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The Bloodline with Blood Cancer United Podcast

A podcast for patients and caregivers

Episode: 'Myelofibrosis (MF): More Options, More Hope'

Description:

What does a myelofibrosis (MF) diagnosis really mean, and how does it fit within a group of conditions called myeloproliferative neoplasms, or MPNs? In this episode, we're joined by Dr. Tania Jain of Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore, MD, who helps break it all down in a clear and approachable way.

She discusses how myelofibrosis affects the bone marrow, common symptoms to watch for, and how treatment options are tailored to each person. From managing day-to-day challenges to understanding when more advanced treatments may be considered, this conversation focuses on what matters most to patients and families.

As Dr. Jain shares, "every patient writes their own story," noting that advancing research offers genuine 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'll be speaking to Dr. Tania Jain, a physician scientist in the Hematological Malignancies and Stem Cell Transplantation Division with the Johns Hopkins, Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland.

Her primary research focus is to develop strategies to improve outcomes and prevent relapse of hematological malignancies, especially myeloproliferative neoplasms, or MPNs, and their overlap with myelodysplastic syndromes, or MDS, following allogeneic bone marrow transplantation. She also serves as the Director of the Immune Effector Cell Therapy Program, where she is studying aspects of the safety of CAR T-cell therapy with an aim to improve long-term outcomes for these patients. Welcome, Dr. Jain.

Tania Jain, MBBS: Thank you for the very kind and generous introduction. I'm glad to be here. Thank you for having me.

Elissa: Well, we are very happy to have you here. So, our episode today is on myelofibrosis, which is a diagnosis that falls under the umbrella of myeloproliferative neoplasms, or MPNs. Before we get into myelofibrosis, could you tell our listeners what MPNs are?

Dr. Jain: So, great point to start with. MPN, as you mentioned, which refers to myeloproliferative neoplasms, let's just break down how the nomenclature is, right? So, "myelo" usually refers to the bone marrow. So, now you're starting to talk about a condition or a disorder or an abnormality in the bone marrow, which is our factory of making blood cells, right? Proliferative refers to growing out of control, so to speak, in this context.

Elissa: Oh.

Dr. Jain: And neoplasm is a terminology that is commonly used for a cancer diagnosis. So, the term together refers to a bone marrow condition where your bone marrow is growing out of control as a result of usually an aberrant or a mutated baby blood cell or a mutated stem cell, which is giving it the advantage to grow or proliferate out of bounds. And, obviously, when one particular cell proliferates, the others can suffer, which is why you see one typical cell line proliferating whereas others sometimes going down or cytopenias in the other cell lines.

Elissa: So, I mentioned that myelofibrosis is under the umbrella. What other diagnoses fall under the umbrella of MPNs?

Dr. Jain: So, MPNs is a rather broad category, maybe not as broad as lymphomas; but it's still pretty broad. The common things that we see in that context include ET, so essential thrombocythemia. And the proliferative cell lineage in this case is platelets or megakaryocytes. So, a typical presentation would be high platelets.

The second early MPN or more early phase MPN would be polycythemia vera. Now, the proliferative cell lineage here is erythroid cell lineage, so you see high hematocrit. You see erythrocytosis, high hemoglobin. Myelofibrosis is another one. Obviously, we'll talk a little bit more about that, but again, associated with increased inflammation in the

bone marrow and just increased systemic inflammation, splenomegaly, and other features.

CNL, so chronic neutrophilic leukemia; and, again, as the name suggests, the proliferative lineage here is the neutrophils or the granulocytes. Technically, CML, or chronic myeloid leukemia, is also an MPN. Right, it's the Philadelphia-positive MPN. So, we tend to separate it out a bit because it's very unique in terms of its diagnosis, the causative mutation, and its treatment, but that's very much an MPN itself.

And then, I also tend to think about, under the same umbrella, is MDS/MPN overlaps, which technically may be somewhere in between MDS and MPNs; but many of those have proliferative features. And those include things like CMML, or chronic myelomonocytic leukemia; MDS/MPN with neutrophilia, which used to be called as atypical CML in the past – again, associated with dysplastic neutrophils plus proliferative neutrophils; MDS/MPN with SF3B1 mutation and thrombocytosis. So, as the name suggests itself, there is thrombocytosis but different from ET in that this is driven by SF3B1 mutation as opposed to JAK2 or CALR mutations in ET. And then you have MDS/MPN not otherwise specified, so this is what I call as the diagnosis of convenience when we categorize them as any one of the above. Then we tend to call them as MDS/MPN-NOS.

