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The Bloodline with Blood Cancer United Podcast

A Podcast for Patients and Caregivers

Episode: 'After Diagnosis: Finding Hope with Myeloproliferative Neoplasms'

Description:

In this episode, we are joined by Dr. Abdulraheem Yacoub of The University of Kansas Cancer Center to discuss myeloproliferative neoplasms (MPN), a group of rare blood cancers that affect how blood cells are produced. We explore what MPNs are, the most common types, and the signs and symptoms that lead to diagnosis. We also answer real questions from members of our MPN online chat community, covering topics like life expectancy, genetic mutations, and managing side effects. Finally, we discuss current treatment options, emerging therapies, and share a message of hope for patients and their loved ones.

Transcript:

Elissa: Welcome to *The Bloodline with Blood Cancer United*. I'm Elissa.

Lizette: And I'm Lizette. Thank you so much for joining us on this episode.

Elissa: Today, we are speaking to Dr. Abdulraheem Yacoub, a Professor of Medicine with the Division of Malignant Hematology and Cellular Therapeutics and the Clinical Director of Ambulatory Hematology Clinics at the University of Kansas Cancer Center. Dr. Yacoub's research interests lie in myeloproliferative neoplasms and their treatments. Welcome, Dr. Yacoub.

Abdulraheem Yacoub, MD: Thank you very much, Elissa and Lizette, for having me and Blood Cancer United for taking care of our patients and spreading the knowledge to everybody.

Elissa: Well, thank you so much for being here with us today. So, our episode today is on myeloproliferative neoplasms, or MPNs. Could you tell our listeners what those are?

Dr. Yacoub: Yes, so myeloproliferative neoplasms are a group of blood cancers that have a lot in common in terms of symptoms and blood findings; but they do have a spectrum of severity. Some diseases are mild and manageable, and some are more advanced and serious. They have common features in terms of abnormal blood counts, enlarged spleen, extramedullary hematopoiesis, increasing constitutional symptoms, and also risk of transformation or progression to higher-risk cancers. These are not common diseases, but they're not rare. Patients live with them usually for multiple years and decades, sometimes the rest of their lives. And they will require ongoing therapy for as long as they live with their diseases. So, usually more of a chronic cancer set of diseases that patients have to live with.

The most common types are essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (MF). There are other types, more specific, like CML (chronic myeloid leukemia) that is a unique disease by itself.

Elissa: That's interesting that CML is under the umbrella term of MPNs.

Dr. Yacoub: Absolutely, yes. Actually, CML is a stereotypical myeloproliferative neoplasm, except for it has a very clear driver event which is the BCR-ABL1 rearrangement, or Philadelphia chromosome, which has a specific therapy. So, it really branches out of the other classical MPNs as an entity by itself. But the other MPNs have more common features, more generalizable themes that seem to cluster together. So, there's a lot more common between ET, PV and MF than there are differences. And that's why when we discuss the term of classical MPNs, where really, most people are specifically referring to ET, or essential thrombocythemia; PV, which is polycythemia vera; and MF, which is myelofibrosis.

Lizette: Sure. And what are the common signs or symptoms that might bring someone to the doctor and then get diagnosed with one of these MPNs?

Dr. Yacoub: So, usually patients would start with an abnormal blood test. So, adults should be seeing primary care doctors and having routine labs. This has become really the most common way of identifying these diseases by abnormal blood numbers. Usually MPNs are proliferative, which means patients produce more blood than their body needs; and that is actually the disease. So, you have excess blood elements and excess blood production; that is a problem and can cause complications to the patients.

Now, as you produce more blood, usually patients would also have more constitutional symptoms, which is really integrated into the process of proliferative bone marrows. So, patients could have excessive symptoms that are abnormal but not necessarily specific to MPNs. For example, fatigue. I know fatigue is a universal symptom of really anything, including having a bad day.

Elissa: Right.

Dr. Yacoub: But patients with MPNs have excessive fatigue that is not relieved, even when they rest. So, it's really got a different level of fatigue that is pathological in that sense. But some of the more classic symptoms are fevers, but that can happen without an infection, night sweats that can be drenching, unexplained weight loss. Some of the other symptoms include itching, which is also hard to relieve, tingling in the fingers and toes that could be painful, and severe headaches that look like migraine, but they're more protracted and more long.

