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The Bloodline with Blood Cancer United Podcast

A podcast for patients and caregivers

Episode: 'Myeloproliferative Neoplasms (MPNs): New Therapies, New Hope'

Description:

Myeloproliferative neoplasms (MPNs) are rare blood cancers that alter how the body produces blood cells, requiring individualized care. In this episode, Catriona Jamieson, MD, PhD, of the University of California San Diego, shares the latest breakthroughs in MPN research, from detecting disease progression earlier to developing targeted, personalized therapies.

We explore MPN subtypes, the role of genetic testing, and current and emerging therapies. Whether you are navigating polycythemia vera (PV), essential thrombocythemia (ET), or myelofibrosis (MF), this conversation offers practical insights into today's care landscape and new reasons for hope.

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 will be speaking with Dr. Catriona Jamieson, a physician scientist, professor, and Chief of the Division of Regenerative Medicine in the Department of Medicine at the University of California, San Diego School of Medicine. She also serves as Director of the University's Sanford Stem Cell Institute. Dr. Jamieson's research

interests are in the treatment of myeloproliferative neoplasms or MPNs and acute myeloid leukemia or AML. Her work has led to the advancement of several new innovative therapies for blood cancers. Welcome, Dr. Jamieson.

Catriona Jamieson, MD, PhD: Thank you so much, Elissa and Lizette, for having me here.

Elissa: And thank you for joining us.

So, our episode today is on myeloproliferative neoplasms, or MPNs. Could you explain what those are?

Dr. Jamieson: Sure. So, myeloproliferative neoplasms, MPNs for short because it's easier to say, are a stem cell disorder. So, people with MPNs, 1 to 5 per 100,000 people in this country, will be diagnosed with an MPN. And it usually starts from a mutation in a blood forming or hematopoietic stem cell. And the reason that matters is these are long-lived cells. They last our lifespan, so that mutation in that stem cell can make it go the wrong way and make too many of one type of blood cell – either too many red blood cells, too many platelets that clot our blood, or too many white blood cells. And ultimately, these disorders in aggregate can lead to scarring of the bone marrow. That's called myelofibrosis, and then myelofibrosis can progress to acute myeloid leukemia, AML for short. So, we want to predict and prevent that progression. Ultimately, if people present with acute myeloid leukemia, we want to reverse it.

So, we've had a lot of challenges in the field; but the good news is patients are the champions, and they've made a huge impact together with Blood Cancer United® and the MPN Research Foundation turning back the clock on this disease, so it just can't move forward, and it stops it in its tracks.

Elissa: That is great, and we will get into the current treatments and emerging therapies a little bit later. But first, what are the primary types of MPNs or what is called *classic MPNs*?

Dr. Jamieson: Sure. So, classic MPNs when they were first discovered or talked about, they were called myeloproliferative disorders. Myelo means bone marrow, proliferative means you make too many of one type of cell in the bone marrow. And this was by William Dameshek in 1951 where he said, "Wait a minute. There are these disorders where you make too many red blood cells; that's called polycythemia vera (PV). Or you make too many platelets; that's called essential thrombocythemia, ET for short. Or you make too many white blood cells; that's called chronic myeloid leukemia (CML) or you scar down your bone marrow, myelofibrosis (MF)."

Because CML, chronic myeloid leukemia, has one driver gene called BCR-ABL, we don't really include that now in the MPN discussion because we have so many treatments for that. It really is a different entity from the non-BCR-ABL MPNs that are primarily JAK2 driven. So, that's the JAK/STAT signaling pathway that drives the increased

production of red blood cells, platelets, or scarring of the bone marrow, depending on which type of stem cell that mutation lands in.

Lizette: So, there's all these different types of MPNs, so it's more like an umbrella term basically.

Dr. Jamieson: Exactly.

Lizette: And I know that you just talked about it, but what makes them so unique? They all have different types of treatments?

Dr. Jamieson: Yeah, I think what makes them unique is that they're rare disorders. They're actually stem cell disorders and that they drive the production of too many of one type of blood cell. The other thing that makes them unified is they tend to activate JAK/STAT signaling, and J-A-K, just another kinase, is what it was originally called by Andrew F. Wilks in Australia when he discovered it. He thought this is a useless kinase. It doesn't mean anything. But it tells a stem cell what it's going to grow up and become, and they later called it Janus kinase because it has two faces. It can be good or bad.

So, we use that signaling pathway to make red blood cells. We make platelets. And sometimes when you have too much proliferation of these immature stem cells, it causes scarring in the bone marrow. So, they're united by this JAK/STAT pathway, but they use it to different extents, based on which mutation. So, we have the JAK2

mutation, JAK2 V617F. Ninety-seven percent of people with polycythemia vera have that. We have that JAK2 mutation in about 50% of people that have essential thrombocythemia and same percentage for myelofibrosis.

But then there's this other mutation that can activate JAK/STAT signaling in the gene called CALR, calreticulin. More common in essential thrombocythemia. We almost never see it in polycythemia vera, but it still activates JAK/STAT signaling.