So, those are some of the common ones, and then some of the other rare ones would include eosinophilic syndrome, so HES or chronic eosinophilic leukemia. Even systemic

mastocytosis sort of falls under this same umbrella, so there's a lot of diversity in there. But these are some of the common ones that may land in my clinic, or any typical MPN clinic under the MPN umbrella.

Lizette: So, let's get to myelofibrosis. What is myelofibrosis; and how really is it different from the other MPNs that you mentioned?

Dr. Jain: Yes, that is a great question that we often deal with in clinic. So, myelofibrosis is, again, if you split the term itself, "myelo" meaning the bone marrow; "fibrosis," in this case, refers to the scarring in the bone marrow, which results from either proliferation happening for a long time or increased inflammation happening for a while. And that's a characteristic feature in terms of the diagnosis of myelofibrosis. Even if you look at the WHO (World Health Organization) or the ICC (International Consensus Classification) criteria for myelofibrosis diagnosis, one of the diagnostic features is a certain level of fibrosis or scarring in the bone marrow. So, usually we say Grade 2 or above in terms of the diagnostic criteria.

What else happens in myelofibrosis is, as a result of this scarring, a few things can happen. One is in a more proliferative phase, as a result of inflammation, systemic as well as in the bone marrow microenvironment, there could be high cell count, especially the white cells. So, as a result of this inflammation, you could see a more proliferative phase. You could see anemia thrombocytopenia at the same time or later as a part of the spent phase of the myelofibrosis where there is more fibrosis in the marrow, less

space in the bone marrow to make healthy blood cells, and more of that marrow being taken over by the fibrosis or scarring. So, you see changes in blood counts. You see fibrosis in the bone marrow. You see changes in the progenitor cells. You see changes, especially, in the megakaryocytes when you look at the bone marrow samples under the microscope.

Then, the other thing that happens in myelofibrosis is splenomegaly. Now, the spleen is a very interesting organ and, in this case, tries to take over some of the hematopoiesis, take over some of the blood synthesis in, an attempt to try to help the bone marrow. And it does that, to some extent, but it also becomes an inconvenience in a way that now you have a large organ sitting in the left upper quadrant of your abdomen because the spleen is enlarged; and it can cause systems in terms of being painful, in terms of limiting your activity, and so forth.

And then the other thing that's hovering on your mind when you're thinking about myelofibrosis is what it can do in the future, right? So, myelofibrosis is arising because of an aberrant stem cell or mutated stem cell with either a JAK2 or a CALR or an MPL mutation. And if you were to leave this long enough, eventually, at some point, and that time duration could vary in every patient, but at some point, this would have the potential to evolve or progress into a more advanced phase, a more aggressive version of myelofibrosis in the form of what we call as accelerated phase or blast phase MPN, or myelofibrosis, which is sort equivalent of an acute myeloid leukemia with more than

20% blasts in blast phase MPN or more than 10% blasts in accelerated phase MPNs, both referring to the high risk or the advanced nature of that entity that can evolve from a chronic-phase MPN where the blasts themselves are not increased but have the features that I mentioned before.

Lizette: So, when somebody is diagnosed, is it because of their blood counts being off, as you mentioned, or are there any other signs or symptoms?

Dr. Jain: Usually, yes. Usually, the blood counts is what drives the diagnosis. So, a lot of times, someone's getting their annual blood check; and either they had some level of anemia that was investigated further and couldn't find common things like iron deficiency or vitamin deficiencies.

Sometimes, an enlarged spleen will, draw attention; and, you're having symptoms related to the large spleen or the constitutional symptoms, which is also quite a hallmark of myelofibrosis, which includes things like night sweats, weight loss, bone pains, unexplained pruritus, just lack of energy; and it's a very inexplicable lack of energy, very different from what you get, the way you feel tired after a red-eye flight or not sleeping overnight. It's a very different level of fatigue. Different, very different kind of lack of energy. So, those symptoms can sometimes get some testing underway, which may eventually lead to this diagnosis. But you're exactly right. A lot of times it is the blood counts that tend to draw attention towards this diagnosis.