And then patients with MPNs are at risk of clotting and bleeding a lot more than other patients. So, sometimes patients can present by having a clot or having an abnormal bleed that is unexpected. And those clots can be a leg clot, a lung clot, or an arterial event like a heart attack or a stroke, so that could be the first presentation for our patients. So, your patients can present asymptomatic, with just an abnormal blood number. They could present with a significant event with clotting or bleeding, or they can present from their symptoms that have been unexplained, which leads to the diagnostic workup and leads to the diagnosis. So, there's really many different ways on how patients can present; but now with the increased awareness, I think many doctors have MPNs on their radar. And a lot of the doctors, even primary care physicians, are very comfortable running a JAK2 test, CALR test, MPL test, or a BCR-ABL1 test to try to find the diagnosis early.

Lizette: And so, if most of the MPNs have similar signs and symptoms, how do you know what type of MPN somebody has?

Dr. Yacoub: Yeah, so among the classical MPNs, and that's a very interesting question because there's patients who are, obviously, easy to classify in one category. And there are patients who are not. So, it's not always as easy as it sounds. But the simplest way to describe this, essential thrombocythemia is a disease that classically produces platelets at a high rate. And polycythemia vera is a disease in which the dominant problem is excessive production of red cells; but those patients can also produce too many platelets and too many white cells.

And then myelofibrosis is a disease in which you produce fewer good cells, so fewer platelets, fewer red cells, more nonhelpful cells, but more white cells that are not necessary. And then those patients have scarring in the bone marrow and the large spleen as the dominant presentation. So, the perforation is more in the scarring phase and the bigger spleen and more white cells, not necessarily in the mature blood elements. So, that is generally the way we classify patients is based on their blood counts and also the bone marrow biopsy results; and that is really the classification for most of the patients.

There is a group of patients who are hard to classify. They have pictures in between ET and PV. Sometimes you need more time to tell if they're going to swing one way or the other. Patients who are between ET and myelofibrosis, sometimes you need more time for the disease to mature and show its full picture. And then patients can actually transform, so you could start as ET and five to ten years later you're actually polycythemia vera or start with PV and transform to myelofibrosis. So, there's many different complexities to classification because patients can fit into a box, or they might not fit in a box at the beginning; and they can actually shift boxes with time.

So, they're reclassified in a different box, appropriately so over time. So, it's a dynamic process; but we really describe the disease, when we make a diagnosis and put a label on it that doesn't make the disease behave differently. We describe the disease the way it presents to help us classify the disease and how to treat it. But, we're very open and now used to this reclassification that could happen every now and then for patients. And then we would adjust the treatment accordingly.

Lizette: And I did hear you say primary myelofibrosis. So, what's the difference between primary versus secondary types of myelofibrosis? I don't know if this is something that you also use that term with PV or ET.

Dr. Yacoub: Yeah. So, thank you for that. The proper medical terminology that we use is primary myelofibrosis is myelofibrosis diagnosed without a preexisting blood disease.

Myelofibrosis can start as myelofibrosis, or it can be a transformation from ET or from PV. So, the terminology we use is post-ET myelofibrosis or post-PV myelofibrosis for those patients, rather than secondary.

Lizette: Okay. Is it harder to treat one versus the other?

Dr. Yacoub: Not really. If anything, the secondary myelofibrosis, or post-ET, post-PV are easier to treat; and they usually do better than primary. But honestly, sometimes we don't know. And when a patient comes in and they've had abnormal counts for ten years and now they have myelofibrosis, and a patient coming to you this year with myelofibrosis, you can't treat them the way they are and their history, whether they did have a preexisting ET that was not diagnosed or they didn't was sometimes hard to elicit. Sometimes you'll never know.

But in general, for patients who already are known to have ET or PV and they transform to myelofibrosis, in general, they're easier to treat and they do well or better than the primary myelofibrosis.

Elissa: Okay. So, before we get into current and future treatments, we have done something a little different for this episode. We asked members of our MPN online chat group, called Living With Myeloproliferative Neoplasms, for their questions about MPNs. For our listeners, we'll be sure to have a link to this group chat at the end of the episode and in our show notes if you'd like to check it out.

So, let's go to our first question. What are we learning about age stratification of MPNs? Does one type tend to have older patients than other types?

Dr. Yacoub: So, that's a good question because we're often asked. Let's go by essential thrombocythemia, just because their different diseases. So, when we talk about essential thrombocythemia, and if you ask me to paint a picture, how does a classical ET patient look like, there isn't one. There isn't the expected age; and we have 18 years old and 90 years olds' who got diagnosed with ET this year. There isn't really a classic demographic that describes an MPN patient.

