Diagnostic Criteria of Myelofibrosis

Aaron Gerds, MD: One of the key pitfalls in diagnosing myelofibrosis is this newer entity of prefibrotic myelofibrosis. Prior to the 2016 World Health Organization (WHO) classification system, there was a whole group of patients who did not really have ET, did not really have overt myelofibrosis, but fell in between the 2 diagnoses. As [with] all things in real life, there is no discreet bins; everything is on a spectrum. The entity of prefibrotic myelofibrosis was developed to capture those patients and give them a more accurate diagnosis. This was carried forward in the 2022 iteration of the ICC classification system, and the key piece with prefibrotic myelofibrosis is there is not a lot of scar tissue. Grade 0,

grade 1 (bone marrow fibrosis) can certainly be seen, but anything greater than that (grade 2 or grade 3) is certainly overt myelofibrosis.

Prefibrotic myelofibrosis patients tend to have a better prognosis. They tend to have better blood counts. They tend to be less symptomatic compared to overt myelofibrosis. If you are seeing large degrees of fibrosis, grade 2 or grade 3 and certainly collagen fibrosis develops, you want to think about overt myelofibrosis for those patients and the diagnostic criteria really split those 2 groups out. We may not have much historic data for prefibrotic myelofibrosis, you can imagine their outcomes are quite comparable to high-risk ET or low-risk myelofibrosis from analysis prior to that. The better we can do at identifying different patients within these categories, we can then, in the future, do a better job of determining what drives disease and applying appropriate treatment for these patients.

The 2022 ICC update of the diagnostic classification also added post-PV, post-ET myelofibrosis, sometimes referred to as secondary myelofibrosis, although a key flaw with calling it "secondary" is that it can be confused with autoimmune myelofibrosis which is also called secondary myelofibrosis. Autoimmune myelofibrosis is scar tissue in the bone marrow seen as a result of a rheumatologic or inflammatory disorder. Post-PV, post-ET myelofibrosis, it is a true malignant process where aberrations in the JAK/STAT pathway are present. The IWG, the international working group for myelofibrosis, always had a diagnostic plan and schema for diagnosing post-PV and post-ET myelofibrosis, but now it has been officially incorporated into the formal diagnostic classification system with the ICC here in the most current edition.

The key pieces are you had a diagnosis of PV or ET in the past and now you have significant scar tissue in the bone marrow, grade 2 or grade 3. There are always these cases that you suspect they had an ET or PV all along, but never had the official diagnosis. Even though you that might have been going on, you still have to call them primary myelofibrosis just because they have not had that clear, defined diagnosis prior to that. That is another pitfall with this diagnostic category.

Signs and Symptoms of Myelofibrosis

Aaron Gerds, MD: There are signs and symptoms that are quite common in myelofibrosis that we see over and over, from patient to patient, that we consider cytokine-mediated symptoms. Fevers, night sweats, fatigue, itchy skin are really driven by cytokines and, again, recurrent in patients with myelofibrosis. Some other symptoms we associate with splenic enlargement or splenomegaly can be early satiety and weight loss. Often, we see bone pain in some of these patients and that is driven also by cytokines, we think, as well as histamine release in the periosteal areas of the bone. These signs and symptoms are quite prevalent and might lead to a diagnosis of myelofibrosis or, on reflection of getting that diagnosis, make you look back and see how long these things have been present. The reason we focus so much on signs and symptoms of myelofibrosis is they are key at determining which treatments might be appropriate for an individual. Asymptomatic patients may not require a JAK inhibitor or other therapies, where a patient who is heavily symptomatic, even if they have low-risk disease, could clearly benefit from some of these therapies.

Myelofibrosis Burden of Disease

Aaron Gerds, MD: With the burden of disease, it is key to point out that this is a disease of chronic inflammatory states. Lots of research has gone into this, looking at the elevated cytokine levels and other inflammatory markers. It leads, again, to a lot of the symptoms that patients experience, including fatigue and night sweats and can also contribute to 1 of the major cytopenias, anemia. Anemia of chronic inflammation is often present in patients with myelofibrosis.

Fatigue is by far and away the most frequent and can often be the most burdensome symptom for patients, and often goes together with poor sleep hygiene, as well as psychiatric disorders like depression. There are complications arising from the underlying disease. The inflammation, and just the presence of the JAK2 V617F mutation, we know can increase the risk for blood clots, whether arterial or venous blood clots, which you see at a much higher rate in these patients, even when they are cytopenic. We can see inefficient hematopoiesis leading to infection risk, as well as anemia and thrombocytopenia, as well as extramedullary hematopoiesis, meaning blood-forming elements outside the bone marrow where they

normally live. And we see that often in the spleen, the liver, omental tissues, and lungs. I had a case where a patient had extramedullary hematopoiesis in their breast tissue, and we were thinking it was potentially breast cancer. Extramedullary hematopoiesis can happen almost anywhere. That is something that certainly occurs in patients with myelofibrosis.

The underlying risk that the disease might progress to something worse, which is a blast phase MPN, also known as acute leukemia, when those blast counts continue to rise due to the acquisition of additional mutation leading to a very aggressive myeloid malignancy.

Myelofibrosis Risk Stratification and Scoring System Tool

Aaron Gerds, MD: When you diagnose someone with myelofibrosis, the next logical question is, how bad is this and when you think about cancer medicine, we often think about staging. But, of course, geographically based staging does not work for blood diseases because the blood is everywhere. It would not help identify patients who are at higher or lower risk. We use disease models, where we take clinical parameters to understand who may have an aggressive disease. There are a few models that have been published in myelofibrosis that are used often in everyday clinical practice. One of the key features of these different models is they use different information.

You can think about choosing a model based on the information you have in hand. For example, if you have age, their symptoms, their blood counts available, which are all easy to get, you might be able to calculate a Dynamic International Prognostic Scoring System (DIPSS) score to determine risk. If you get additional information, such as a mutation analysis, you can start to calculate more advanced models, a Mutational Enhanced International Prognostic Score System (MIPSS) score. You can flip from the models based on the information you have. The 1 exception being the Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM) which was specifically developed in patients who have post-PV and post-ET myelofibrosis or secondary myelofibrosis.

And the National Comprehensive Cancer Network (NCCN) has tried to come up with a way to help determine which model to use and when and which patient might fall in the higher or lower risk categories, independent of the model being used. There are a lot of models, there are a lot of ways to think about this. Mike, I'm going to ask you, how, in your everyday practice, do you use these prognostic models to help inform patient treatment decisions?