Elissa: Now, could you discuss primary versus secondary myelofibrosis? What does that mean if they have either primary or secondary?

Dr. Jain: Yeah, so that's a great point. So, primary, you will hear us refer to primary myelofibrosis where these features, the bone marrow fibrosis, the cytopenias or low blood counts, the large spleen, the constitutional symptoms, when they develop without a preceding ET, or essential thrombocythemia, or PV, polycythemia vera diagnosis, so myelofibrosis, the scarring in the bone marrow and the resulting features of that developing de novo, so to speak. What is usually referred to as secondary myelofibrosis, but technically it is either post-ET myelofibrosis or post-PV myelofibrosis, and as the name suggests, that someone has had ET or essential thrombocythemia for many years, usually decades, or polycythemia vera, again, for many years, usually decades. And now more recently, instead of the blood counts being high, because that's what you see in ET or PV, they're now sliding down; and that's usually what will trigger the thought for repeating a bone marrow biopsy to look for or to diagnose or rule out what may be an evolution from ET to myelofibrosis or PV to myelofibrosis. And that is what is called as post-ET or post-PV myelofibrosis, which together, sometimes is clumped together as being called secondary myelofibrosis.

Lizette: And we know that there are different risk categories for myelofibrosis. So, how are those determined, and what does that mean for treatment or prognosis?

Dr. Jain: That's a great point and something that has been in constant evolution over the years. So, risk stratification in myelofibrosis, needless to say, it's critical. It's very important. It's all the more important for determining time to transplant; and I'll come back to that in a bit. But how we risk-stratify is something that has evolved over the years in the form of different risk factors that have shown to be meaningful in myelofibrosis.

So, when we first started, we started with blood counts and symptoms. Then we evolved into more about blood counts, more about symptoms, more about high white counts; and more proliferative features seem to be more high risk. And that led to the development of the DIPSS (Dynamic International Prognostic Scoring System) score with a lot of emphasis on anemia. Then, we realized that there is a fair bit of contribution from the cytogenetics also and from thrombocytopenia; and those two factors were added and became DIPSS Plus, so, a more revised version of this.

And as we have learned a lot over the last decade or so about the somatic mutations, not just cytogenetics, not just chromosomal mutations, but gene mutations in specific genes that are relevant to myeloid malignancies, so, you know, all of these diseases in this part of the bone marrow. There has now been evolution into something called MIPSS, so mutation-enhanced prognostic scoring system, which gives a lot of emphasis to what's the driver mutation that is JAK2/CALR versus MPL and a fair amount of emphasis on how many other high-risk mutational or somatic mutational

signatures that are present, in addition to cytopenias, in addition to the symptoms, in addition to the fibrosis and cytogenetics and everything.

So, those are several ways. Now, there have also been scoring systems or risk stratifications that are developed specifically for post-ET or post-PV myelofibrosis because when the first version or the first iteration of these scoring systems came about, they were mostly validated in primary myelofibrosis. So, there's specific ones sometimes that are use in post-CT or post-PV. And then, there are some specific for transplant. In a nutshell, how to think about them and how to use them really is to understand the factors that matter. And if you put all these together, the factors that matter or adversely impact prognosis in myelofibrosis includes cytopenias, include progressive leukocytosis, include rising blast cell count, include adverse-risk cytogenetics or adverse-risk somatic mutations, which we know are high risk.

And another feature that has recently come to light and probably being highlighted more and more is lack of response or losing response to first-line JAK inhibitors, specifically studied in ruxolitinib, but showing that if you do not have a meaningful response to ruxolitinib in the first six months, those patients tend to do less well compared to people who have a good upfront response to ruxolitinib. So, the ultimate idea is not to put someone in a box of a risk category but more to understand what risk features are present in a certain scenario and how that may or may not impact the long-term prognosis.

I will also add that these risk stratifications can change over time, right? Someone may start as a low risk because they did not have cytopenias to begin with or did not have a high level of bone marrow fibrosis to begin with or did not have high-risk somatic mutations to begin with but can develop these things over time. These risk factors are important to assess over time because these can change as someone's disease may evolve.