But as a rule, MPN patients are young to middle aged patients. They're among the younger patients in our cancer center. They're usually a lot younger than that. And age alone is not going to predict which histology that the patients will have or how they're going to be classified. So, there isn't necessarily an age discrimination in terms of this disease. It's really age blind in that sense.

Interestingly, it's not gender blind. The book says it's more men with myelofibrosis and more women with PV or patients who have JAK2 and they're women, they're more likely to have a PV phenotype, than ET phenotype. And that has been actually described a lot more. It seems to be a real phenomenon in which gender affects which phenotype patients end up being. So, in terms of how do we distinguish diagnosis and classification, you can't change your age or your biological gender, so those things we don't have control over.

Now what we have control over when it comes to age is how we treat patients. So, patients who are younger, with whichever disease, we do have a slightly different priority in how we treat them. So, it does play a factor when you're young. We don't treat patients indiscriminate of their age. That's definitely not true. We do tailor our therapy differently and our risk assessments based on age, for sure.

Lizette: It's interesting. Our next question is are there any models to predict life expectancy based on various factors, such as subtype, age, symptoms?

Dr. Yacoub: Absolutely, yes. So, the good thing is for many of our MPNs, especially ET and PV, the life expectancy with these diseases is not different from patients who don't have cancer. So, that is almost always a sigh of relief when you have that discussion with patients. So, for a newly diagnosed standard ET or PV patient, when we talk about longevity and life expectancy, fortunately there's not a measurable decrement in life expectancy in these patients. So, that is a discussion we can always dodge because the answer is, yes, in this day and age for the majority of patients who come in with lower-risk MPNs, ET and PV, that the life expectancy is not shortened by that disease. Now, that's provided it's managed correctly and that patients are getting the right therapy and that we're not having complications and clotting and bleeding and other complications that can shorten the life expectancy.

Lizette: Okay.

Dr. Yacoub: Now, for myelofibrosis, that's a different issue. So, patients with myelofibrosis will have, unfortunately, adverse outcomes from their cancer; and they will have shortened life expectancy because of their cancer, even in their lower-risk myelofibrosis. For those patients, we do have very sophisticated and pretty accurate calculators that help us guide and provide some prognostication on their outcomes, including their survival. Of course, in medicine, trying to predict survival or life expectancy is very much like forecasting the weather. So, when you provide a life expectancy for a patient, it really represents the average life expectancy for patients who were diagnosed in the last ten years based on ten-year-old science and ten-year-old treatments and what happened to them. It really is hard to apply that to a future. You could tell somebody how was the median weather for this day of the year for the last ten years. It's hard to predict the next ten years. Similarly, when we give a patient life expectancy based on a model that we use right now, it's exactly the same metaphor. You tell him that ten years ago patients with your diagnosis averaged this long life expectancy. And that just to give you a ballpark of what to expect.

For us, it's really more important at deciding on more critical decision-making for treatment, like who gets a transplant, who gets in a clinical trial and who doesn't, who needs therapy this year and who could wait three years, right? But it really doesn't give us the right tools to tell any human being that you will live so long, and that's when you're life will end. That is never something we can tell with confidence because the nature of diseases that we are getting better at treating them. So, hopefully, the life expectancy of patients we diagnose this year is much better than patients who were diagnosed ten years ago. And that is actually true. The life expectancy now is much better, at least twice as good as patients who were diagnosed ten years ago.

Elissa: That is always wonderful to hear. So, our next question, I thought this was a really interesting question. Is there a difference in onset between germline and somatic mutations? And, of course, can you define these terms and what they mean for MPNs?

Dr. Yacoub: All right, excellent question; and it's a very specific question. So, the terminology of germline, meaning in patients who have been born with a mutation that causes disease, and that really is, a lot of examples of this, like sickle cell disease and cystic fibrosis. These are diseases in which you inherited a mutation that causes a disease.

Elissa: Okay.

Dr. Yacoub: While somatic is, basically, an acquired mutation that caused a disease as you grow older. Almost all cancers are somatic, are acquired. None of us are born with ET or PV or myelofibrosis, and these are diseases you acquire after your body has acquired a new mutation, a somatic mutation in a clone that led to the cancer.

Elissa: Does that mean that they did anything to cause that mutation to be acquired?

Dr. Yacoub: So, why do MPNs happen? We don't know. Or at least we have not identified the reason why, if there's a sentinel event that causes MPNs. This is one of those diseases that still does not have an environmental cause or a true cause and effect; and we have been associating MPNs with inflammation. There is increased MPNs in patients with chronic inflammatory diseases like arthritis or inflammatory bowel disease, so there's some correlation between chronic inflammation and MPNs. But we have not been able to find a specific cause/effect for why patients would acquire a somatic mutation.

