

## THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

### ***Episode: 'Living with Myeloproliferative Neoplasms (MPNs)'***

#### **Description:**

In the episode, we explore the family of diseases called myeloproliferative neoplasms (MPNs). Dr. Anand Patel and Dr. Olatoyosi Odenike of The University of Chicago Medicine share the latest advances in treatments for MPNs, including myelofibrosis (MF), polycythemia vera (PV) and essential thrombocythemia (ET). We also highlight how treatment teams prioritize the improvement of patients' quality of life as a key aspect of care.

#### **Transcript:**

**Elissa:** Welcome to *The Bloodline with LLS*. I'm Elissa. Thank you so much for joining us on this episode.

Today, we will be speaking to Dr. Toyosi Odenike and Dr. Anand Patel about myeloproliferative neoplasms, or MPNs. Dr. Odenike is a Professor of Medicine and Director of the Leukemia Program at the University of Chicago Medicine and is an expert in care of adults with myeloproliferative diseases, leukemias, and myelodysplastic syndromes, or MDS. She has served as the principal investigator of several clinical trials to develop new drugs and targeted treatments for these diseases with a goal to improve patient outcomes.

Dr. Patel is a hematologist/oncologist at the University of Chicago Medicine who specializes in the treatment of leukemias, myelodysplastic syndromes, and MPNs. In addition to treating his patients with standard treatment approaches, he is committed to delivering novel therapies through clinical trials that combine basic and translational research into groundbreaking advancements in medicine for better outcomes and quality of life.

You may recognize Dr. Patel from when he joined us in previous podcasts, including "Hopeful Advancements in Chronic Myeloid Leukemia" in February of 2023. Welcome Dr. Odenike and welcome back, Dr. Patel.

**Anand Patel, MD:** Thanks so much for having us.

**Toyosi Odenike, MD:** Thank you so much.

**Elissa:** So, our episode today is on myeloproliferative neoplasms, or MPNs. Could you explain to our listeners what that is?

**Dr. Patel:** Myeloproliferative neoplasms, or MPNs, are a family of diseases; and they are a family of stem cell disorders. So, in our bone marrow we have our stem cells, which then differentiate and turn into the blood cells that we need for day-to-day existence – our white blood cells, which do things like fight off infection; red blood cells or hemoglobin, which carry oxygen to important organs; platelets that help with clotting.

So, broadly speaking, myeloproliferative neoplasms, it kind of describes what they are in the name. There is an excess production of these blood cells because of a genetic insult that happens in one of these hematopoietic stem cells. This is considered a cancer or a clonal stem cell disorder; and what someone's blood counts look like, what we find on a bone marrow biopsy, symptoms they may have, and genetic or chromosomal mutations can then help us to better characterize what subtype of MPN someone may have.

**Elissa:** Before we get into the subtypes of the MPNs, I'm really glad that you mentioned that it is considered a cancer. I think a lot of MPN patients are just told that this is a blood disorder, which is true, but it does leave out those extra resources that they could get from a cancer organization like LLS, correct?

**Dr. Odenike:** Yes, Elissa, you are correct. I think this is a big question that we get asked by our patients all the time. Is this a cancer? My answer to that is generally,

yes. Scientifically speaking, it is a cancer because these are mutations that result in the stem cells, turning over sometimes quicker than we would like, resulting in all of these, excess blood cells. Even though these are chronic diseases, meaning that individuals can survive for very many decades, depending on the type of MPN that you have, they are all characterized by the potential that other downstream complications can occur for which patients need to be monitored very carefully over time, including transformation to a more aggressive cancer or leukemia.

**Elissa:** Now, what are the subtypes of MPNs that you were just referring to earlier?

**Dr. Patel:** So, when we think about MPNs, the first thing that we kind of think about is does this MPN have what's called the Philadelphia chromosome or not? And if they do, we characterize that as CML or chronic myeloid leukemia.

Now the treatment approach for CML is quite different than it is for some of the other MPNs, so we really think of it as its own disease entity; and these days we talk about it in its kind of own separate package because there's a class of oral drugs that are very effective and act specifically on this Philadelphia chromosome.