Elissa: Now, you mentioned a little bit, but could we talk about the current treatments for myelofibrosis?

Dr. Jain: Yes, absolutely. So, I said that the risk stratification is an evolving space. But that applies even more to the treatment strategies because that is even more so of an evolving space. And that's a good thing because that only means that we have more options for patients in terms of what to offer them for treatment.

So, usual frontline need is large spleen or symptoms commonly. Not everyone exactly, but a majority of patients, that's what the need is to address.

And that is where the role of JAK inhibitor sits in the best. Our usual first line ends up being ruxolitinib. It's the oldest. It's something that we have the most experience with. I think we're all very well-versed with the nuances around it. But there are other JAK inhibitors that have a very significant paramount role in treating myelofibrosis.

For example, fedratinib, which was the next one to get commercial approval in 2019, is a pretty strong JAK inhibitor, can bring about spleen responses in a reasonable proportion of patients – probably about one-third or so, even if they have previously not responded to ruxolitinib, as well.

Pacritinib has a very unique role because it's something that we can use more safely in people with extreme thrombocytopenia. So, people with platelets under 50,000, which were mostly not included in trials with ruxolitinib and fedratinib; but pacritinib was specifically studied in people with lower platelets. And while you still have to manage and monitor for cytopenias, that's something that has become a go-to choice for that subset of population.

And then the most recently approved JAK inhibitor is momelotinib, and that is a JAK inhibitor plus an ACVR1 inhibitor. And the reason that's important is because that blocks hepcidin pathways. As a result, tends to improve anemias. So, in patients who have anemia as the major barrier, as a major presentation of their disease, often momelotinib will be something to consider. Even pacritinib has some ACVR1 inhibition, so momelotinib or pacritinib would be considered as frontline options.

The reality, if I were to speak to this from the physician sitting in the clinician's chair, right, and treating a patient, every patient with myelofibrosis is unique. They're unique in a way, what is their disease presentation? What needs treatment at this time? So, people who have no cytopenias, people who do not have, or have very minimal

cytopenias or do not have much in the way of spleen and symptoms, there are scenarios where you tend to monitor them or watch them closely. I wish I had a treatment in that early phase that could change the natural history of this disease such that it could delay evolutional progression. But until I have something that is commercially available for a process like that, the usual strategy would be to watch them carefully.

Now, there is data for ropeginterferons in earlier phase of disease like ET and PV where we see some clonal burden reduction. Whether that applies to early-stage myelofibrosis also is an active, area of discussion of research.

Then there are patients where anemia is the most important presenting feature, and that is where the role of things like momelotinib comes in. And then, there are patients where splenomegaly and symptoms are the major burden of disease; and that's where the role of JAK inhibitors, including momelotinib, including ruxolitinib comes in.

Now, people who have more advanced disease, what one means by higher-risk myelofibrosis is the subset of patients where you're worried about transformation or evolution or progression through blast phase in a more near future. And the things that make one worried about that evolution in a more near future are exactly the risk factors that we spoke about earlier – the progressive leukocytosis, blast count increasing in the blood, progressive anemia, high-risk mutations, whether it's cytogenetics or somatic lack of response to ruxolitinib at six months.

So, when those things are happening, then transplant becomes a very meaningful treatment option, as well. It is the only potentially curative option, right? It is fraught with complications, but that is why, can leads to decision that's not taken lightly. It's a decision that takes a lot of discussion, a lot of reasoning about what's the risk of transplant, and what's the risk of disease? And it makes sense to pursue a transplant when the risk of transplant would be lower than the risk of disease.

Dr. Krisstina Gowin, who I've had the privilege to work with as a co-fellow and is now faculty at City of Hope, she led this study with CIBMTR and showed that people with intermediate 2 or high-risk DIPSS myelofibrosis benefitted long term from transplant in a very meaningful and statistically significant manner.

And some patients, even with intermediate 1, may have some benefit with transplant. But I think that's something that's to be evaluated more. In practice, sometimes if people have high-risk mutations and otherwise intermediate 1 disease, those patients would be considered for transplant.