But going to the original question, there are no inherited germline MPNs that we can describe.

Elissa: Oh.

Dr. Yacoub: Yeah, that doesn't exist. All MPNs, by definition, are somatic acquired cancers in people who did not have them, and one day, they got a mutation and they got a cancer. Now, is there a germline susceptibility possible as being, that's the topic of a lot of research. But we also have not found a germline mutation that causes somatic mutation, right? So, we have not yet found any gene susceptibility that is the cause of why would you get an MPN; and there is no inherited MPNs in that sense of germline mutation.

Elissa: That is always good to know. I think patients are often wondering if they're going to pass it onto their children, if they might have gotten it from their parents. So, it is good to know, I think, for patients listening that it was not inherited.

Dr. Yacoub: Yeah, it's a hot topic in MPNs because it's not inherited, but it's not, not familial, right? So, patients who have MPNs, there's 10 to 15% chance they will have a family member with an MPN; and that is way more than the natural statistics of that happening. So, obviously, there is familial clustering of MPNs, so that's why we really think there might be some genetic makeup that makes you more susceptible to have MPNs. And if you have an MPN family member, your risk of having an MPN is higher.

But it's not linear in the same way as if your father had it, you should have it. That is not the same sense. So, that's really the difference between a familial tendency versus an inherited cancer syndrome. And there are inherited cancer syndromes, like BRCA and TP53. So, there are syndromes like that, but MPNs are not in the same category as inherited cancer syndromes.

Lizette: Now, I know that you mentioned some common side effects of the MPNs, such as itching; stroke; TIAs (Transient Ischemic Attack), which are essentially mini strokes. The question that came in is why do these happen, and is there anything that could be done to manage these side effects?

Dr. Yacoub: Absolutely. I think we spend the most time trying to manage these side effects. Thank you for that question because that really is the whole core of what we do for MPN patients because we just talked about their life expectancy being long, provided we manage those complications. So, the biggest threat to our patients is really the risk of thrombosis. It is highest with PV but also increased in ET. And also, the quality of life and the symptoms and the symptom burden. Let's talk about the clotting part.

So, why do patients clot? Number one is that they actually do produce more cells. Right, there's more red cells, there's more platelets, there's more white cells. And those cells could, just by having a higher number, cause a clot. So, to the simplest way, we just try to lower the numbers by phlebotomy, by drugs. We lower those numbers to the normal range, and that actually have shown to reduce the clotting risk significantly, up to ten-fold.

So, obviously, we know that bringing down some numbers to a normal range or even subnormal range will be protective for patients. So, that's one answer. And the other answer is the quality of the blood that is made by patients with MPNs might be at higher risk of clotting and also bleeding. The playlist that we produce in MPNs might be subquality, so why patients might actually bleed abnormally or if you have too many platelets, they can stick to clotting proteins and consume them so patients can have acquired bleeding disorders.

Also, by using our medicines to lower the platelet or red cell or white cell number to the normal range, we are very good at reducing the clotting risk and the bleeding risk to a risk that is almost close to normal people. So, that is actually the thing we spend the most effort on is cytoreduction or control of blood numbers to a range that protects the patient from their own blood.

Now, in terms of symptoms, it's the same rationale. Some patients are more symptomatic than others, and some symptoms are more bothersome to patients than others. And some symptoms are more responsive to therapy than others, and patients come in with different background symptoms and different tolerance to symptoms, so this really is a very individualized situation. For each patient, what are your symptoms, and what bothers you the most, and what are the tools we have to help with these symptoms?

Now, because this is such a core problem in MPNs, MPN is a role model for all other cancers. We actually have a tool called MPN-SAF, a tool to measure those symptoms. This is a tool that we developed and validated and now has become how we measure symptoms. If anything, we've done such a good job that many other cancers, including solid tumors and blood cancers, are adopting the same model. They're creating symptom scores to mimic what we did in MPNs to try to apply that to other patients and their symptom burden and quality of life.

Elissa: Wow.

Dr. Yacoub: So, these tools are basically the vital signs that we use in clinic to measure symptoms in a clinical trial. So, if you fill a questionnaire with symptoms. This questionnaire can go up to 100, down to 0. Each patient has a score. Patients actually very good at being consistent. If somebody states that I'm 70 today, I'm 70 next week, I'm 40 now, that means they improved. Right, so we actually use that as a tool. And, so in general, the total score is important. So, somebody with a symptom of 70 that is really poor quality of life, when they go down to 15, that's a lot of improvement, right? So, we're very happy with that-

Elissa: Yeah.