Moving beyond that, someone having an MPN that does not have the Philadelphia chromosome, there are three subtypes that are the most common. I'll emphasize these three are not all-encompassing. There are several different subtypes of MPNs. But the three most common are polycythemia vera, or PV for short, which is typically characterized by an increased red blood cell count or hematocrit, which is another way of looking at the red cells. There's essential thrombocythemia, or ET, which is typically characterized by a high platelet count, platelets being the clotting blood cells. And primary myelofibrosis, which can actually be quite variable in terms of what the blood counts look like.

Early on in the disease state with primary myelofibrosis, or PMF, blood counts can actually be high, whether it be the white blood cell count, platelet count, or even sometimes the hemoglobin count. As the disease progresses, as more of the bone

marrow has fibrosis or scarring, those blood counts can actually drift into the normal range and, with further progression, can drift down into the lower-than-expected range. So, for PMF, depending on at what stage of the disease someone's diagnosis is made, their blood counts can be high, they can be normal, or they can even be low.

**Elissa:** So, of the classic MPNs that you just mentioned, myelofibrosis, polycythemia vera, and essential thrombocythemia, what are the common signs and symptoms that a patient may have? So, what usually would bring that patient into a doctor in the first place?

**Dr. Odenike:** Those signs and symptoms are variable, depending on the type of MPN and the phase at which the patient presents. Sometimes, patients can be totally asymptomatic, meaning they have no symptoms. They go into a doctor's office for a routine check, and for some reason, that routine check involves getting a CBC or complete blood count; and that CBC may then demonstrate that one or more blood cell lines are high.

So, for example, for polycythemia vera, there would be a higher than expected red blood cell count or high hemoglobin as Dr. Patel had, nicely outlined. With polycythemia vera, although again this is a chronic disease where patients can live for decades, it's very important to make the diagnosis in a timely fashion.

Acute problems that can arise from polycythemia vera include a stroke, a heart attack, or blood clot that maybe arises in the legs and goes to the lungs, which can be potentially life-threatening. So, even though the patient may have no symptoms or mild symptoms, maybe headaches, dizziness, or none at all, it is very important to make the diagnosis and institute treatment to try to head off some of these acute complications.

So, that would be just one example; and Anand can weigh in on some of the other MPNs and how they might present.

**Dr. Patel:** Yeah, and I think the point that Toyosi made is a very important one, which is that oftentimes it's a blood count abnormality that is the first tipoff as to further workup being required and then a diagnosis of MPN being made.

The reason that's so important is I really think of those complications that Toyosi mentioned as clotting complications – stroke, heart attack, blood clots – as being things that need intervention. And being able to catch someone when they are relatively asymptomatic allows for us to intervene on these diseases before they may suffer one of those devastating complications.

So, Toyosi has talked about PV. I'll talk some about ET and myelofibrosis. So, ET, again, many times patients are asymptomatic, meaning this is an incidental finding. Blood counts are drawn, and the platelet count is high.

There may be some overlap in the symptoms that patients can have between PV and ET, such as nonspecific fatigue, just feeling kind of rundown or not quite themselves, maybe some achiness that can't be well described. Sometimes patients will report pins and needles sensation in their extremities or things like cold sensitivity. And with myelofibrosis, many of those symptoms can persist.

One other thing that can happen is, as the bone marrow scars down, the spleen can try to pick up some of the slack when it comes to the production of blood cells. That can lead to enlargement of the spleen. And because of that, patients can have bloating. They can feel like they eat a meal and only about halfway through it they feel incredibly full because the spleen is very close to the stomach. And when it's quite large, it can actually press on the stomach and make you feel full a bit earlier.

So, those are some of the additional symptoms that we can think of related to the size of the spleen. So not all patients with MPNs will have an enlarged spleen, but those that do can certainly have more abdominal symptoms, whether it's bloating, some discomfort or pain, or it's related to their appetite or getting full early.

**Elissa:** Now Dr. Patel, earlier on you mentioned that CML is associated with the Philadelphia chromosome. We know that most blood cancers have genetic mutations or chromosomal abnormalities. Is that the case also with the classic MPNs that we've just been talking about? If so, what are the mutations that occur?

**Dr. Patel:** Yeah, that's a great question; and I'll start by saying MPNs, given that it's a family of diseases, the mutations similarly are not just restricted to one specific mutation. There are a family of mutations that these diseases can have.

So, the most common mutation is in a gene called JAK2. So JAK2 is seen in virtually 100% of cases of PV or polycythemia vera. When you look at ET and PMF, however, it's probably more like 50 to 60%.