Michael Grunwald, MD: We do, we always calculate risk scores in our patients, and, in fact, we have employed some help from our pharmacists who are engaged in our clinic and making sure we get risk scores on patients when patients are coming into their clinic visits. We always calculate the DIPSS-Plus and sometimes 1 scoring system might be more appropriate than another, but I find that the DIPSS-Plus is a good one-size-fits-all. Almost all our patients will have the information that is required to calculate a DIPSS-Plus and then, in addition, we will calculate other risk scores if they are applicable. For example, if we have molecular data, we like calculating the MIPSS70+ version 2.0. If a patient has post-PV or post-ET myelofibrosis, we will also calculate the MYSEC-PM. How about you, Aaron?

Aaron Gerds, MD: I would echo all those points. Seeing a patient for the first time as a consult, I always have the information to calculate a DIPSS score and often have the information required to calculate a DIPSS-Plus score. Sometimes, metaphase karyotype or cytogenetic just do not grow on a bone marrow aspirate sample that you get in a patient with myelofibrosis. Sometimes we miss out there because you must have that cytogenetic analysis. If reasonable FISH (fluorescence in situ hybridization) was done, you could probably plug and play from there. Most of the high-risk cytogenetic abnormalities are captured on most FISH panels. I would go so far [as] to say that a broad-based NGS (next-generation sequencing) panel of a couple dozen, up to 50 genes, is the standard of care in myeloid malignancy in the year 2023. If not already done, I always get that on patients and then afterwards calculate a MIPSS70 score. The key piece with MIPSS70 is it was only developed and validated in patients up to the age of 70 because they were trying to identify "transplant-eligible" patients and so it would not apply to someone who is 75 years of age, but honestly, I still use it anyway as a frame of reference. In patients who have post-PV or post-ET myelofibrosis, we also look at the MYSEC-PM. Sometimes, you calculate all the models, and they say very different things and often, while sitting down with a

patient, I say, the truth is somewhere probably in between all these models. None of these are perfect, so the statistics for these models are going to be around 0.6 or 0.7 where 0.5 is a coin toss and 1 is perfection. We are probably a lot worse at predicting outcomes than we really think we are with these models, but it is a good place to start.

The MIPSS70 scoring system is going to include anemia, leukocytosis and platelet count. Things that are readily available on a standard complete blood count (CBC). Then, if you get a differential, you will get a blast count which can also factor into the MIPSS70. Other things, such as myelofibrosis grade on the bone marrow, as well as the molecular and cytogenetic testing, are all key in developing and calculating the MIPSS70 and MIPSS70+ version 2.0 risk scores. You can always take it that level further, but when you look at the MIPSS70, it shows you how heavily these things are weighted and I always find it interesting that leukocytosis is so heavily weighted as well as platelet count, just as much as say 2 high-risk molecular mutations. While mutation risk does capture a lot of risk, it probably does not capture all the risk because these generic clinical variables are still so incredibly important at predicting prognosis.

The MYSEC-PM does not include as much molecular data. The only molecular data in the MYSEC-PM is whether a patient has calreticulin-mutated disease or unmutated disease. It uses all the kind of typical clinical factors, like age and constitutional symptoms and circulating blasts and other blood counts, but it does add in that little bit of twist with the calreticulin mutation because we know that patients who are calreticulin-mutated, whether we are talking ET, myelofibrosis or post-ET myelofibrosis, tend to do much better than patients who do not have the calreticulin mutation and have the other mutations. Of course, there are always those rare patients that are comutated. We talk about JAK2, MPN, calreticulin being mutually exclusive, but they are not truly mutually exclusive. We will sometimes see 2 clones, and these are a little harder to interpret, but those are pretty rare patients.

Current Treatment Approaches for Myelofibrosis

Myelofibrosis Treatment Landscape & Goals of Therapy

Michael Grunwald, MD: The current myelofibrosis treatment landscape starts with diagnosis. Patients undergo symptom evaluation which can be done using tools including the Myeloproliferative Neoplasm Symptom Assessment Form (MPN/SAF) total symptom score as well as risk stratification which incorporates multiple features. Patients can be treated along with [a] clinical trial, and this can incorporate low-risk and/or high-risk patients. In the approved therapy setting, we have targeted treatment, and our targeted treatments are JAK2 inhibitors, currently. We also have supportive care that we can offer patients, especially for anemia, and this can consist of erythropoiesis-stimulating agents (ESAs), danazol, lenalidomide and sometimes luspatercept. Then we also have hematopoietic stem cell transplantation in our tool kit for myelofibrosis and it is complex when to consider transplant for a patient, but selection can be based on disease features, age, performance status, comorbidities, and patient/provider preference.

As a general algorithm, we think about patients as divided into 2 categories. It is not always this simple, but we think about patients as lower-risk myelofibrosis patients or higher-risk myelofibrosis patients. And for lower-risk patients, we think of them as asymptomatic or symptomatic. If patients are asymptomatic, they might not require any treatment. A lower-risk, asymptomatic patient can be managed with observation alone. There are many clinical trials now in this space and lower-risk asymptomatic patients can be treated on a clinical trial.

Now, lower-risk patients with symptoms are a little different. These patients can have impaired quality of life and oftentimes we think about a JAK inhibitor, usually ruxolitinib for these lower-risk, symptomatic patients. A clinical trial may also be appropriate, and sometimes we consider other therapies, including pegylated interferon alfa-2a and sometimes hydroxyurea.

Higher-risk patients are a little different. If patients are transplant-eligible, we at least consider allogeneic

transplant, which is the only potentially curative treatment option for these patients. If patients are not eligible or they are not considered fit enough for transplant, we think about JAK inhibitor therapy or a clinical trial. Finally, if a patient is transplant-ineligible and has significant anemia, we think about targeting that anemia and trying to improve the hemoglobin and then additionally we think about a JAK inhibitor or a clinical trial to try to target the patient's disease a little better.

Ruxolitinib in Myelofibrosis

Michael Grunwald, MD: Looking at some of the ruxolitinib data, we have the results of the Controlled MyeloFibrosis Study with Oral JAK Inhibitor Treatment COMFORT-I and COMFORT-II studies which looked at intermediate-2 and high-risk myelofibrosis patients. These are both randomized, phase 3 studies in intermediate-2 and high-risk myelofibrosis. In COMFORT-I, ruxolitinib was compared to placebo. In COMFORT-II, ruxolitinib was compared to the best available therapy (BAT).