Dr. Yacoub: -as a total symptom score but also in terms of individual symptoms. So, for example, itching is a very, very bothersome symptom with MPNs. There's patients who can't shower for years because of itching because it's aquagenic pruritus. It's mostly driven by touching a wet surface or being wet. So, those are some of the symptoms we're really good at controlling. Night sweats in which you wake up every night, multiple times because you're sweating and have to change. That is very disruptive to life and quality of life.

So, some of those symptoms are a lot more responsive to our interventions. Cancer fatigue improves with therapy. Now, some of the symptoms are more refractory, pain, for example. Bone pain is really hard to control with the medicines we have right now. So, those are some of the symptoms we really need to collaborate with palliative care doctors and integrative medicine doctors to try to find methods to control the pain, especially that is a very chronic problem. So, yes, treating the symptoms and treating the complications is 99% of what we do for our patients, actually.

Elissa: Okay, I'm glad that you mentioned fatigue because that was actually our next question to ask if there was research to help with extreme fatigue that patients have.

Dr. Yacoub: Yes, so fatigue is a very complicated symptom.

Elissa: Yeah.

Dr. Yacoub: And there's so many things that can contribute to fatigue, and some of them are tangible, modifiable disease symptoms. For example, if you have PV and your hemoglobin is 18 or 19 all the time, patients will be very tired. Once you reduce their hemoglobin, there is a very rapid improvement in fatigue, right? It's hard to actually eliminate fatigue. It really is more of getting enough control to improve quality of life.

Now, interestingly, the same score we talked about, this MPN-SAF that we applied to patients without diseases, we did apply it to healthy volunteers once. And they also have fatigue, by the way.

Elissa: Oh.

Dr. Yacoub: It is one of those symptoms that is universal, but it's really what we're trying to do is to try to improve fatigue in MPN patients down to a level that is probably comparable to patients who don't have MPNs, which is not going to be zero, all right?

Elissa: Yeah.

Dr. Yacoub: And that's with the pharmacological interventions that we have. Adding to that, there are nonpharmacological ways to improve energy and fatigue. And that is really what we also counsel patients about, which is activity, aerobic exercise, better diet, control the weight, better sleep habits. So, there are many other ways that apply to MPNs and to other non-MPN, patients and healthy patients to improve their energy that will be accurate or applicable to MPN patients.

So, having a healthy lifestyle with healthy choices, healthy dietary choices, healthy sleep habits, healthy exercise habits, all of that pools into improving energy and fatigue for all patients and for MPNs. So, this is really one of the topics that takes also a lot of discussions and counseling in our clinic.

Lizette: Sure. So, the medications do help with the blood counts, right, so people aren't as fatigued?

Dr. Yacoub: Yes. So, I think there is fatigue that is associated with abnormal blood count; and I would say 50 to 60% of that gets better when we address the blood counts, yes.

Lizette: Okay. And another question that came in. For a smaller indication like MPNs, do you feel that worldwide collaboration between MPN researchers is moving the needle towards better treatments or cures?

Dr. Yacoub: Absolutely. Actually, almost all our collaborators are international.

Elissa: Wonderful.

Dr. Yacoub: And the MPN Society is probably one of the most collaborative and global, disease teams in all oncology. MPNs are rare cancers, and many of the efforts to generate data has, had to be collaborative. And there's no single institution that has enough patients and expertise to move the needle on their own. And every effort that has been successful has been collaborative and global. So, honestly, in my email, there's so many emails with foreign languages that I can manage just because a lot of our collaborators are from all over the world – from Asia and Europe and South America and, honestly, every meeting we have has members from every continent in the world. And this has been a wonderful, wonderful community of researchers and investigators and MPN heroes from all over the world, and that's really how we have been able to be successful.

Lizette: That's great to know. I know that when I was doing some research on MPN, I did find like an MPN Research Consortium Tissue Bank and was very surprised. But it does seem like that's the best way for everybody to have that information.

Dr. Yacoub: Correct. So, let's talk about that for a second. So, the MPN Research Consortium, which University of Kansas is a founding member of that actually.

Lizette: Oh.

Dr. Yacoub: We're a founding member of that and a part of the NIH grant that is funding that consortium and one of the bigger contributors to the bank.