The other two mutations that are very commonly seen are CALR and MPL, and those are seen when you add the two of them together probably somewhere in the neighborhood of 25 to 30% of the time in ET and in PMF. So, those astute mathematicians out there may have noticed it didn't add up to 100%. So, somewhere in the neighborhood of 5 to 10% of cases with ET and PMF will not have a mutation in any of those three – in JAK2, CALR, or MPL – and we will refer to those as triple-negative disease.

Now, there are a host of other mutations that can be seen in MPNs, but JAK2, CALR, and MPL are very commonly what we refer to as typical driver mutations – meaning the vast majority of patients will have mutations in one of those genes.

Toyosi, I'd love to hear your thoughts on how that gets incorporated into the conversation you have with patients and really how you talk about things with patients if they don't have one of those mutations. How we talk about the fact that this is still an MPN even though it may not have one of the mutations that we typically associate with an MPN.

**Dr. Odenike:** Yeah, so, these mutations help us in making the diagnosis. So, we now know, as Anand carefully outlined, that if you have a mutation in JAK2, MPL, or CALR (calreticulin), and your blood counts are off in some way – higher – or if you have PMF, maybe lower than the normal range, and we incorporate also your bone marrow findings, we can then subcategorize you into a particular MPN. It helps when you can put a name to it because it tells us then how the disease may behave over time and how to approach the disease.

There are patients who will have an MPN that does not have a driver mutation, but where we can still combine looking at your blood counts, how long those blood counts have been high or abnormal, how you're presenting in terms of signs and symptoms what your bone marrow looks like, and can still integrate all of that information to be able to classify the patient as having, ET; PMF, primary myelofibrosis; or PV, polycythemia vera.

There will be some patients who we would classify as MPN, not otherwise specified, NOS, which is always a little bit vexing because both the patient and the doctor would like to put a name on it. But once in a while that does happen. And our job as doctors who treat individuals with these diseases, is to look at how they are presented, what the issues are that we want to head off and develop a treatment plan or treatment recommendation regardless.

**Elissa:** Now, you just mentioned primary myelofibrosis. Does that mean that it is a brand new disease and it hasn't evolved from a different cancer?

**Dr. Odenike:** Yes. Primary myelofibrosis means that at the time that we made the diagnosis of the MPN, the original diagnosis of that MPN was myelofibrosis, meaning, the MPN manifested primarily as myelofibrosis, whereas post-MPN myelofibrosis is a term that's sometimes used; and that means myelofibrosis that arose from a background of prior polycythemia vera or ET.

**Elissa:** So, it can evolve from one MPN to a different MPN then?

**Dr. Odenike:** That's correct. And that's not always obvious when we are talking about these diseases, but we can certainly see that over time. We were talking at the beginning that survival for some of these diseases is measured in several decades. Some of my patients are, thankfully, growing old with me-

**Elissa:** That's what we like to hear.

**Dr. Odenike:** - which is nice to see with appropriate management. But regardless, there will be a fraction who will suffer, what I call late complications of the disease where 20-something years, sometimes even 30-something years, of following a patient with PV, one may then run into issues like myelofibrosis and, unfortunately, a small proportion may transform to acute leukemia, as well.

**Dr. Patel:** One thing that I find very helpful for me and for patients when we're talking about MPNs is I think of the diseases in phases. So, you really have the cellular phase of disease, meaning that the major issue is that blood counts are high; and your treatment strategy is geared towards that. Some of those patients will then potentially develop the fibrotic phase of disease. Meaning myelofibrosis, scarring of the bone marrow, and low blood counts being the major issue that we are concerned with or having to navigate. And then an even smaller subset may develop the accelerated or blast phase of disease, meaning an MPN that's starting to behave more like an acute leukemia.

And it's kind of like a pyramid where the cellular phase of disease kind of makes up the biggest part of the pyramid. It's the base. And as you kind of go up that pyramid, a smaller percentage may have development of fibrotic phase of disease or of accelerated or blast phase of disease.

And while we think of these as different diseases, PV, ET, PMF, there is some overlap; and sometimes the disease over the course of many, many years can start behaving like a different MPN than the one it was at the outset. And I think having that kind of framework of cellular phase, fibrotic phase, and then an accelerated/blast phase can



help to remind us that sometimes these diseases can wear a different disease hat than maybe it was at the beginning.