MPL, the thrombopoietin receptor mutation, more common in essential thrombocythemia. That is more rare, but it also activates JAK/STAT signaling. So, the one unifying feature is this one signaling pathway that allows the cells to be more responsive to inflammatory growth factors like IL-6. So, they're just supercharged and able to respond or like erythropoietin or thrombopoietin. And so, the galvanizing, unifying theme for MPNs is JAK/STAT signaling.

Elissa: Now, can patients have more than one MPN at a time or can one transform into another?

Dr. Jamieson: It's such a great question, Elissa. I'm really glad you asked that. So, people can have what they think is polycythemia vera where there's a JAK2 mutation at the hematopoietic stem cell level. They make a ton of red blood cells until they start to become iron deficient from phlebotomies. Then the body can't make red blood cells, but it can still make platelets. So, now they start to make more platelets.

So, they say, "Wait a minute, I thought I had PV, not essential thrombocythemia." But it's what the stem cell has access to. If you don't have iron, it's really hard to make red blood cells. You're going to make more platelets. So, I just call them JAK2-driven MPNs.

Elissa: Okay.

Dr. Jamieson: You know, people have a propensity to make more red blood cells. They usually stay within that group unless they've had a ton of phlebotomies. Similarly with ET.

For myelofibrosis, both PV and ET can progress to myelofibrosis; and the key is trying to predict who's likely to progress to myelofibrosis, so post-PV myelofibrosis versus post-ET myelofibrosis. They behave very similarly. We just want to prevent myelofibrosis because that leads to new blood cell production in the spleen, ultimately the liver. That can be painful, but it's also not very productive. We just don't make good blood cells when the marrow is scarred down.

So, the stem cells leave the bone marrow, and they go, "Where else can we go? Oh, we can go to the spleen. Take over there." It becomes uncomfortable. It increases the rate of clotting. There's more inflammatory growth factor signaling with myelofibrosis.

So, that's what we're trying to predict, prevent, and ultimately reverse if people already have myelofibrosis when they present; and, also, we definitely don't want them to get acute leukemia. So, we're trying to prevent that progression in MPN.

Elissa: Yeah. Now, as you're looking at predicting those things, is there a risk classification for all of these different MPNs?

Dr. Jamieson: Yeah, and this is available to everyone. We have the Dynamic International Prognostic Scoring System (DIPSS). We have the DIPSS Plus. We have the Mutation-Enhanced International Prognostic Scoring System, and we've improved upon that to have a 2.0. I think those are the prognosticators. They're clearly very defined diagnostic criteria. So, we have the diagnosis, but then we have the prognostication tools saying, "Where is this disease going? This is where you're at now. Where do we think that this is going to go based on your white blood cell count, your hemoglobin, your platelet count?" It takes into account age and constitutional symptoms like fever, chills, night sweats, and weight loss.

And then we're starting to take into account the level of bone marrow scarring, bone marrow fibrosis, myelofibrosis, in other words. And then where the models became much more predictive is when we started to add high molecular risk mutation. So beyond just, "Oh, you got a JAK2 mutation, calreticulin or chromosomal abnormalities. What is your molecular risk?" So, their high molecular risk mutations, for example, in ASXL1, IDH1 and 2, and by a risk, we mean of progression to leukemia.

U2AF1, these are the higher-risk molecular mutations where we go, "Okay, we're going to have to keep a close eye on these people." And how many of these are inherited as opposed to acquired? We tend to look at the acquired mutations, but we are having people come in who have a, 50% variant allele frequency, VAF, of P53. You know, they've mutated P53, the guardian of the genome. So, they don't have that tumor suppressor capacity. So, if they have a mutated stem cell, it's more likely to survive. And there are people with DNA repair mutations in ATM, for example. They don't repair DNA that well. So, these are the mutations that have now been looked at; and, we're basically looking at these mutations through a new lens of should those patients be considered for early intervention and not just transplant but just early treatment instead of just waiting for symptoms.

And actually, if you ask people, in terms of the MPN-SAF, the Symptom Assessment Form, a lot of people really have symptoms. You know, the ten symptoms that people have; and then when you go through it, "Do you have difficulty concentrating?" Oh, yeah, I do, actually. "Do you have abdominal pain, or do you feel full early, early satiety?" Yeah, I have had that. "Have you lost weight?" Well, maybe. And then, "Have you lost energy?" Everybody. You know, there are these very stereotypical symptoms that we go through. So, I think that the Symptom Assessment Form is a very, very good tool to see where people are at and also where the disease is going when you combine that with the molecular features of the disease.

And then there are some other more interesting earlier diagnostic tools that we can now start to develop, considering that we can do whole genome sequencing, single cell RNA sequencing, and functional assays. So, the field is getting interesting. I think AI is helping with that because we can help to really look into very deep data sets, and we're not just beholden to next-generation sequencing. We can make it much more personal and do this at different timepoints we can say, "Ooh, you know, your spleen got larger. Your variant allele frequency is going up for your JAK2 mutation, CALR, or MPL or you have these other mutations that you've acquired so we can start to look at earlier interventions to see can we augment the immune response against these premalignant conditions or can we eradicate the driver clone and I think both are on the table."

Elissa: Now you mentioned that some MPNs can be inherited. Is that very common?