So, basically, over the last 15 to 20 years, there has been NIH funding to create a US-based myelofibrosis and MPN consortium for research and for tissue banking. And we have been asking patients to volunteer samples from their blood and bone marrows prospectively, along with clinical data so that we can provide tissue or samples and data to help move the science. So, patients would donate yearly a blood sample and also a symptom questionnaire and some clinical data. And those would be done every year prospectively.

We use those samples to test the progression of MPNs because you have prospective samples over years, you'll be able to evaluate for markers of progression and markers for patients who don't progress. We also use those samples to test drugs in vitro and tubes so that if we find drugs that work in the tube, then they potentially could work in humans. So, this has been an absolute constructive and contributory work that is an example of collaborative efforts from many institutions, many heroes with NIH funding that went to a good cause.

And we still contribute to that. So, University of Kansas has actually been recognized multiple times for the contribution they made for that; and they advocate for research and for many other institutions to join the consortium and to contribute to that as well.

<u>Elissa</u>: That is just fantastic. We love to hear it. So, that is actually all the questions from our patients; but I'd like to give a special thank you to our MPN chat group members for their thoughtful questions. And I hope this answered a lot of questions that our listeners may have today. So, let's move onto current treatments for MPNs. Could you tell us what the treatments are for the various MPNs?

<u>Dr. Yacoub</u>: Let's split it to three different diseases because we treat patients differently. So, for essential thrombocythemia, the standard of care has been, after we do risk assessment and risk stratification only in the higher-risk patients who require therapy, we're offering medical therapy with drugs. And hydroxyurea has been a drug that's been used for a long time. More of the current data have shown that interferons have actually been very effective, and we are expecting an FDA approval for interferons for ET in the next few years. But we have been using interferons as a possible disease-modifying therapy that is more safe, more effective, and with higher ceiling than hydroxurea for many patients. And beyond that, so many agents have been studied and showed data, like ruxolitinib has shown good data but doesn't carry an FDA approval. And there are many agents in clinical trials right now trying to find a way to help patients in ET.

Polycythemia vera has been more dynamic. So, the higher the risk of MPN, the more options we're going to talk about because most drugs are being studied in patients with higher risk. So, PV is a higher risk disease than ET. So, research is more advanced in PV than ET. We use hydroxyurea. Interferon is already approved for PV, and I think of it as really the first-line therapy for PV in the majority of patients.

And ruxolitinib is also approved for PV in second line. So, these are the agents that are already available. Some of the agents that are about to be approved is rusfertide, which is a really innovative therapy that has been in research in the last few years with remarkable outcomes and likely will be FDA approved by the end of next year for patients. And there are many other drugs that are in research as well. So, our options are increasing; and we don't have enough options, but we still keep moving the needle forward and trying to get more agents approved and more tools for our patients.

Now myelofibrosis is the more serious cancer of all these three, and it's the one with the busiest clinical trial portfolio and the largest number of drugs that are being investigated. So, so far, we have four JAK inhibitors that are approved for myelofibrosis. JAK mutation is one of the driver mutation in myelofibrosis. But the JAK-STAT pathway activation is almost universally the driver for MPNs and for myelofibrosis. And there's many ways to acquire JAK-STAT activation. One of them is JAK2 mutation, but there's CALR mutation, there's MPL mutation. So, there's many different insults or mutations that can eventually cause the same effect inside the cell by activating the JAK/STAT pathway.

And we have been using a JAK/STAT pathway inhibitor as a treatment for myelofibrosis for the last 15 years with excellent results. So, this is the backbone therapy for all myelofibrosis patients; and it's always going to be a backbone therapy for patients with myelofibrosis going forward.

We have four drugs that are approved. They are unique. They have different attributes. They have different patient profiles where they work. We're very glad that we have them. Unfortunately, that's all we have, these four JAK inhibitors, interchangeable drugs that work in the same spot in the cell. And that's really all the tools we have. All of them work in some patients, but not in every single patient, and all of them eventually stop working, even when they work. So, we are not really rich with options for our patients. That's why we're really advocating for research.

One path of research has been combinations. So, you use JAK inhibitor plus a drug. So far, many large trials ended negatively that we could not actually use combination in all-comers. We're still trying to work on a better combination, so that's going on.

Another path in which we're trying to help patients is to add on therapy for patients already on a JAK inhibitor to just add a different drug to help them respond even better. And also, for patients who have had all the JAK inhibitors and now they're not responding to them, we're trying novel agents that are not JAK inhibitors. Hopefully, we'll find a different angle at this.