**Elissa:** Can a patient ever have two different kinds of MPNs at the same time?

**Dr. Patel:** So, that's a very good question; and sometimes there can be patients that meet criteria or have hallmarks of a couple different MPNs at once. Sometimes, we end up terming those patients, much like Toyosi was saying earlier, MPN not otherwise specified or NOS. And then clinically, us as physicians and our patients, we have to sit down and really figure out what are the main issues that are of concern to a patient? What are the main blood count issues we're dealing with? And how do we then fashion a treatment plan to address those, even if there's this "not otherwise specified" term that's been given to the MPN?

The other distinction is that both PV and ET can progress to myelofibrosis. Certainly, these are patients who, for example, if you had ET and with time your platelets may stay high. But other blood counts may start dropping; and you may do a bone marrow biopsy that then shows that there's been development of myelofibrosis. So, you still have some things that are behaving like ET in the bone marrow and some things that are behaving like myelofibrosis, now which can be evidenced by, not just the bone marrow, but that, perhaps the other blood counts are low instead of high.

**Elissa:** That's interesting. Now, you've talked a lot about how MPNs are chronic diseases; and the prognosis could be very, very good. But can they be cured?

**Dr. Patel:** In general, the only way we know how to cure MPNs definitively is with what's called an allogeneic stem cell transplant. So, donor stem cells coming from someone else, that would then be administered to the patient after they received conditioning treatment, that would wipe out their own stem cells.

Now, stem cell transplant is something that we typically only consider in patients who have MPNs that are high risk. So, when we think of high risk, that term is broad. But

things that could potentially characterize high risk is what mutations their MPN may have, what blood count abnormalities a patient may have, if there's evidence that the MPN is starting to behave more like a leukemia, if there is a dependence on blood transfusions, meaning the bone marrow is not able to keep up and develop the amount of blood or platelets or anything else that we need. Those are some of the things that really make us strongly think about, is stem cell transplant the right thing for the patient that we're seeing in the clinic? And that's always a decision that needs to be weighed carefully because stem cell transplant has its own specific considerations and potential complications that need to be addressed.

Toyosi's point of many MPNs having a life expectancy of decades, I think, really underscores the fact that many patients may live with their MPN for years and years and with appropriate management may not need a stem cell transplant to definitively cure their MPN. It may be something they live with, much like say someone may live with diabetes or high blood pressure, where you really need to manage the disease but not necessarily cure someone of the disease.

**Elissa:** So, at that point, quality of life is the goal then?

**Dr. Odenike:** Quality of life, thank you, Elissa. Yes, I agree 100%. And also trying to head off complications.

**Elissa:** Right.

**Dr. Odenike:** At any age having a stroke or heart attack, a blood clot, can be life-threatening and these are things that, oftentimes with excellent management, we can head those things off.

I like Anand's idea of thinking about these diseases with a pyramidal kind of structure in one's head. In fact, I may borrow that for my next conversation with one of my lovely patients.

And if we think about that pyramidal analogy, then when the disease is at the base, when the problem is generally having too many cells which can lead to bleeding or clotting complications interestingly, there can be paradoxical bleeding complications. We didn't talk about that much. But, at that time, we have various drugs we can use to try to manage that and other approaches to minimize those sorts of bleeding and clotting complications.

As we head up the pyramid where the issues then become more myelofibrosis, scarring within the bone marrow, a bone marrow failure presentation, then really thinking about stem cell transplants, that's the only way we can really get rid of these diseased stem cells and restore a healthy, normal functioning bone marrow. Those are the same patients oftentimes who have a higher tendency to acquire more mutations, that are not good generally and facilitate progression to an acute leukemia or blast phase type of situation. So knowing when to intervene, how to select patients in a way that would facilitate the best outcome is essential. And following patients longitudinally over time, cannot be overemphasized.

**Elissa:** Yeah. Now let's discuss current treatments. You've already talked about stem cell transplant, what are the other treatments for MF, PV, and ET?

**Dr. Patel:** So, for PV, as mentioned earlier, really our primary goal is to bring the hematocrit, which is a percentage of the red blood cells, down to reduce clotting risk. And that can be done in a few different ways. There's phlebotomy, meaning you go and you have a certain amount of blood that's drawn off; and that can be done, a couple times a year, sometimes even as frequently as every two to three months with the goal of driving that hematocrit down.