In COMFORT-I, ruxolitinib achieved a spleen volume reduction (SVR) greater than or equal to 35% in 41.9% of patients compared to 0.7% of patients receiving placebo. We can also see that patients achieved a greater than or equal to 50% reduction in their MPN-SAF total symptom score with ruxolitinib 45.9% of the time vs 5.3% with placebo and this was also statistically significant. Then we see that patients had comparable rates of discontinuing ruxolitinib and placebo on COMFORT-I.

With COMFORT-II, we can see that spleen volume reduction of 35% or more was achieved in 28% of patients receiving ruxolitinib vs 0% on best available therapy. Adverse event discontinuation was 8% with ruxolitinib vs 5% with BAT. There are hematologic side effects with ruxolitinib and grade 3 and 4 cytopenias occurred 45%, 13%, 7% of the time, for anemia, thrombocytopenia, and neutropenia, respectively, with ruxolitinib, vs 19%, 1% and 2% of the time on placebo. Certainly, some hematologic toxicity where patients had lower blood counts over time on ruxolitinib.

On COMFORT-II, a post hoc overall survival analysis was performed as there was significant confounding present due to large amounts of crossover in the COMFORT trials. The median follow-up was 4.3 years and the majority of patients who started on BAT crossed over to ruxolitinib later on in the study. And then, RPSFT (rank-preserving structural failure time), is a method that was used to estimate treatment effect correction for crossover to understand whether there was a statistical benefit to overall survival in patients receiving ruxolitinib vs placebo. There was a 33% reduction in the risk of death with ruxolitinib over BAT and, with this model that accounted for crossover, the reduction in the risk of death was 56% with a hazard ratio of 0.44.

Ruxolitinib can overcome the adverse prognostic risk associated with anemia in myelofibrosis. Anemia is incorporated into the risk factors or the risk scoring systems that help us prognosticate among myelofibrosis patients. However, anemia is not a contraindication for ruxolitinib use. COMFORT study analyses reveal improved overall survival in the ruxolitinib arm vs control arm seen both in patients with and without anemia at baseline. New or worsening anemia developing postbaseline did not affect overall survival during ruxolitinib therapy and transient changes in hemoglobin during ruxolitinib initiation and treatment should not lead to premature interruption or discontinuation.

Hemoglobin changes while on ruxolitinib treatment did not result in the same adverse prognostic implications compared to hemoglobin changes due to myelofibrosis pathophysiology. If the anemia is due to myelofibrosis, it is considered an adverse risk feature. If the anemia is due to ruxolitinib, it is not considered to be an adverse risk feature. Some clinical pearls related to the use of ruxolitinib include that it can be effective regardless of a patient's mutational profile. It's not specific for a JAK2 V617F mutation. We should start the dose based on the platelet count. The development of anemia does not affect the benefit of ruxolitinib, especially the survival benefit of ruxolitinib. Avoid abrupt interruption of therapy in patients who are responding. There was a story about long-term risk for secondary hematologic malignancies, in particular non-Hodgkin's lymphoma, on ruxolitinib, and further analyses calls this into question and now some of these findings appear to be unsubstantiated. Patients on ruxolitinib are at risk for dyslipidemia and we should check a lipid panel approximately 2 to 3 months after ruxolitinib initiation and monitor lipids regularly thereafter.

Fedratinib in Myelofibrosis

Michael Grunwald, MD: Fedratinib for primary or secondary myelofibrosis was evaluated in the JAKARTA study. Fedratinib is a highly selective, potent inhibitor of wild-type and mutant JAK2. It also inhibits FMS-related receptor tyrosine kinase 3 (FLT3). JAKARTA is an international, double-blind, randomized, phase 3 study. The patient population on this trial included adults with intermediate-2 and high-risk myelofibrosis who were previously not treated with a JAK2 inhibitor. Patients had splenomegaly. Patients had a performance status of 0 to 2, according to the Eastern Cooperative Oncology Group (ECOG) scale, and a life expectancy of at least 6 months. These patients were randomized to receive fedratinib at 1 of 2 doses or placebo, and the 2 fedratinib doses were 400 mg by mouth daily and 500 mg by mouth daily. Patients were treated for at least 6 consecutive 4-week cycles, regardless of whether they received fedratinib at either of these doses or placebo. Treatment was continued until disease progression or unacceptable toxicity and crossover was allowed for the placebo group.

The primary endpoint was 35% or greater spleen volume reduction. Fedratinib 400 mg daily led to an SVR rate of 36.5%. Fedratinib 500 mg daily led to an SVR rate of 40.2%. Placebo led to an SVR rate of 1%, and this was statistically significantly different between the fedratinib arms and the placebo arms. Important secondary endpoints were overall response rate and a 50% or greater reduction in total symptom score, and we can see here that both of these favored the fedratinib arms over placebo as well. Fedratinib spleen response efficacy was also seen in patients previously treated with ruxolitinib on another study called JAKARTA-2.

Clinical pearls regarding fedratinib are first that it is approved by the US Food and Drug Administration (FDA) for adult patients with intermediate-2 and high-risk primary or secondary myelofibrosis. Patients can rarely experience Wernicke's encephalopathy—in about 1.3% of patients—therefore we should not start fedratinib in patients who have thiamine deficiency, and we should measure a thiamine level before starting fedratinib. I always start patients on thiamine supplementation when starting fedratinib in a preventative way. Dose reductions are required for patients who have severe renal impairment or patients receiving strong cytochrome P450 family 3 subfamily A member 4 (CYP3A4) inhibitors, such as clarithromycin, ketoconazole, and ritonavir. Some of the clinical features of Wernicke's encephalopathy include ataxia, altered mental status, and ophthalmoplegia.

Pacritinib in Myelofibrosis

Aaron Gerds, MD: In addition to ruxolitinib and fedratinib, we have a third JAK inhibitor that is approved for the treatment of myelofibrosis, called pacritinib. Pacritinib is unique from the other 2 where it does inhibit JAK2, but it also inhibits JAK3 but spares JAK1. It also has off-target effects on interleukin-1 receptor-associated kinase (IRAK), which we think is important in patients who have more dysfunctional bone marrow or cytopenic myelofibrosis.