So, that has been the summary of all the trials we've done in the last 10 to 15 years. Now, a lot of the recent innovations have become more smart, in which we have individualized therapy with newer classes of drugs that have different ceiling. For example, we talked about the JAK inhibitors and the JAK-STAT pathway inhibitors; but now we have an even better JAK inhibitor, selective JAK inhibitor. We actually have a JAK inhibitor that is selective to the mutated JAK inhibitor, not to the unmutated one. So, for patients with JAK2 mutation, our most current one is JAK2 V617F, and there's a drug very selective to that mutation. That spares the wild type unmutated JAK2, and this could be of a higher ceiling or higher benefit to patients than the old generation of JAK inhibitors.

There's also a complete new class, which is the Type 2 inhibitors that are even more efficacious than the Type 1 JAK inhibitors that we already have. So, there's a lot going on in that direction, so better drugs.

And there's also a complete different new class of drugs, which is the calreticulin (CALR) inhibitors. So, calreticulin is the second-most common mutation after JAK2;

and it causes a new antigen that is available for us to target by immune therapy. So, we're using antibodies and BiTE (Bi-specific T-cell engager) antibodies and CAR Ts [cell therapy], trying to tackle patients with that mutation. So, this started a whole lot of wave of very ambitious and high ceiling clinical trials that can result in an impact that is much bigger than the drugs we've had so far.

And that also opened up a whole new arena of individualized therapy. So, if you have a JAK2 mutation, you go this path. If you have a calreticulin mutation, you go this path. So, t's really starting to increase the algorithms, make it more complicated, more exciting, and more individualized for our patients.

Elissa: So, the goal of treatment has seemed to be more quality of life and management of the disease versus looking for a cure. But are they eligible for stem cell transplants or CAR T-cell therapy that might have the potential for a cure?

Dr. Yacoub: Yeah, let's talk about the cure. So, there is a cure for MPNs-

Elissa: Okay.

Dr. Yacoub: -and we gear our therapy to the patients who are more likely to benefit from it or more likely to be harmed by their disease. So, when you have a low-risk ET and you're likely to live a full natural life, with or without therapy, it is probably not a good investment to invest in a curative therapy that will have side effects when you don't need to.

So, we gear our cure intent treatments to patients who are likely going to have a compromised life, quality or quantity, from their cancers; and they can tolerate the therapy. So, bone marrow transplantation is the only curative therapy; and the disease in which we use it for is myelofibrosis and usually in patients with higher-risk myelofibrosis.

So, going back to a previous question when we talk about those models that predict life expectancy, so, those models are actually very good tools at guiding who should get a transplant. Even though our model cannot tell me how long the patient will live, it will tell me in a ballpark that if you have these sets of DNA findings, and lab findings, and symptoms, that your life expectancy is likely going to be a lot shorter than your natural life expectancy from this cancer. So, this cancer will lead to many years of life lost from this disease.

That is really the situation in which we discuss a bone marrow transplantation. So, we discuss bone marrow transplant in patients with myelofibrosis who have relatively higher risk early on in their journey with myelofibrosis. A transplant can be curative, and the odds now in good hands of transplant is more than 50/50 that patients who go through a transplant will come in cured at the other end and live their full natural life without myelofibrosis. So, this is a discussion we have early on with all our myelofibrosis patients with particular emphasis on patients with the higher end of risk based on our predictive models.

CAR T has not yet been used in MPNs or myeloid cancers in general, but it's happening. There will be products that might make it to humans in the next few years in which we think we might be able to help patients. But again, this is definitely ambitious; and research is moving in that direction very robustly; and hopefully we'll have more to talk about in the next few years.

Lizette: Sure. And talking about research and the future of treatment, what research or clinical trials are you particularly excited about when it comes to MPNs?

Dr. Yacoub: Oh, we've really been very blessed with a really robust community of MPN investigators, dedicated to these diseases for the last 15 years, since we got all this attention.

So, MPN is one of the younger fields in oncology. I know we've described MPNs since 1800s. Those been very well-known cancers, but the JAK2 mutation was only discovered in 2004. And the first approved therapy for myelofibrosis was in 2011. This is a very young disease in terms of medical advancements, and we've come so far in the last 15 years since the first approved therapy for MPNs. Since then, we've had four JAK inhibitors. We have interferon. We have a very robust clinical trial portfolio. So, I'm excited at all research. You don't have enough time for me to answer your question.