There are also medications that can be used. So, one medication that we very commonly use is hydroxyurea. So, hydroxyurea is an oral medicine that can be used for a variety of different hematologic conditions. So, it's actually used for sickle cell

anemia as well. And really, the goal of using hydroxyurea in PV is to drive down that hematocrit.

Another drug that is approved for use in PV is ruxolitinib. So typically, that's utilized in patients who may not have adequate control of their hematocrit with phlebotomy and with hydroxyurea. And then, we also have a class of drug called interferons. So, there's a specific subtype of the interferon that's approved for use in polycythemia vera as well. And this is an injectable that's used.

For ET, really the goal is helping to drive down the platelet count. That can be achieved with hydroxyurea. It can also potentially be achieved with interferon-based therapies, although technically those are not an FDA-approved method of bringing it down, but there's lots of evidence to support it, both from here in the United States and internationally. So, interferon can potentially be used. There's a medicine called anagrelide which can help bring down the platelet count as well.

When thinking of PV and ET, really the goal is normalization of the blood count that's high. We call these drugs cytoreductive drugs, meaning drugs that are going to help to bring down the blood counts to the range that they need to be.

Now an area of active investigation is whether any of these approaches not only help to normalize blood counts but potentially reduce the risk of progression of the disease to myelofibrosis.

So, that is very much an area of active investigation, thinking about, if any of these drugs are better suited to help achieve that goal. That's something that's being looked at in the context of clinical trials and studies to really get a more definitive sense of whether drugs cannot just reduce the platelet count or the hematocrit but also reduce the risk of progression to myelofibrosis. So, I think as an MPN community, that's at the forefront of our minds, thinking about not just normalizing blood counts but really reducing the risk of progression of disease.

I'll turn it over to Toyosi to talk about myelofibrosis, and I'm also eager to hear if she has any additional thoughts about PV and ET.

**Dr. Odenike:** Oh, thank you so much, Anand, for that, very detailed explanation.

For PV and ET, I would say the other thing to encourage our patients to remember is that everyone is different. It's never a one-size-fits all; and it's important to make that clear when we're having this sort of general conversation.

Because, for example, for ET, there will be some patients who we will just be observing, where we will not be recommending any medication to bring those high platelets down, although we see the number. And that is because we know that patients can do well, especially younger patients with ET for many years before they need any particular drug to bring the counts down.

And then, the other thing to say generally about both ET and PV is that there are some diseases, such as PV, where it's very clear what the goal is in terms of what the blood count should be, where we want to get it to, and it's been strongly evidence based. Many papers outlining what the gold [standard of] hematocrit is for PV. Whereas, for other diseases where we're looking at the platelets, for example, there isn't a particular hard and fast number that we can all agree to.

For myelofibrosis, this is a disease where it depends on what stage one is. This can range from no treatment needed very early on for myelofibrosis to treatment when signs and symptoms of the disease become obvious, such as having a big spleen and getting full easily, having fatigue, night sweats, weight loss. Managing those symptoms are a big part of what we do with myelofibrosis.

And ruxolitinib, which is a JAK inhibitor, it's also used for PV in certain situations, can be used to treat patients with myelofibrosis, and helps with improvement in the spleen size and improvement in symptoms. And these results can be dramatic.

There are a number of other drugs that have recently, over the past several years, been approved that fall into that class of JAK inhibitors. And it's wonderful that we now have these in our armamentarium, and some are less harsh on the blood counts. So, we now have various types of JAK inhibitors that we can reach for, depending on the patient's signs and symptoms with their myelofibrosis and what their blood counts look like. And I'd be very interested to hear from Anand about how he approaches that issue of treatment of myelofibrosis in the context of blood counts.

**Dr. Patel:** Yes, so as Toyosi alluded to, we now have four FDA-approved JAK inhibitors that are meant for myelofibrosis. So, we have ruxolitinib, fedratinib, pacritinib, and momelotinib.

And ruxolitinib is the one that we have the most familiarity with. It's been approved now for ten years plus, and it's been available. We know it's very effective, as Toyosi mentioned, at bringing down the size of someone's spleen and improving symptoms. However, the main side effect we see with ruxolitinib is sometimes it can worsen blood counts, which, obviously, we're combating in parallel with someone's symptoms, given that the reason we're treating a patient is their myelofibrosis.