Dr. Jamieson: Very rare. And I think what they're not really inheriting the JAK2 mutation or the MPL mutation or CALR. They're inheriting a predisposition to not fix mutations in DNA. So, an ATM mutation, DNA repair mutation, or their immune system is a little too tolerant. Their immune system doesn't see those mutated stem cells as foreign, and it doesn't get rid of them. It just says, "Okay, you guys are good. You keep going." And I think that's really what we're dealing with more in MPNs, that people acquire their tolerant immune or inherited the tolerant immune system. And

then on top of that, they acquire these mutations that their immune system just doesn't see as foreign.

Elissa: Yeah. And another thing you mentioned a few times is the possibility of turning into AML, or acute myeloid leukemia. Is that just myelofibrosis or can any of the MPNs turn into AML?

Dr. Jamieson: It would be extremely rare for polycythemia vera or ET to transform into AML, just without going through a myelofibrotic phase, because it's really that myelofibrosis that leads to massive inflammation. And that inflammation helps to fuel progression. And the reason inflammation fuels progression is it activates these stem cell pathways that allow malignant regeneration, so the precancer cells now learn to clone themselves; and the problem is they can't shut it off.

So, one of the pathways that does that is called ADAR1. ADAR1 has been on our radar for more than ten years now. That gets activated by increased inflammatory growth factor signaling in the setting of myelofibrosis because that's a highly inflammatory disease. That leads to cancer cloning and immune evasion. That's just one gene.

APOBEC is another one. There are a number of genes that get turned on that set these mutated stem cells on a path to make these daughter cells that aren't that functional. And those cells then start to clone themselves, and they just can't shut it off.

So, I think there are ways to intercept that biology because we're now starting to understand it. And then the next challenge will be to say, "Okay, your immune system doesn't seem to be working that well. How can we boost your immune system?" And the mutated stem cells are hanging out; how do we target what makes them survive and clone themselves? And then is there a way to deal with genetic risk? You know, is there a way to look at families and say, "Hey, your brother had PV, you have ET, you have two different mutations of JAK2 mutation, PV, CALR mutation. Is it just that your immune system, was genetically not set to get rid of these mutations? And then is there a way to look at the effects of stress or circadian rhythm changes in this kind of clonal competition biology where the bad, mutated clones win or could we augment resilience and allow the good stem cells, the more powerful regenerative stem cells to win?"

So, I think that's where the field is going, augmenting resilience.

Elissa: Okay, now what is the likelihood of turning into AML if you already have myelofibrosis?

Dr. Jamieson: It depends on what stage of myelofibrosis you have. But if you're MIPSS70-plus, meaning your 70 years old, you could still be a candidate for transplant 70 or younger. And we look at all the markers for Mutation-Enhanced International Prognostic Scoring System to say what's the likelihood of progressing to AML or

having a shortened life expectancy because it could just be bone marrow failure. You get more infections. You don't have AML, but you still succumb to the disease.

So, the likelihood when somebody has high-risk myelofibrosis is much higher than if you have low-risk myelofibrosis. And in the MIPSS70-plus, you can have very low risk. So, your life expectancy is essentially going to be normal. But if you have high-risk myelofibrosis, you have a 30% chance of developing AML within the next one to five years. So, even in five years, 30% is too high. The life expectancy for high-risk myelofibrosis can be as low as 18 months. So, it isn't just that they develop acute myeloid leukemia, they have more risk of clotting. They have a higher risk of having infections, having hemorrhagic events, you know, bleeding because their platelets aren't made properly or they get stuck in the spleen.

So, there are a lot of issues with having higher-risk myelofibrosis. So, we want to make sure that people don't progress through the stages of myelofibrosis; and we see if we can actually reverse myelofibrosis, which is something we're starting to see in people who have been on longer-term therapy.

Lizette: Wow. Now, let's discuss the current treatments for myelofibrosis, polycythemia vera, and essential thrombocythemia. What are the treatments, and are they based on the risk categories that you previously spoke about?

Dr. Jamieson: Yeah, I think for the risk categories, we really need to be careful to make sure that we're documenting people's symptoms because a lot of people would just say, "Oh, I'm tired. Everybody else is tired." They don't really think about their decreased concentration and their weight loss and, intermittent night sweats and things like that. So, I think we have to be very careful to look at what their risk of progression to myelofibrosis is; and people need a bone marrow biopsy.

A lot, of people like to avoid a bone marrow biopsy and say, "Well, we'll just do that when they have symptoms." But when you see that they have some early scarring of their bone marrow, I think that actually changes the risk for polycythemia vera as well as essential thrombocythemia in terms of progressing to higher-risk myelofibrosis. And I think that's the stage we need to intervene at.

So, I think poor prognostication is, you have to make the diagnosis. I do think everybody needs a bone marrow biopsy if they come in with a JAK2 mutation, elevated hemoglobin. Usually, we go by hemoglobin as opposed to hematocrit because hematocrit is just three times the hemoglobin level. Same with essential thrombocythemia to make sure they're not in that early myelofibrosis stage because then the treatment is different.