Pacritinib was tested in a number of studies. The key study being the PERSIST-2 trial which was a phase 3 trial in myelofibrosis with patients with a platelet count less than 100,000 per microliter. Again, focusing on the cytopenic population; its key endpoints were a coprimary endpoint of spleen volume reduction of 35% or greater as well as a total symptom reduction of at least 50% where it did outperform best available therapies on both marks. It had a better spleen volume response and total symptom reduction.

In an ad hoc analysis, looking at PERSIST-1 and PERSIST-2 evaluated all together, spleen responses with pacritinib were observed across all allele burdens. Even [in] patients who have very low JAK2 V617F allele burdens, we did see responses. There were way more symptom responders in the pacritinib group vs best available therapy. I want to make an additional point that most patients in the best available therapy group received ruxolitinib as the best available therapy.

One of the other key points with pacritinib is it was put on a clinical hold during its development over concerns of increased bleeding and cardiac risks. It is important to look at the safety with pacritinib. Data from the prospective, randomized PERSIST-2 trial, which served as part of the foundation of the regulatory approval of pacritinib, identified certain side effects.

We want to look at bleeding and cardiac events, but first, the most common side effect is diarrhea. GI upset is common with diarrhea and nausea being prevalent. That

is largely due to the targeting of FLT3, like we saw with fedratinib. It is advisable to start patients on loperamide and antiemetics to get patients through the early phases of the treatment.

We did not see any cases of Wernicke's encephalopathy during the development of pacritinib. The warning about thiamine levels and checking thiamine and starting thiamine supplementation is not with pacritinib. Being tested in a patient population of patients with low blood counts, we see significant numbers of patients having or developing thrombocytopenia and anemia while on treatment with pacritinib. This did not seem out of proportion with the cytopenias developed on ruxolitinib when you pull that out of the best available therapy arm. There was a fair number of patients on ruxolitinib as well as simple observation and supportive care on this trial. In terms of developing congestive heart failure, there were a handful of patients that developed congestive heart failure in both arms.

With the hold on pacritinib after the PERSIST-2 trial due to the bleeding and cardiac concerns, the PAC203 study was launched. PAC203 is a randomized, phase 2 trial looking at 3 different doses of pacritinib, to find the optimal dose incorporating both efficacy and safety endpoints. Additionally, in this study, a more rigorous cardiac evaluation, both at the time of initiation of treatment, as well as observation throughout the study, was employed. This gives us a better sense of how we should monitor cardiac toxicity in these patients. The primary endpoint of this study was to confirm or determine the recommended dose going forward, as well as looking at dose response curves for this drug. We want to see, as the dose goes up, do we see better symptom and spleen responses? In fact, that was the case. As the dose went from 100 mg daily to 100 mg twice daily to 200 mg twice daily, we saw the proportion of patients who had spleen volume change by week 24 increase from 0% to 4% to 19%. In those who had evaluable SVR, in patients with severe thrombocytopenia, platelet counts less than 50,000 per microliter, 31% of patients had at least a 35% reduction in their spleen volume. By looking at this dose-response curve, we confirmed that the 200 twice daily dosing was the optimal dose in these patients.

Symptom response was less obvious when looking at the proportion of patients who had at least a 50% reduction in their symptom scores from dose to dose. But when you analyze total symptom score (TSS) as a continuous variable, there was a clear dose response curve where few patients who were on the 100 mg once daily had a symptom response, while those who were on 200 mg twice daily had a significant reduction in their total symptom scores.

The other major component of the PAC203 study was looking at safety. The take-home point was there did not seem to be an increased risk of major adverse cardiac events, specifically when patients were screened prior to study looking for these events and managed tightly throughout the treatment course. An electrocardiogram (ECG) is recommended per package insert prior to starting treatment with pacritinib, looking for prolongation of the corrected QT interval or measurement of QT interval at a standard heart rate of 60 beats per minute (QTc). You want to be mindful, if a patient does have a cardiac history—whether cardiac or heart failure or myocardial infarction (MI)—you would want to monitor much more closely.

There does seem to be increased risk of bleeding over best available therapies, so there may be some inhibitory effect, although the rates of bleeding in both the PAC203 study and the PERSIST-2 study were relatively low, given the group of patients with significant thrombocytopenia.

The most impressive part is the hematologic stability in patients. When we treat patients with ruxolitinib, we often see a significant dip in the platelet counts and certainly in the red cell counts or hemoglobin counts. When we treat patients with pacritinib, these blood counts are relatively stable. Platelet counts do not really change week over week in patients treated on any dose of pacritinib, whether 100 mg daily all the way up to 200 mg twice daily. In terms of anemia, we see improvements in some patients who are treated with pacritinib which opens the idea [that] pacritinib might be doing something else. There was an abstract presented at the 2022 American Society of Hematology annual meeting that suggests that pacritinib can inhibit activin A receptor, type I (ACVR1) and improve anemia of chronic disease or anemia of inflammation in these patients. Pacritinib may not only stabilize anemia in patients with myelofibrosis, but improve it as well.

There is an ongoing trial, largely outside the United States, since pacritinib is now approved here for use in myelofibrosis by the FDA. It is a phase 3 trial looking at pacritinib with patients who have myelofibrosis and platelet counts less than 50,000 per microliter and it randomizes patients between pacritinib vs physicians' choice. The primary endpoint is spleen volume reduction at week 24.

Myelofibrosis Management Overview

Aaron Gerds, MD: Now that we have 3 FDA-approved JAK inhibitors for myelofibrosis, treatment decisions used to be easy to make because you would just put ruxolitinib everywhere, but now there are a couple of different JAK inhibitors and potentially a fourth coming along soon. How do you arrange all these therapies and select a therapy for a given individual? The NCCN and other disease experts try to put this all together and largely arrange the treatment recommendations based on 2 axes. One is often disease risk where [with] lower-risk, asymptomatic patients you continue with observation and high-risk patients are considered for transplantation and then also JAK inhibitors, either as a definitive therapy, terminal therapy for these patients, or on their way to transplant with a special case being made for anemia, where you can use ESAs, luspatercept or danazol, to fix their anemia.

Mike, if you get a patient with a new diagnosis of myelofibrosis sitting in front of you and they are symptomatic and somewhat higher risk and you are thinking about transplant, how do you pick one JAK inhibitor vs the other? I think there is a lot of data for all these JAK inhibitors in all kinds of situations, but how do you work through that process?