Fedratinib has been approved, and there is data not just for its use in patients who have not been on any JAK inhibitor but also patients who have previously been on ruxolitinib, had inadequate control of symptoms, and then were transitioned to fedratinib. So, some patients can benefit from switching from one JAK inhibitor to another potentially.

And then, pacritinib has been specifically studied and developed in patients who have myelofibrosis and a low platelet count. So, it seems to be relatively safer to use in patients with a low platelet count.

And momelotinib, the most recently approved JAK inhibitor, it has specifically kind of been developed and studied in patients who have myelofibrosis with anemia, meaning their red blood cell count or their hemoglobin is lower than it should be.

So, really, someone's blood counts, what JAK inhibitors they may have already been treated on and whether their predominant symptom is spleen-related or more general, like fatigue or aches and pains and those sorts of things, those are some of the things that can help to arrive at what the best JAK inhibitor may be for a patient if they need treatment. So, much like the point Toyosi made earlier about PV and ET, in that every patient's kind of treatment plan is individualized to them, the same holds for myelofibrosis.

Just because someone has myelofibrosis does not mean that there's a specific JAK inhibitor that is right for all of those patients. It depends on their symptom burden, it depends on their blood counts, it depends on what their goals are. And then we arrive at kind of a shared decision about what the right JAK inhibitor may be.

**Elissa:** That's good. Now, you mentioned a little bit earlier about medications being in clinical trials to prevent progression. Are there any other emerging treatments or clinical trials that either of you are particularly excited about?

**Dr. Patel:** Yes. This past year has been an incredibly exciting one for MPNs, and I think a couple of things that I'll highlight go back to findings that were presented at our annual meeting, the American Society of Hematology (ASH) meeting in 2023.

So, one of the strategic approaches that's being investigated in myelofibrosis is combination therapy, meaning using a JAK inhibitor and adding on a second medicine to see if that will improve the effectiveness of a treatment approach.

So, two Phase III studies were presented at this past ASH conference looking at the JAK inhibitor ruxolitinib. The first study combined it with a drug called navitoclax. The second study combined ruxolitinib with a drug called pelabresib, and both of those studies found that the combination treatment was more effective at controlling spleen size than just ruxolitinib by itself.

The other thing that was looked at were symptom scores, and it did seem like the symptom scores were fairly similar in terms of improvement, whether it was with rux(olitinib) alone or with the combination treatment.

But that's the tip of the iceberg. There's several studies that are looking at this combination approach in myelofibrosis that are ongoing and really may significantly change how we think about the treatment approach to myelofibrosis.

I think it is important to note that, while these combination strategies are very exciting, we still do not think of them as curative. So, we talked earlier about how do we think about cure in MPNs. Currently, even with these very exciting treatments that are in development, stem cell transplant still appears to be the one way to potentially cure these diseases. Toyosi, any other drugs or strategies that you're excited about in the space of MPNs?

**Dr. Odenike:** Yes, those were the two that I thought really captured my attention in the myelofibrosis space at ASH. Again, because it was a large group of patients that were looked at in both of those trials; and it was what we call randomized, right? So, we could test how effective these add-on strategies are as opposed to the smaller trials that don't have a control arm. So, then it's hard to know how much the new drug is adding to the established.

But I think these two were very interesting, and I am hopeful that perhaps one or more of these approaches will make their way eventually to FDA approval, so that this kind of approach will be available for our patients.

In general, I think one vexing problem that all of these MPNs variably share, thankfully it is not the majority as a whole of patients who will experience that. But it is this idea of the disease evolving to an accelerated or blast phase. The outcome is not great at all when that happens. This is very hard to treat, much harder to treat than acute leukemia that happens without having had a prior MPN.



So, it is a big focus of Anand and mine as well, just in terms of trying to find ways to help patients who have this. Many people who are interested in treating patients with MPN, we all struggle with this as a community; and we are now trying to develop clinical trials, taking advantage of the mutations. Some additional mutations that develop, some of them that are quote/unquote what we call "targetable" and trying to use that knowledge of the mutations to develop approaches that may be more successful in putting these sorts of diseases into a remission as they are trying to evolve.