We don't just do phlebotomies for polycythemia vera if they have early-stage myelofibrosis because if you see that prefibrotic myelofibrosis or early-stage myelofibrosis in that setting, they tend to respond very well to interferon-related

drugs, whether it's Pegasys® or BESREMi®, to reduce the ability of that mutated stem cell to gain hold in what's already a corrupted environment. So, you seed versus soil. You can improve the immune response and improve the soil so normal stem cells have an advantage as opposed to the mutated stem cells. And I think that's a huge advance to know that for patients that we're starting to see early signs of scarring of your bone marrow. There are these really well-tolerated medications, the interferons that boost the immune response.

So, as I mentioned before, the problem in these MPNs isn't just that you make more blood cells. It's actually that the immune system doesn't know how to tell the difference between mutated stem cells and normal blood stem cells. So, with the interferon-related drugs, whether it's Pegasys or ropeg (ropeginterferon-alfa-2b-njft), which is also known as BESREMi, they tend to boost the immune response. So, the immune system goes, "Hey, why didn't I see that guy before?" I can actually get rid of that stem cell. And so, we're seeing very nice responses to either of those medications when they're implemented early. And I think the issue is we wait too long to make a decision because we're waiting for people to have drenching night sweats and 10% of their body mass reduced, and those are the bad old days. Now we have the ability to have earlier warning signs for disease progression and the opportunity to prevent that progression and treat early.

Lizette: So, when you say that sometimes you wait, are some folks on like a watch-and-wait protocol before starting treatment?

Dr. Jamieson: I think they are because we used to think that the treatments were worse than the disease. The thing is, with most of these diseases, polycythemia vera, essential thrombocythemia, or myelofibrosis is they progress. When you just leave them, they progress. If you do phlebotomy, take blood off people that have higher hemoglobin, you'll prevent a stroke or a heart attack, but you're not necessarily going to prevent progression of that mutated clone. That mutated clone is going to take over more of the bone marrow, and then you get more inflammation, more scarring in the bone marrow. So, it's not necessarily going to prevent progression to myelofibrosis. And, in fact, it generally wouldn't.

Essential thrombocythemia, same thing. You leave it untreated; it's most likely going to progress. So, it's like hypertension and heart disease or stroke risk. If you treat your hypertension extremely well, then you're less likely to have a stroke or a heart attack. But in this case, we're dealing with mutated stem cells that need to be put at bay. And we need to prevent them from making more of themselves and allow normal stem cells to take over.

Obviously, I believe in preventing progression and early intervention. Now that we have the NCCN (National Comprehensive Cancer Network) MPN Panel, we're able to

look at what the recommendations are and what is actually very, very effective in terms of intervention strategies.

We started that panel in 2016, and at the time, I actually thought why are we doing this? We only have one FDA-approved therapy that isn't a transplant. That's ruxolitinib, also known as Jakafi®. And Ruben Mesa MD., who insisted that we start the panel said," Because we'll make more. We'll make more therapies, and we have at least six approved therapies in this set of diseases; and we're just getting started."

So, I think that getting everybody together, convening to see yearly what are the data, how can we move forward, and then working with groups who develop larger datasets that are linked to, what medications people are taking, other things that have to do with lifestyle choices, we can actually start to make stronger predictions.

So, for example, Epic®, the electronic medical record system started by Judy Faulkner has a research arm and a whole research portal called Cosmos that has 300 million people in it. So, in these disorders that are, affecting 5 per 100,000 people, 1 per 100,000 for myelofibrosis but up to 5 per 100,000 for ET or PV, how do we say what problems they have? How many people actually progress to AML?

Well, we can actually look in the Epic database in Cosmos and say how many of these folks with MPNs progress? So, it is all predicated on how we code. So, ICD 10 codes.

You know, if we say somebody just has an MPN as opposed to myelofibrosis, then it's going to change what we think the disease is. But anyway, I think these are really, really important tools that we can start to use in the MPN community to say what's the likelihood of having your disease progress? And what have other people done to prevent that progression?

So, these tools are now at our disposal as are things like whole genome sequencing to look at your immune health. We can do RNA sequencing that can change faster and maybe be a stronger predictor. So, there are a lot of things we can do now to predict and prevent progression. People in my clinic have next-generation sequencing looking for acquisition of mutations or a reduction in their mutations. They have that every six months.

Lizette: Wow.

Dr. Jamieson: And because we made the test, it's in-house here at UC San Diego, the Department of Pathology did a wonderful job; and it's half the price of a commercial test. And, we can have that turnaround in two to three days. Generally, I do the full panel that takes about two weeks. But people like to know that.

Lizette: Yeah, and it definitely helps you with treatment decisions, right?

Dr. Jamieson: Really, really does. And I think that, as we start to have more actionable mutations, we can start to say, well, maybe we should be targeting the other mutation

or the RNA alterations that drive disease progression, splicing changes, you know, as we start to understand more about not just DNA biology but also RNA biology and then delve into why do some people have disease that progresses and other people that don't? I mean you asked the question about can people have both polycythemia vera and essential thrombocythemia at the same time. Extremely rare.