Michael Grunwald, MD: In my mind, the 2 frontline JAK inhibitors that are currently approved are ruxolitinib and pacritinib. For patients with a robust platelet count, I still think ruxolitinib is the go-to option. It has proven efficacy, a relatively tolerable profile from a nonhematologic perspective and even to a degree from a hematologic perspective. It also has an overall survival advantage that we've seen with the COMFORT-II analysis. And for patients with lower platelets, certainly patients with platelets less than 50,000 per microliter, I go to pacritinib as a frontline agent. For patients who are in this intermediate zone between 50,000 and 75,000 per microliter or sometimes even between 50,000 and 100,000 platelets per microliter, I have a conversation with the patient about whether we should try to start off with ruxolitinib vs pacritinib and those are on a case-by-case basis. As part of that type of patient that you described, if the patient is fit enough to potentially undergo transplant, I start having the transplant discussion with them. It is very hard with some of these intermediate-2 and higher-risk patients because we know that a lot of them can live for a significant amount of time without a transplant now. I also discuss transplant or no transplant with those patients and some of them end up getting transplanted earlier if we think that they are toward the higher-risk end of the spectrum. Some of the patients who might be in the intermediate risk and they might prefer not to take on the risk of transplant early, we might treat them with a JAK inhibitor and watch them for some time.

Aaron Gerds, MD: One of the other challenges is what do you do after the initial JAK inhibitor does not work? For patients who start off on pacritinib who already have low platelets, it is a tough argument to jump to ruxolitinib or even fedratinib. Certainly, in patients who have more preserved counts, the JAKARTA-2 data is very compelling for using fedratinib as second line, even in patients who were optimally treated with ruxolitinib or even had good responses to ruxolitinib initially. The major challenge is that middle group, patients with platelet counts less than 100,000 per microliter but maybe greater than 50,000 per microliter and I have been using more and more pacritinib in that space, based on the PERSIST-2 data and have had some good outcomes there. I think there's room to wiggle there. Of course, the challenge is getting insurance to pay for a lot of these things, and we are often beholden there, but a lot of this data can actually bolster your arguments with those payers to get these drugs for these patients.

Michael Grunwald, MD: I am excited that we have a lot more options than we used to have. When you and I started treating myelofibrosis, we really were very limited in our tool set. We have more, so at least we can have these conversations and I think these conversations are benefitting some patients now and I think we have more options on the way, both single agent and new combinations that are going to help patients even more.

Aaron Gerds, MD: It is absolutely an exciting time. We are getting there and certainly I am excited about the combination therapies coming along, the new JAK inhibitors and even agents further down the road like monoclonal antibodies and bispecific therapy. These next 5 years are going to be exciting times with new therapies in myelofibrosis.

Emerging Treatment Options for Myelofibrosis

Novel Molecular Targets

Michael Grunwald, MD: Now with all this excitement about novel therapies, we're going to talk about some of the emerging treatment options for myelofibrosis patients.

There are a number of targets that are being evaluated right now in myelofibrosis. We have a group of therapies that fall into the epigenetic modifier category with DNA methyltransferase (DNMT) inhibitors, bromodomain and extra-terminal motif (BET) inhibitors, isocitrate dehydrogenase (IDH) inhibitors and lysine specific demethylase 1 (LSD) inhibitors, with therapies that target host immunity, looking at cluster of differentiation 123 or interleukin-3 receptor (CD123) as a target, as well as checkpoint inhibitors to try to get the immune system revved up against myelofibrosis. We have a telomerase inhibitor that targets DNA replication and then we have multiple signal transduction inhibitors, including JAK inhibitors, proviral integration site for Moloney murine (PIM) inhibitors, phosphatidylinositol-3 (PI3) kinase inhibitors and heat-shock protein 90 (Hsp90) inhibitors.
We have therapies that are trying to disrupt the tumor microenvironment and that includes tumor growth factor-beta (TFGβ) trap, R human fibrocyte 1 and P-selectin. And finally, we have apoptotic pathway enhancers, including B-cell lymphoma 2 (BCL-2) inhibitors, B-cell lymphoma homology 3 (BH3) mimetics, murine double minute 2 (MDM2) inhibitors, second mitochondria-derived activator of caspases (SMAC) mimetics and tumor necrosis factor-related apoptosis inducing ligand (TRAIL) inducers.
And many of these therapies are now in phase 3 trials, including the BET inhibitors, telomerase inhibitors, JAK inhibitors, PI3 kinase inhibitors, and BCL-2 inhibitors.

Momelotinib (JAK/ACVR1 inhibitor

Michael Grunwald, MD: MOMENTUM is a phase 3 trial of momelotinib for anemic patients with myelofibrosis who received prior JAK inhibitor therapy. Momelotinib is an oral inhibitor of JAK1, JAK2 and ACVR1 with the potential to improve anemia and symptoms in patients with myelofibrosis. We know that anemia in myelofibrosis is multifactorial. It results from dysregulation of the JAK-STAT pathway and ACVR1 hyperactivation. ACVR1's involved in hepcidin regulation, so elevated ACVR1 in myelofibrosis changes hepcidin levels and results in poor iron homeostasis. Momelotinib can improve anemia in patients with myelofibrosis through the ACVR1 pathway.

On the MOMENTUM study, patients were randomized to receive momelotinib or danazol. These were all patients with intermediate-2 or high-risk myelofibrosis and hemoglobin less than 10 g/dL. Patients had splenomegaly and they also had symptoms. They had total symptom scores of 10 or greater and they all received a prior JAK inhibitor. Two-thirds of patients received momelotinib, one-third received danazol, and the primary endpoint was the total symptom score at week 24. There were several important secondary endpoints that were evaluated, including transfusion independence at week 24 and splenic response rate at week 24.

The primary endpoint of total symptom score response was reached in this study with 24.6% of patients who received momelotinib achieving the total symptom score response whereas only 9.2% of danazol patients achieved this response. The total symptom score was maintained from week 24 to week 48 in 97% of patients receiving momelotinib and in all 6 of the 6 patients who received danazol; these 6 patients were switched over to momelotinib midstudy.

There were some patients who did not initially achieve a total symptom score response to momelotinib at week 24 who later achieved a response by week 48. And this was 12% of patients. There were 17% of patients who were switched over from danazol who did not initially achieve a response, but then had a 48-week response in their total symptom score with receiving momelotinib. There were a number of total symptom score responses after week 24 in the patients who switched from danazol to momelotinib.