Ultimately, stem cell transplant is the gold standard if we can get our patients there. And Anand, I would be very interested to see if you have any additional thoughts about that. I know this is an area that you are very focused on trying to move the needle forward.

**Dr. Patel:** Yeah, and to give a little background, if and when an MPN starts behaving like an acute leukemia, it typically will evolve into what's called acute myeloid leukemia. And, in the last several years, we've had several drugs that have been approved for AML, or acute myeloid leukemia. And we in the MPN community will then borrow, so to speak, those drugs and use them for patients who have accelerated or blast-phase disease, meaning an MPN that's now behaving like an acute leukemia.

In general, as Toyosi mentioned, these approaches don't seem to be as effective in accelerated and blast-phase MPNs as they are in AML as a whole. So, I think really pushing our ability to specifically design trials and test promising drugs in patients with accelerated and blast-phase MPNs instead of potentially lumping them in with all AML is, I think, a very critical aspect of how we can potentially identify effective treatment strategies for this patient population specifically.

Like Toyosi said, it's not a common complication. It's quite rare in the scheme of things, but, of course, if you are a patient that has that happen where your disease becomes the accelerated or blast phase, it doesn't seem very rare. And I think it's very

important to highlight the fact that this is something that we as a community of physicians and patients and MPN community as a whole are very focused on is how do we improve the standard for our patients if their disease turns into this accelerated or blast-phase disease?

**Elissa:** Well, it's good to know that there is so much progress; but also, things really being looked at for those patients that are a little more rare, but still just as important.

And so, our final question for today, on our patient podcast home page, we have a quote that says, "After diagnosis comes hope." What would you say to patients and their loved ones to get them hope after a diagnosis of an MPN?

**Dr. Patel:** So, really, when I meet a patient with a new diagnosis of an MPN, I tend to highlight the fact that in general this is a family of diseases where patients live for decades; and really the goal is to control the disease and try to head off any potential complications. And while labeling it as a cancer can be scary for patients, I think much of that reassurance and much of the hope I try to give patients is really centered around the fact that broadly speaking, these are diseases that we can manage and can control and try to head off the major complications that are related to.

At the same time, we have made incredible progress in the field of MPNs when thinking of drug options that have become approved and many more that are in investigation. So, even for those patients who have what we may call high-risk disease that may be more prone to turning into myelofibrosis or turning into a leukemia, the hope I give those patients is that really that the landscape is one that's rapidly changing, even compared to five years ago when we had one approved JAK inhibitor for myelofibrosis as an example. We now are in a time where we have four approved JAK inhibitors, and really ones that are specifically available for what your blood counts may be and kind of all sorts of nuances. So, I think there's much in the way of hope when it comes to thinking about MPNs.

**Dr. Odenike:** Oh, I couldn't agree with Anand more. I think he has summed it up so well.

I am particularly encouraged just at how many clinical trials we have in the MPN space. That is something I could only dream of 10, 15 years ago. And now, there are so many options, so many approaches being investigated.

Because to be able to have good drugs become available to patients, oftentimes you need to know about the biology of the disease. Why is this happening in the first place? What are the potential Achilles heel of the development and the progression of these diseases that we can tag it for the benefit of our patients? That requires a whole community of people – basic scientists, people at the lab, working on mice. And some of those mice experiments, not all, but some of them translate into human trials. For example, there are trials now that are just opening for patients who have calreticulin or CALR-mutated MPN. These are too early to know how those will fare; but I can envision a future where you come in. You know all your different mutations. There are wonderful drugs that can target those, and you live a long happy life thereafter. That is my dream. And I don't think it's pie in the sky when you think about how far we've come in such a short time.

**Elissa:** Yeah, I love it. I think that is a really good dream to have, that everybody lives a good, long life.

Well, thank you Dr. Patel, Dr. Odenike, for joining us today. We really appreciate you telling us all about the different types of MPNs under this big umbrella, but also just how much progress has been made, even in this past year. And so, again, we really thank you for joining us today.

**Dr. Patel:** Thanks so much for the invite. It's really been a pleasure getting a chance to chat with you, Elissa, and chat with Toyosi.

**Dr. Odenike:** So nice to be here. Thank you so much.



**Elissa:** And thank you to everyone listening today, with a special thank you to the University of Chicago Medicine for their support of this episode.

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