Can people have the JAK2 mutation and the calreticulin mutation? I have one patient that has that, and it's extremely rare. I see 12 to 14 patients a week with these disorders, so I have a lot of patients that I see with MPNs. Extremely rare. But what I am seeing more of is people that have a lymphoproliferative disorder as well as a myeloproliferative disorder. So, they have CLL, chronic lymphocytic leukemia and myelofibrosis.

Elissa: Oh.

Dr. Jamieson: Or multiple myeloma or the antecedent disease MGUS (monogamopathy of undetermined significance) and an MPN like PV or ET. So, this comes back to the immune question. How much of this is just that immune system does not see these mutated clones? And so that's what we're really trying to unravel. Did both cancers arise from one stem cell?

So, there are these new things we're starting to see is people are just living longer with their MPNs. Now we're starting to say, "Oh, wait a minute, you have this low-grade

lymphoma." So, is the disease switching course because we've been so effective at treating the MPNs that now that mutated stem cells goes, "Well, I'm going to go this other way because you can't find me over there." So, that's become very interesting but, honestly, a little bit vexing because, you know, it's like Whac-A-Mole. How do you get this? So, I just think we're going to need to use more advanced sequencing technologies to understand that clonal evolution isn't always in the myeloid lineage, meaning red blood cells, platelets, or the white blood cells like neutrophils; and it could be T and B cells.

Lizette: Right. Now, I know that you mentioned certain medications. So, those medications are approved for one specific type of MPN or are they approved for multiple types of MPNs?

Dr. Jamieson: It depends on the medication. So, for the interferon drugs like Pegasys and ropeg, which is also known as BESREMi, we can use those in patients who have polycythemia vera who are definitely showing evidence of progression with a little bit of scarring in the bone marrow. We're starting to be able to get that for patients with essential thrombocythemia that are starting to progress, so they have a Grade 0 or grade, generally a Grade 1. So, it's WHO grading for the myelofibrosis. World Health Organization grading goes 0, 1, 2, or 3. If they have Grade 1 fibrosis in the marrow, it's still considered pre-myelofibrosis, prefibrotic myelofibrosis. Grade 2 gets you, okay, that is myelofibrosis now. But we're starting to treat people where they have Grade 1

myelofibrosis with Pegasys or ropeg, and what we're starting to see is a reduction in the mutation burden which to me was a bit of a surprise.

I've had people on these medications. They're on them for a couple of years, and then I start to see this reduction in their JAK2 mutation burden. In some cases, their CALR or MPL burden; and that's something that Radek Skoda predicted because if you boost the immune response against these mutated stem cells, then the percentage of mutated stem cells should go down. So, I'm really happy to be seeing that.

Why don't we use that in everybody? Because interferon can increase immune responses. So, if anybody has an autoimmune disease, that's kind of tough. It can cause a flare of psoriasis or inflammatory bowel disease. But, that's a risk that we know.

The other thing is depression. Depression can creep up on people who are on Pegasys or ropeg, so you have to know to look for it.

Elissa: Yeah.

Dr. Jamieson: It's not very common. It's usually in people that have had a history of depression. I don't put anybody who has had a history of suicidal ideation on interferon because it's too risky or who has severe autoimmune disease. Very rarely we can see pulmonary issues where people just feel like they have a bit of restricted breathing, but that's extremely rare. And so overall, these are extremely effective

medications that we couldn't get insurance to approve until the ropeg trials were done in Europe; and then they said, "Wow, they really work." And so then, we were able to start getting in just patients who are on Medicare approval for either Besremi or Pegasys. So, I think that's been quite an advance. I'm pretty excited about that.

And then, of course, we have the JAK2 inhibitors that have been approved. Ruxolitinib, or Jakafi, was the first one to be approved. That was in 2011. Very effective for reducing all the inflammatory symptoms of polycythemia vera as it progresses. So, it's approved for polycythemia vera. It's approved for myelofibrosis and post-PV and post-ET myelofibrosis. It doesn't really work that well in essential thrombocythemia. I don't think that the increased production of platelets in ET is really JAK2-, STAT3-, or STAT5-dependent. It looks more like it's STAT1-dependent. And JAK inhibition with Jakafi doesn't really do that much. But it's a very, very good drug, particularly if we start earlier. So, approved in 2011. It can be very effective. You can't get the full benefit if you're taking a proton pump inhibitor. So, if you're taking Prilosec® or something else, it doesn't get absorbed.

The other drug that's also FDA approved for myelofibrosis is fedratinib, also known as Inrebic®. So, that was approved in 2019. Initially, we thought, oh, maybe it causes vitamin B1 or thiamine depletion. Yeah, I think it's just nausea. Some people don't want to eat, so we have to make sure that they eat properly or get thiamine supplementation. So, that's easy.

They're both effective in myelofibrosis, and then we've got VONJO®, pacritinib, that's approved for people who have myelofibrosis with lower platelets. We've got momelotinib, which is for people that tend to have red blood cell transfusion issues with their myelofibrosis. So, there are a lot of things. We're very excited that the MPN community keeps rallying around the patients, and the patients keep rallying around each other to say to the FDA, "We need more therapies."