In terms of safety, for patients who were on momelotinib throughout the study, there were 49.5% who had grade 3 or higher adverse events and 46.3% of the patients who initially received danazol and later received momelotinib had grade 3 or higher adverse events. In terms of serious adverse events, that first group had 31.2% and 29.3% of the second group had serious adverse events. When we look at grade 3 or higher side effects that were possibly attributable to momelotinib, there were some patients who had thrombocytopenia, anemia, and neutropenia, but relatively small numbers with grade 3 or higher adverse events. And we can also see that relatively small numbers had diarrhea, hypertension, asthenia, and there were cases of Coronavirus disease 2019 (COVID-19) pneumonia.

Navitoclax (BCL-2 inhibitor) Combination

Michael Grunwald, MD: There is an ongoing combination study looking at navitoclax, a BCL-2 inhibitor, in combination with ruxolitinib for patients with myelofibrosis and no previous JAK inhibitor therapy. This is called the Trial of Navitoclax with Ruxolitinib for Myelofibrosis (TRANSFORM) study and the concept here is that navitoclax has potential synergistic properties and the ability to overcome JAK inhibitor resistance. There was a previous trial, the REFINE phase 2 study, looking at patients who had received a previous JAK inhibitor and, on this study, the combination with navitoclax helped patients achieve splenic volume reduction as well as total symptom score reduction, 26.5% and 30% respectively.

On this TRANSFORM-1 phase 3 international, double-blind, randomized study, we have patients with intermediate-2 and high-risk myelofibrosis who are symptomatic, who have splenomegaly and who are naïve to JAK inhibitor, BET inhibitor and BH3 mimetic therapy, being treated either with navitoclax plus ruxolitinib vs placebo plus ruxolitinib. And the primary endpoint is splenic reduction of greater than or equal to 35% at week 24. There is also the TRANSFORM-2 study, which is a phase 3 study evaluating patients who have been previously treated with JAK inhibitors.

Parsaclisib (PI3K inhibitor) Combination

Aaron Gerds, MD: Ruxolitinib has been the mainstay of treatment for so long and it is proving to be a key component of what we are doing going forward, serving as a backbone for combination therapy. Certainly, I do not want to take anything from ruxolitinib, but we always want to do better and certainly navitoclax is one of those combinations we're closely watching.

Another combination that we are closely watching is parsaclisib plus ruxolitinib in patients with myelofibrosis. Parsaclisib is a PI3 kinase delta inhibitor, so you may be familiar with this pathway in treating lymphoid diseases. Just like we use BCL inhibitors in lymphoid diseases, this translates onto myeloid disease. It is a common deranged pathway in hematologic malignancy.

Parsaclisib trials are built on a phase 2 study where patients were treated with parsaclisib and showed significant disease control. It was one of these add-back strategies where patients who were suboptimally treated, when you added parsaclisib back to the ruxolitinib, we saw a regain of symptom and spleen control, as well as some interesting correlations in terms of better, deeper responses.

From that spurs the Leading in MPNs Beyond Ruxolitinib (LIMBER) -313 and -304 studies and the key difference there are different populations. LIMBER-313 is going to be patients who are naïve to treatment, have never had a prior JAK inhibitor or PI3 kinase inhibitor where they are randomized between ruxolitinib with parsaclisib or placebo. And that study has a primary endpoint of a spleen volume reduction at week 24. The LIMBER-304 study is similar to the phase 2 trial that preceded it where patients who were on stable ruxolitinib and had a suboptimal response or lack of response and you add back a therapy like parsaclisib to regain those responses or deepen the response or get a better response. Again, this is ruxolitinib with parsaclisib or placebo with a primary endpoint of spleen volume reduction at week 24 as well.

Pelabresib (BET inhibitor) Combination

Aaron Gerds, MD: The next kind of combination that is coming rapidly, along with the navitoclax combination, is that with a BET inhibitor, pelabresib. Again, this is an all-

oral therapy, ruxolitinib plus pelabresib, and the MANIFEST-2 trial is a prospective, randomized trial comparing ruxolitinib plus placebo vs ruxolitinib plus pelabresib. And this is following the MANIFEST study, which is a phase 2 trial that looked at ruxolitinib plus pelabresib in both the up-front and second-line settings, as well as pelabresib as a single agent. A number of different arms for phase 2, but the key take-home points from the MANIFEST study were that, in the up-front setting, the response rates seen with the combination were double that of what we would normally expect with ruxolitinib alone. That certainly heeded on the development of this MANIFEST-2 trial.

The MANIFEST-2 trial randomized patients in a 1-to-1 fashion between ruxolitinib with pelabresib or placebo with a primary endpoint of spleen volume reduction at week 24 and a secondary key secondary endpoint of total symptom response at week 24. This study has completed enrollment and patients are now in that initial evaluation. There is no data lock yet at that week 24 endpoint, but there will be very soon. Potentially, by the end of 2023, we could see some results from this study. The navitoclax study, the TRANSFORM study, as well as MANIFEST-2 are the 2 most closely watched, up-front studies, and we eagerly await these results.

Imetelstat (telomerase inhibitor)

Aaron Gerds, MD: A bit of a departure from these other studies is this study with imetelstat. And the reason it is a major departure [is, number] 1, it is a single agent study, so it is not combination therapy. It is a radical treatment, working on a telomerase, which is the end component on chromosomes and holds all the DNA together. Cells that can become immortal, they get telomerase and that keeps stacking on these caps to the ends of the genes and then the chromosomes and, if you block that pathway, the telomeres become very short, and the cells can then die.

In the phase 2 trial, there was a suggestion that patients were living longer when they received this telomerase inhibitor, imetelstat. The phase 3 trial that was planned, based on the phase 2 study, is a bold one for the fact that its primary endpoint is overall survival, which is the goal for our patients to not only live better, but to live longer. Credit is given to the team who are putting this study together because it is looking at a primary endpoint of overall survival. This trial is currently open and enrolling patients. Enrollment is going well and should finish in the near future. Over the next couple of years, we are going to have read-out of multiple large, pivotal, randomized phase 3 trials in myelofibrosis. I cannot overstate how exciting this time is in the field.