I will say, I don't think we have the magic answer for myelofibrosis; and until that is available, I would continue to emphasize consideration for clinical trials. There's several out there that could be meaningful for an individual patient. So, always consider clinical trials as an option; and some of those resources that Blood Cancer United has and other foundations that want to help patients with these diagnoses, especially rare diagnoses like MPNs-

Elissa: Yes.

Dr. Jain: it's important to look up these resources or talk with your physicians or get a referral to a tertiary center for consideration for clinical trials.

Elissa: Yes, and we'll be sure to have our link to our Clinical Trial Support Center (CTSC) in the show notes so they can contact one of our Nurse Navigators to see if they qualify for a clinical trial anywhere around the country.

Dr. Jain: That's wonderful.

Elissa: Yes, yes. I did want to be clear for our patients listening. When you're talking about transplant, you're talking about allogeneic stem cell transplant, so the use of donor cells?

Dr. Jain: Yes, I should have specified that. But when I see transplant in the context of myelofibrosis, I mean allogeneic stem cell transplant, which means that the cells or the stem cells come from a person different from the patient themselves. So, there is a donor involved in the process, which could be a family donor or an unrelated donor from the registry. A family donor could be a full match donor or a haploidentical donor, which means a half-matched donor. And yes, it will be a transplant that was done using donor cells.

At least at Hopkins we have used all types of donors, including full-matched family donors, half-matched family donors, full-matched unrelated donors, and mismatched unrelated donors. And we led this large study with CIBMTR data, including over 1,000 patients which showed that the outcomes are more or less the same. There was some advantage with matched sibling donors in terms of engraftment; but overall, if you looked at long-term outcomes, it was very similar between all four types of donors.

Elissa: Wonderful.

Lizette: Yeah, now, what happens if myelofibrosis progresses to acute myeloid leukemia, AML? And not everybody progresses to AML, correct?

Dr. Jain: Yes. I mean the biology of this or the natural history of this would be to evolve into acute myeloid leukemia. But like I mentioned earlier, the timeline of that can be different for different people. The rule of allogeneic stem cell transplant in chronic phase myelofibrosis is also to prevent evolution into blast phase or acute myeloid leukemia.

When and if acute myeloid leukemia develops, we use our best options to treat that. The challenge, however, is that those best options, while they may be more effective in a what we call as de novo AML where the AML is not developed with the preceding MPN, or myelofibrosis diagnosis, they often have higher rates of response in de novo AML, whereas the same strategies have a much lower rate of response in AML that

develops out of MPN. And that speaks to the more aggressive biology of this particular type of AML that develops out of myelofibrosis.

Our usual strategies outside of a clinical trial would include things that we treat AML in general with. So, for example, 7+3, which is the intensive chemotherapy induction used in AML. Usually that's something that we can use in younger people. And in post-myelofibrosis AML, I would use it in people who I know can go to transplant because it appears that the benefit of heavy intensity induction is best in people who we can use a stem cell transplant to consolidate that response with.

The other strategy that is catching practice pretty quickly is, again, derived from de novo AML, but a combination of hypomethylating agents like azacitidine with venetoclax, which was studied extensively in primary AML, in AML not deriving out of myelofibrosis but has been used in post-myelofibrosis AML, as well, and different centers, including ours, have published on the role of aza-venetoclax combination in this particular type of AML with responses anywhere from 40 to 45% compared to 70+% in primary AML.

And then other strategies could include targeting particular mutations. So, there are a few mutations that we have specific targeted agents for, like IDH1 mutation, 1DH2 mutation, FLT3 mutations. And if these particular mutations are present, then either as a first line or a subsequent line or in addition to the backbone with induction or aza-

venetoclax that I mentioned, they could be options to consider with a very meaningful response rate.

Something that I often say though is that the post-myelofibrosis AML is something that we do not cure without a stem cell transplant. So, if someone is otherwise transplant-eligible, meaning that they are otherwise well enough to be considered for a therapy like stem cell transplant, that would be on the back of our minds as we're thinking about planning for induction or any treatment to bring about a strong response.

And again, I don't want to belabor the point, but this is another space where we need better therapies and, hence consideration for clinical trials to help improve options because what we have right now, there's certainly room for improvement.