It isn't one size fits all, and that's what the CML kind of experiment taught us. You can push for new therapies, even when they're rare diseases. And these rare diseases become the test case for understanding how to deal with other cancers. And I think that's been the really important lesson we've learned from MPNs. You have to start early. Start early in terms of diagnostic indications, prognostication and then therapy.

Lizette: Sure. And we do have people ask about CAR T-cell therapy, bispecifics. Are any of these therapies utilized for MPNs?

Dr. Jamieson: Not yet. And the reason is, you know, for CAR T-cell therapy, chimeric antigen receptor T-cell therapy, it's really that T-cell has something on the surface that's going to allow it to target the T cell so it can kill whatever it attaches to with what's on the surface. So, if we want to target a CD19-positive T cell, it will engage that because it's got the ability to bind that cell and then release the toxic contents from that CAR T cell.

We don't have a cell surface marker like that for MPNs. You know, we try and go after CD123 or IL-3 receptor alpha. It's also known as that. It wipes out all normal myeloid progenitors, and people become very pancytopenic and at risk for infection. So, we don't have a good cell surface marker for MPNs, for CAR T cells, or for a bispecific T-cell engager, also known as a BiTE yet. It doesn't stop looking. We had one that was an embryonic cell surface marker called ROR1 that looked pretty good, but the cell surface density of that antigen wasn't high enough.

So, I think as we start looking at different kinds of biology through RNA sequencing, we're going to learn more. I think from a mutation standpoint, calreticulin is one that is actually looking very interesting because that is expressed on the cell surface.

So, I was just referring in the last comment to the JAK2 mutation. But with a CALR mutation, it does look like it leads to something on the surface that a CAR T-cell monoclonal antibody or bispecific T-cell engager can actually see. And those clinical trials look very exciting, and I think are leading the way for really boosting an immune response against the disease. So, I'm pretty thrilled that those are moving ahead, primarily for patients with essential thrombocythemia, so CALR is usual mutation we see in patients with ET. They're often young.

So, I think that's a huge advance. I'd expected them not to be as effective as they are because I thought, well, calreticulin signals through JAK/STAT, so how is this going to look different than a JAK2/STAT3 inhibitor. But it actually seems to boost the immune

response against the disease. And I think that's a huge advance. I hope we get something like that for myelofibrosis because, again, I think we have to start earlier. But if you prevent myelofibrosis progression from a calreticulin-mutated stem cell, that's pretty good.

Lizette: Yeah.

Dr. Jamieson: I honestly think that's a huge advance for the field.

Lizette: Definitely. And I know that we've also had some PV patients asking about side effects for rusfertide.

Dr. Jamieson: Yeah, I think that one looks very interesting as well. I think, hepcidin is an interesting target. Prevent that increased absorption of iron, so you just can't make those red blood cells. I think that's a really clever approach.

I think hypertension, you know, having blood pressure that goes up and down when you're at risk for cardiovascular events from polycythemia vera, their main cause of morbidity and mortality is stroke and heart attack. I think that's been the issue.

But again, I think in some situations, we're waiting too long before we're instituting the therapy. And what happens with polycythemia vera, it isn't just about red blood cell production. It's a stem cell disease. So, you're going to make more red blood cells. But, Elissa, you asked this as well, what else is going on? Well, stem cells can make

more white blood cells and more monocytes, and they can actually trigger endothelial cell injuries to our blood vessels that are aligned by these endothelial cells. And those monocytes can injure the endothelial cells or release this clotting factor called tissue factor. And then the platelets go, "Wait, what is this?" And they have a jamboree around that.

And so, even if you're reducing red blood cell production, you may still have more monocytes, more endothelial injuries. So, we have to think about that, preventing the platelets from sticking together is still important in polycythemia vera. And also, in essential thrombocythemia. So that baby aspirin a day. I think we're still going to need that. It isn't just about red blood cells sludging in a traffic jam. Often, it's this, coincidence increased monocyte level or activity where we see more clotting.

So, I think it is a real advance though, and I think we've got to look at, "Okay, we'll be just more careful of about people's cardiovascular risk." And I think phlebotomies seem innocuous, but they're hard for people to take over a longer period of time. You know, they get these fluid shifts. So, I think it's an advance, for sure.

Elissa: Yeah. Now, you have talked about a lot of side effects with these different medications. Are these manageable?

Dr. Jamieson: Absolutely. So, with Jakafi, the biggest side effect is, actually, weight gain. So, I think it's just knowing when people are going to be snacking. The other

thing is immunosuppression. So, we have to make sure that they don't have John Cunningham (JC) virus titers that are high, that they don't have a previous risk of Shingles. If they do, we want them to be vaccinated. Totally manageable.

The thing is the disease has side effects, so we've got to manage the side effects of the disease and side effects of progression. So, Jakafi is very, very well-tolerated in most people that take it. Inrebic, different drug. Some people get nausea. Some people get diarrhea. But once you get on the schedule, their body gets accustomed to it. Generally, very well tolerated.

Pacritinib, that's not really a tolerance issue. It's more of a kidney issue. A little bit harder on the kidneys, so we've got to be careful about who we give that drug to and at what dose. And I think the same thing for momelotinib.