Novel Therapy Clinical Trial Summary

Aaron Gerds, MD: We have drugs that are on the cusp of approval potentially, such as momelotinib. We have MDM2 inhibitors, navtemadlin and imetelstat, being developed. There is an LSD1 inhibitor, bomedemstat, that has been studied in a phase 2 trial in myelofibrosis and is also being tested in phase 3 trials in ET and a phase 2 trial in PV. There are all these combinations that are upcoming. One we did not mention already was the combination of ruxolitinib and selinexor. The myeloma world will be familiar with that drug. Hypomethylated agents have been combined with ruxolitinib as well as IDH inhibitors. IDH inhibitors are approved for the treatment of acute myeloid leukemia, but IDH1 and 2 mutations do occur in myelofibrosis, and it would make sense to use an IDH inhibitor in combination or by itself in these patients with such an advanced disease.

Future Myelofibrosis Management Considerations

Aaron Gerds, MD: How is future management going to look when momelotinib gets approved or some of these other new drugs are approved? We are going to have to revamp all our treatment algorithms. For those of us who work on guidelines, it is going to be a nightmare, but a nightmare we want to be a part of because it means we have more treatments for our patients.

The trickiest part in the near future is if momelotinib becomes approved, how are we going to splice that in with the other JAK inhibitors? Is it solely going to be for anemia patients? Do we consider patients with thrombocytopenia because the MOMENTUM study included patients with platelet counts as low as 25,000 per microliter. When we start thinking about combination therapies, how do you decide to use a combination, especially in the up-front setting, vs a single agent JAK inhibitor? It is really going to be a challenge and so we will have to parse through the data from these trials. Are

treatment responses deeper? Are they more durable to suggest that we should use combination therapy over single agent? This is going to be the hardest question moving forward.

I want to bring you back in, Dr. Grunwald, to talk about this. You know, in the advent that momelotinib gets approved and we have then 4 JAK inhibitors, what places would you consider using momelotinib either in the front-line or second-line setting?

Michael Grunwald, MD: I would consider using it in both front-line and later lines of therapy. Especially in front-line patients who are already transfusion-dependent or the front-line patients who might be on the verge of becoming transfusion-dependent, patients who have a hemoglobin in the 8s (g/dL) or the low 9s (g/dL). If I start them on ruxolitinib, they are going to need transfusions, which is a little scary for patients and can sometimes impact quality of life, if not length of life. I would consider momelotinib as a transfusion-sparing agent early on and then, later, if a patient were on ruxolitinib and started to develop significant anemia to the point where they are requiring transfusions, that is where I would think about switching to momelotinib. What is a little tricky is that the pacritinib inclusion criteria had a lot to do with the platelet counts. Momelotinib inclusion criteria on MOMENTUM had the hemoglobin of less than 10 g/dL. These drugs were studied in certain specific context and now we are learning that perhaps hemoglobin can be maintained or increased in pacritinib patients. We are learning that platelets do not necessarily drop in momelotinib-treated patients. We are going to learn more about both drugs as time goes along.

Aaron Gerds, MD: For combination therapies, which are the next wave in myelofibrosis certainly in the up-front setting, I would want to see a deeper response than with just ruxolitinib alone or a more durable therapy long-term to justify using combination over single agent ruxolitinib. Do you have any thoughts on what would push you more towards using combination therapy in the up-front setting vs ruxolitinib or other JAK inhibitors alone?

Michael Grunwald, MD: It will be a balance between toxicity and benefit. An overall survival benefit would be a pretty strong argument to be able to make if a study were able to show overall survival with combination. Of course, all the combination studies that we discussed today were looking at other endpoints aside from survival. A lot is going to depend on toxicity and benefit and what that ratio is. It might be the case that there are some patients who are well toward the higher risk end of the spectrum with myelofibrosis who are not eligible for transplant and those might be patients who could benefit from a safe and effective combination therapy to provide long-term benefit without a transplant.

Aaron Gerds, MD: Absolutely, and unfortunately some of these studies are just designed to where we are not going to get the best survival data. There is crossover and it will be hard to tease through some of that. Certainly, those are some important considerations for these very exciting therapies to come.

Case Challenges– Myelofibrosis Treatment Individualization

Case 1

Aaron Gerds, MD: We have patient case number 1, which is a 60-year-old woman with a history of thrombocytosis and hypertension and referred for evaluation. She reports fatigue and occasional night sweats that have negatively impacted her daily life and functioning. White blood count (WBC) is $5x10^9$/L, hemoglobin is 14 g/dL, and platelet count is 120,000 per microliter. We have talked about platelet counts, so keying in on those. LDH (lactate dehydrogenase) is 248 U/L, which is a little bit elevated. The spleen is palpable on exam and a bone marrow aspirate is inconclusive, which often occurs in patients with MPN. The patient is JAK2 V617 positive, breakpoint cluster region-Abelson-1 (BCR-ABL1) negative. The patient has normal bone marrow histopathology on the core biopsy. There is grade 2 fibrosis and some hypercellularity. There are no high-risk genetic mutations or cytogenetics present.

Thinking about this individual's diagnosis, the grade 2 fibrosis by the WHO grading system would lead you to a diagnosis of myelofibrosis. There is no antecedent history of PV or ET. They have had a history of thrombocytosis, but have never been officially diagnosed with ET. You would say this is primary myelofibrosis, an overt myelofibrosis.

Aaron Gerds, MD: In terms of risk stratification, we could apply all the models here since we have molecular information, we have nonmolecular information. Without high-risk mutations and relatively preserved platelet counts, you can tell that this person is relatively low risk and doing quite well overall but is symptomatic. When you think about treating this person, they have splenomegaly, they have night sweats that are impacting their functionality every day. It would be fair to think about treating this patient. Certainly, in lower-risk patients, we consider hydroxyurea, which is excellent at controlling blood counts, maybe not the best at doing other things. Interferons can work as well, but often work best in patients with grade 0 or maybe grade 1 fibrosis. When you get beyond that, the efficacy tends to wane.

Aaron Gerds, MD: You are thinking about a JAK inhibitor for this individual and having a platelet count of 120,000 per microliter, my first inclination would be to reach for ruxolitinib. I think 1 of the bigger questions would be perhaps what dose you would start. Dr. Grunwald, are you the type who likes to start low and work your way up or do you follow the FDA-label dosing to the letter of the law and work that way?