But, again, starting from just even that consortium tissue banking study, that is such an important intervention. There are clinical trials that are community based. For example, the MPN Research Foundation have launched a direct-to-patient clinical trial in which patients can sign up online and volunteer their personal information and access to their medical records. They can be extracted and through AI (artificial intelligence) can be tabulated into formats and create a prospective database to answer questions that we were never able to answer. So, that is a great national effort that is happening and started, so there's all kind of research. You don't actually have to even go to a doctor to do that clinical trial.

Now, I'm a clinical investigator, so I focus on clinical trials that deliver drugs to patients, to test that those drugs work or they're effective. Are they safe? Are they a good idea altogether? Are they better than nothing? Are they better than what we do already?

So, this is how we do Phase I and Phase II and Phase III and Phase IV clinical trials. We try combinations. We try; we've been part of many trials. Some of them were positive and helpful and led to FDA-approved drugs. Some of them were unfortunate and disappointing and negative. Some of them were eye-opening. You started studying one aspect of the disease, and you came out exploring ten other aspects.

So, sometimes when you do research, you don't really control the output. And the output might not be what you expect. That's why advocacy for research is the only way to advance the field to describe the cancer better, to describe different therapeutics. Now, if I have to pick one topic I'm super psyched about, it's our own investigator-initiated study.

So, we do have a clinical trial that combines two drugs, one of them is JAK inhibitor. One of them is targeted therapy. That is active at the University of Kansas that I'm very excited about personally and very invested in. And it's one of those projects that you believe in and hopefully you would like to complete and have results out there for everybody to review.

Elissa: That is so exciting. We always love hearing about all this new research coming through, and I love hearing about the clinical trial where patients can just sign up and submit their medical records and have AI be involved in analyzing these records. And so that's really neat.

Dr. Yacoub: Yeah, and that's not the future. That is actually happening right now.

Elissa: Yes, it's actually happening right now, yes. It would be great to see what comes of that and what can be developed.

Dr. Yacoub: And I would invite the audience to actually go to the MPN Research Foundation website and learn more about that. And the trial is opening in phases, and one phase has been completed. So, soon it's going to open the next phase. So, if it's not active this second, it will open soon.

Elissa: That is good to know. We will make sure to have a link in the show notes. Everybody listening, make sure you check out the show notes and go to that link and check it out.

So, our final question 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 give them hope after a diagnosis of an MPN?

Dr. Yacoub: Well, in 2025, soon to be 2026, we have a lot better understanding of why these diseases happen, what drives them. We have better therapies that we actually have had approved for many years, and we know exactly what they do and what they can't do and when to apply them. We have very robust data for bone marrow transplantation and cure rates and outcomes, and this is becoming an acceptable option. This was not the case ten years ago. So, now we have cure on the table. We have many drugs in the pipeline that are about to be FDA approved, so we're going to have a few FDA approvals in the next year or two for more tools for our patients. And the clinical trial portfolio that is going on right now, it's very promising.

In the future, it will happen in which we treat patients based on their mutation, based on the profile, be able to provide therapy that is effective and safe, and patients can have the benefit without the collateral and have excellent outcomes. The future is very promising for our patients, and being part of MPN research team has been the most rewarding and continues to be opening new avenues and new horizons for our patients.

Elissa: That is wonderful.

Well, thank you so much, Dr. Yacoub for joining us today and talking all about MPNs and all the exciting things coming in the future and here already. And so, we really appreciate you joining us today.

Dr. Yacoub: Thank you so much, Elissa and Lizette, and thank you very much Blood Cancer United for putting so much emphasis on helping patients by providing tools and resources and education. I think this is absolutely an important service that patients need. A more informed patient is going to be a healthier patient. Self-advocacy is a must. Patients should advocate for themselves, should learn, should bring science to their doctors, and doctors love to hear all these ideas. Whoever your treating physician is always going to do a better job if you do a better job advocating for yourself.

So, thank you all for bringing all the resources behind it.

Elissa: Thank you. And that is exactly why we do this podcast, so patients can learn more about their disease and feel empowered to go back to their physician and talk more about what their treatment plans are and participate in shared decision-making for their treatment.

So, again, thank you so much for being here with us.

Lizette: Thank you, doctor, for your dedication to our patients. We really do appreciate you.

Dr. Yacoub: You're welcome. Thank you.

Elissa: And thank you to everyone listening today. *The Bloodline with Blood Cancer United* is one part of our mission to improve the quality of lives of patients and their families.

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And for those of you interested in checking out the online MPN chat group, moderated by an oncology social worker, please visit BloodCancerUnited.org/chat. These links and more will be found in the show notes or at the TheBloodline.org.

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