So, the side effects have a lot to do with dosing. And tailor-making the dosing, having the right dose for the right person, I think, is really important. We have to look at kidney function, liver function. We have to look at what is making it so they can't tolerate this drug? Is it the time of day they're taking it at? If the drug causes reflux, you don't want them lying down right after they take the drug. They're going to get gastroesophageal burning. They're not going to want to take that drug.

So, a lot has to do with our habits and when we take a medication and whether or not it's well-absorbed or well-tolerated has to do with diet, exercise, all these other things.

But, I think they're sufficiently well-tolerated that we're seeing people having better longer lives now.

Elissa: Wonderful.

Dr. Jamieson: I think that is a testament to what Blood Cancer United has done. I think MPN Research Foundation patients themselves said, "Hey, I'm still here. I want something better. I was at a meeting recently where somebody referred to it as the lily pad phenomenon. They're on a lily pad here. It's extended their lives, improved their lives in terms that they have a better quality of life with fewer symptoms; and then they jump to the next lily pad as we make the next advance.

And I think that's what this field has done. I started doing clinical trials for this disease with targeted therapies back in 2008.

Elissa: Wow.

Dr. Jamieson: I didn't think we'd be in this position, I mean this great position of just having too many therapies to choose from.

I was a bone marrow transplanter. I thought the only way to fix them curatively is to do a bone marrow transplant. But giving somebody else's immune system to a person can cause what's called graft-versus-host disease. And, you know, survivor rates are lower in myelofibrosis. It's a tough disease to transplant because those stem cells

from the other person are going into this scarred-down environment. They see the bone marrow, and they go, "Yikes. I don't want to go there." And they tend to go to the spleen. And even if you have a splenectomy, then the stem cells go to the liver. They take over liver function. So, it's a tough therapy to have. It's still curative therapy, but you have to be very careful about who you choose to go for transplant. And it's not just about age. It's about a lot of what are you willing to put up with and then knowing that you may get graft-versus-host disease and that that needs to be managed, sometimes, ironically, with Jakafi.

So, I like your idea, Lizette, of focusing more on the targeted immunotherapies like CAR T-cell therapies, bispecific T-cell engagers, or just combining interferon with a JAK2 inhibitor.

Elissa: Yeah.

Dr. Jamieson: You know, just to boost the immune response. Same idea, but start earlier. And I think as we have more genomic prognostication tools, we can do that safely.

Elissa: Yeah. Now, one thing that you didn't mention was fatigue; and I'm sure a lot of patients listening are wondering what they can do about that, if anything.

Dr. Jamieson: Fatigue is the number one symptom, and when I talk to people, generally when they have profound fatigue, I ask, "Can, you have your feet up or be

horizontal after dinner? Are you just unable to go out after dinner?" And they go, "Well, yeah. But I have a busy life. I have kids. I have this. I have that." It's the most common thing. They have to have their legs stretched out. They have profound fatigue. And that usually happens before night sweats, before fever, chills, weight loss.

So, treating fatigue is all about getting the proper diagnosis and seeing do you have that scarring in the bone marrow called myelofibrosis. You can only diagnose that with a bone marrow aspirate and biopsy. The biopsy is where we get a little piece of bone, teeny tiny. It's just with a needle. We do those in interventional radiology with sedation, so people don't worry that it's going to hurt. They just go, "Oh, okay, it's like having a colonoscopy. I just have somebody drop me off, pick me up, and I'll be fine."

So, that fatigue means you need treatment, usually. You need treatment to prevent the disease from causing fatigue, because the fatigue is like when you have the flu. It's a massive release of inflammatory growth factors that cause you to be really tired when you have the flu. You can't think straight. You don't want to do anything. That's that kind of fatigue. And it usually means your PV or ET are progressing to myelofibrosis. And that's when we need to say, "Ooh, we take that fatigue seriously." Sometimes people are fatigued because they have polycythemia vera because their hemoglobin's way too high and they can't think clearly, and they're having sludgy of red blood cells.

Similarly in ET. They're having little areas where their platelets are sticking together and preventing them from thinking clearly. But it's quite different than myelofibrosis where people say, "Look, my muscles are tired. I've got bone aches. I can't think clearly. It's more like a flu-like syndrome." And that means they need treatment.

Elissa: Yeah, yeah. I'm an AML survivor, and my doctor told me with fatigue the one thing you can do is exercise. And that seems so counterintuitive to me. I was like, "I can barely get out of bed. What do you mean?" But it worked.

Dr. Jamieson: Yes.

Elissa: So, is that something that you're talking with your patients about just trying to move your body, trying to move around?

Dr. Jamieson: Yeah, and it does seem counterintuitive. You go, "Look, I'm so tired. I can't do this." We do two things in my clinic. Everybody gets a massage if they want. We have a registered massage therapist. They get acupuncture if they want it because everybody has muscle aches and, you know, a lot of anxiety. And we make sure people aren't hangry. We have food there. We have coffee. We have all of that.