Michael Grunwald, MD: I tend to find that a lot of patients will respond at the 10 mg dose, and I will find the counts are relatively well-preserved. There is time to adjust the dose later if necessary. This case is definitely a ruxolitinib patient and I would tend to start this patient on 10 mg twice a day, see what happens with the symptoms in terms of response, look at the counts over time, and if the patient needs a higher dose later, I would increase the dose, and if the patient dropped their blood counts too much, I would consider dropping the dose to 5 mg twice daily, which I think is unlikely in this scenario.

Aaron Gerds, MD: Absolutely. I think you hit all the great points there and this patient probably does not necessarily need the 20 [mg] twice a day, but certainly from the COMFORT data, we know there is a dose response curve so 5 mg twice a day probably is not going to do much, so starting off at 10 or 15 makes a lot of sense. There is some good prospective data to support that. Subsequent trials done after the COMFORT studies looked at what dose to start at and there is not only practical everyday data that we get anecdotally, but some good trial data to support that. To me, this patient does not jump out at particularly high risk either in terms of needing to get them in with transplant sooner rather than later. I think this is something that could be addressed as time goes along and you develop that relationship with the patient and perhaps get their human leukocyte antigen (HLA) typing over the course of the year or 2. Certainly, a good case, a classic symptomatic myelofibrosis patient starting on ruxolitinib.

Case 2

Michael Grunwald, MD: A 75-year-old male who is diagnosed with myelofibrosis has a white blood cell count (WBC) of $7x10^9$/L, hemoglobin 8.5 g/dL, and platelet count 30,000 per microliter. There is some significant thrombocytopenia here. The patient reports fatigue, night sweats, and bone pain. He is found to have an enhancer of zeste homolog 2 (EZH2) mutation. Bone marrow histopathology reveals grade 2 fibrosis and a hypercellular marrow, as we often see in myelofibrosis. The MIPSS-70+ version 2.0 score is 6 and DIPSS-plus is 4, so certainly a higher risk patient. Our front-line treatment considerations include the patient's risk and health status here as well as the thrombocytopenia. This patient is older, 75 years old, not only the thrombocytopenia with a platelet count of 30,000 per microliter, but also the hemoglobin of 8.5 g/dL. Anemia to the point where this patient might require a transfusion soon and the patient has significant symptoms and an adverse risk mutation with EZH2 mutation present.

Michael Grunwald, MD: All of these factors come into play, as we think about this patient's front-line treatment option. Right now, with our currently available, FDA-approved options, this would be a pacritinib patient in my clinic. I would start this patient at standard-dose pacritinib with 200 mg twice daily and monitor the counts closely. I would offer support for the hemoglobin potentially, so this is a patient where I might check a serum erythropoietin level. I would think about an ESA if the serum erythropoietin level was low. I would offer transfusion support if necessary. I would also have a conversation with the patient about transplant. Now, some might think transplant is not appropriate because this patient is toward the older end of the age spectrum, being age 75 years, but as a transplanter myself, I would have that conversation with the patient and see what the patient's goals are and what the patient's comorbidities

are, because if this is a relatively healthy 75-year-old patient who, without myelofibrosis, might have a life expectancy in the early 90s (years), I think it could make sense to think about transplantation. On the other hand, if this is a patient whose has comorbidities and might not have that long a life expectancy without myelofibrosis, that might guide me away from having the transplant conversation too seriously. If the patient had disease progression or intolerance of pacritinib, we would have to start thinking about second-line treatment options which could be a little bit challenging, given the cytopenias here. What do you think about this patient, Aaron?

Aaron Gerds, MD: I have similar thoughts that you have. Certainly, given the thrombocytopenia and significant disease, pacritinib is the direction I would go first. And you made a really important point of starting out at the recommended dose, 200 mg twice daily. Clearly, there is a dose response curve for response, but not for cytopenias and side effects. You do not receive any benefit in terms of avoiding side effects by reducing that initial starting dose. I would also start with pacritinib 200 twice daily for this patient. I think the transplant conversation is incredibly interesting. We often apply the number (N)plus 5 rule when considering age and transplant, N being the age of the oldest transplanter in the group. You can always guess that practices will transplant people up to 5 years over the age of the oldest transplanter in the group. Certainly, if you have someone who is 70 years old within your transplant group, you might go ahead and transplant this individual. I think it is worth having that conversation, at least, and if they are a fit person, consider doing transplant. Transplant in blood diseases is not like solid organ because it is a renewable resource. You are not taking an organ from 1 person and giving it to another. You are spreading the bone marrow around and it grows right back after you harvest it. There is less of that age factor when it comes to these things and more of an individual's willingness to accept risk. And second-line therapy is going to be tough. If momelotinib were approved, that would be a clear place to go. This person would have been potentially eligible for the MOMENTUM study if they had a previous JAK inhibitor. That would be a treatment option hopefully in the near future if it gets approved. Otherwise, low dose ruxolitinib if pacritinib is not a very effective treatment, especially when you are attenuating the doses, considering platelet counts of 30,000 per microliter. It is a tough place to be in the second-line setting, but hopefully we will have some new agents in the very near future to address patients like this.

SUMMARY

Michael Grunwald, MD: We have learned that myelofibrosis is a rare MPN that contributes to heterogeneous, nonspecific symptoms leading to a significant disease burden. Features of disease include fatigue, infection, anxiety, depression, and progression or transformation to acute leukemia in 10% to 20% of patients. Myelofibrosis involves multiple key molecular mutations associated with disease pathophysiology, severity, and novel treatment target potential. It is not just JAK2 anymore. JAK2 is a big part of it, but we have other targets and a lot of prognostic indicators with molecular mutations.

JAK2 inhibitors and supportive care for anemia are still mainstays of treatment for intermediate to high-risk myelofibrosis. Ruxolitinib, fedratinib and pacritinib, which pacritinib is specifically for patients with thrombocytopenia are now available. Hematopoietic stem cell transplantation is the only curative treatment option currently, but use is limited due to toxicity and the potential for complications.

Novel therapeutic options are currently undergoing clinical trials and offer promise to address current treatment gaps. We have new molecular targets, including ACVR1, MDM2, telomerase and LSD1, for example, as well as treatment options that may be on the way in the near future, including momelotinib and others. We have JAK2 combination therapies currently in studies with the non-JAK2 inhibitor agent targeting BCL2, PI3 kinase, exportin 1/nuclear export protein (XPO1), and IDH, for example. Understanding current and future trends in myelofibrosis and understanding molecular pathways will allow providers to optimize and individualize patient care. Thank you very much for your attention and participation in this activity.

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