But, in terms of fatigue, I think exercise is a huge advance. And I don't mean weekend warrior, I'm going to go and run a marathon. I mean 15 minutes of exercise every single day for two reasons. It changes your circadian rhythm so you're more likely to sleep at night. So, sleep is a big issue for myelofibrosis, partly because of all these

inflammatory growth factors. Like you have the flu, you usually don't have a really restful sleep.

But also, what exercise does, particularly a weight-bearing exercise, if you do some weight, is that it actually circulates the T and B cells, the good cells in your immune system within your lymphatics. These are these little blood vessels that are compressed when you do exercise; and those T-cells from your immune system go to the right place. So, I think it's a really important part of the road to wellness.

So, I was in clinic one day, and this patient said to me, "Oh, well, thank you, Dr. Jamieson." I said, "Eeee, I just diagnosed you with two disorders – prostate cancer and high-risk myelofibrosis." He goes, "I know, but now I know what I've got, and now I'm on the road to wellness because you're going to fix these things, aren't you?"

I said, "Well, I think we're going to do this together." And he had his prostate cancer resected, total prostatectomy, fine. He goes, "Next, what are you going to do?" And he happened to respond to that drug Inrebic; and then he responded so well, actually, we were able to get him onto Pegasys instead because he just had too little disease to even be on Inrebic. So, that was pretty cool, but he really turned around and started to do exercise; and just that 15 minutes a day, it changed his basal metabolic rate. He lost weight, not with a GLP-1 receptor agonist but just by changing his habits.

And I really, really promote exercise in everyone that has an MPN. You'll boost your immune response. You'll improve how you feel. You'll improve how you think, and it actually is part of treatment for your MPN. And I don't mean really vigorous. I mean 15-minute walk a day or some weight.

Elissa: Yeah, yeah.

Dr. Jamieson: You alternate, but you don't get a day off. Every single day. You have your cup of coffee; you go and do some exercise.

Elissa: Do little squats in the kitchen.

Dr. Jamieson: That's it. Go do something after-

Elissa: Easy.

Dr. Jamieson: Dramatic. It's basically tricking your body into thinking it's doing exercise. It actually changes your metabolism. So, I think that's a very important thing to do.

Lizette: What are you really excited about with the new therapies or clinical trials out there for MPNs?

Dr. Jamieson: I'm excited about everyone with an MPN getting onto a clinical trial. So, clinical trials don't have to be interventional therapeutic trials. They could support the use of new diagnostic or prognostication tools. So, I think everybody should be part of

a clinical trial so we can understand how this disease evolves and how we can stop MPNs in general in their tracks and prevent them from progressing to AML. And clearly, we can treat acute myeloid leukemia. There are very effective therapies, but ideally, we'd like to prevent it from getting there in the first place. So, I'm really excited about the new ways we can use sequencing technology and AI to try and come up with a personalized signature for each person to say, "Here's your risk score. Let's intercept that where we can."

The other thing I'm excited about is making new therapies that prevent progression from myelofibrosis to AML and reverse AML. So, as I mentioned, we've made a drug called rebecsinib, which is an ADAR1 inhibitor. It's in a Phase 1 clinical trial at three centers for patients with high-risk myelofibrosis and secondary AML that has evolved from myelofibrosis.

So, the FDA said, "Yup, that looks like an unmet medical need. We want to do that." And then there's another target called APOBEC. It's an enzyme that introduces mutations into our stem cells, and that's our next target. This is a stress-induced enzyme. We want to block it. And we think that that's going to be an important target, not just for MPNs but also for a broad array of other cancers.

So, I think the field is wide open right now. I think the FDA is really looking for, not just safety/tolerability, but proof of efficacy or proof of mechanism early in Phase 1 clinical trials. And I think if we all support clinical trials, we'll get more information and

actually people get better care because we look at everything when you're on a clinical trial. So, I think for patients, there is a lot at your disposal. There are MPN-specific providers that you can see and whole teams that work together to really try and stop MPNs in their tracks. You have access to Blood Cancer United, the MPN Research Foundation, but also each other as a network. So, I think it's a brave new day for people with MPN. So, we're not going to stop.

Elissa: Absolutely. And we will have in our show notes our Clinical Trial Support Center so patients can get connected with a clinical trial nurse navigator and find trials that any time after diagnosis that they may qualify for. So, look in the show notes if you are interested.

And so, one final question for you 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. Jamieson: I think it's the road to wellness idea that they already had something. We're just defining what it is and predicting or preventing progression. So, that's the hope piece. The hope that it won't progress, and actually we may allow it to regress and go back to an earlier stage of disease. And I've seen that in patients in my clinic.

So, I think now that we have better tools to predict who's likely to progress and how we can get the disease to reverse, I think people have every reason to be hopeful. I think

it's just getting to your local MPN center and make sure you're seeing somebody who specializes in this. You know, we are all here to help people; and the FDA is behind us in terms of making new therapies. I think it's an exciting time.

Elissa: Yes, definitely. Well, thank you so much, Dr. Jamieson, for joining us today and telling us all about all the treatments available, which is so great, but also the emerging therapies and what you're really looking to do. And so, I hope that does give real hope to patients and their loved ones. And so, again, thank you so much for being here with us.

Dr. Jamieson: Thanks again, Elissa and Lizette. I really appreciate it.

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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