Elissa: Now, you mentioned gene mutations that are more specific to AML, so like FLT3 or other mutations. Are those seen in the myelofibrosis prior to it progressing to AML?

Dr. Jain: It's a great point, and there will be a paper coming out soon on this. But what it appears is that most of these mutations develop in the chronic phrase, sometimes detected even many years, four or five years prior to the clinical evolution or progression to AML. But it appears that these high-risk mutations either grow in the course of their disease, right? That's why I said something that's low-risk

myelofibrosis may not always remain low risk. It can evolve. So, these mutations can grow or these high-risk mutations can expand.

In certain scenarios, these can also develop very shortly before the clinical conversion to AML or may be detected shortly after or at the time of the blast transformation or AML development. So, yes, these mutations, while in a majority of patients, will be seen in chronic phase and then evolve and then convert into acute leukemia, sometimes or less commonly they can develop right at the time of leukemic transformation or be noted right after that.

Again, speaks to how the individualized nature of this disease is that it has so many varieties that every patient writes their own story. And that story is different. That story is worth recognizing when you're treating patients in the clinic and also dictates or, at least, drives how you think about the treatment options for every patient in somewhat of an individualized manner.

Elissa: I feel like that's a really important point, particularly with the continuing of research and clinical trials to make sure that you're getting treatments that every patient will be able to benefit from so that those patients who may not be responding to the common treatments, that they have an option available. So, I think that's wonderful that we continue looking for new options, more treatments.

Now, going back to myelofibrosis treatments, could you share what common side effects that a patient may experience from the treatment, and can they be managed?

Dr. Jain: Yeah, if we talk about JAK inhibitors, which is the basic backbone of treating chronic failed myelofibrosis in the several different ways that we spoke about, think about this, right? It's a chronic disease, which means that it's something that someone would live with for a long time, many years, and will be on this treatment for many years, which then comes down to the point that the treatment has to be tolerable. It has to have toxicities that are minimal such that someone can take it for years.

If you look at the original COMFORT study, which was the randomized, Phase III trial of ruxolitinib with best available therapy or placebo, COMFORT-I versus COMFORT-II, it showed that, on an average, people were on ruxolitinib for four years or somewhere in the roundabouts of four years, right? That's a treatment that one can take if there are, you know, we never have a treatment with no toxicity. So, I will say something with manageable toxicities.

The usual side effects that we see with JAK inhibitors kind of are the other side of the coin of what you are trying to inhibit, right? On the one hand, you are trying to suppress the bone marrow because it's proliferative. But when you suppress the bone marrow, you just don't suppress the one lineage. You suppress everything, right?

So, the one thing that you commonly see with JAK inhibitors is cytopenia, so you're trying to control the white cell count; but then you start seeing anemia. You start seeing thrombocytopenia, especially with ruxolitinib and with fedratinib. You see those in a more pronounced manner than what you see with momelotinib and pacritinib. As I mentioned earlier, pacritinib is something that's used when you have thrombocytopenia or low platelets, and momelotinib is something that we use to improve anemia in some scenarios. But all JAK inhibitors can do some level of cytopenias in one or another cell lineage.

Some other unique side effects to each JAK inhibitor, so ruxolitinib, usually overall, they'll tolerate it long term. Can have some gastrointestinal effects. There has been some concern about second malignancies long term, but there is a recent SEER analysis which speaks to the fact that it may be more a virtue of second malignancies that are not uncommonly seen with myeloproliferative neoplasms or myelofibrosis itself.

Fedratinib can have cytopenias, can have more gastrointestinal toxicities.

People tend to have impairment in vitamin B1. So, most of the patients who are on fedratinib, we tend to put them on thiamine supplements as well. In the trial, there were a few cases of Wernicke's encephalopathy, which seems to be avoidable if you use thiamin supplements and watch for the vitamin B1 levels carefully.

Pacritinib tends to have more diarrhea, but that's manageable if you drop the dose. So, the usual dose is 200 twice a day. Usually, you see the diarrhea much less commonly at 100 twice a day, and many of those people you can even go back up on the dose without aggravation of diarrhea. And so, something to think about.

Momelotinib is something that we think about in the context of renal function and liver enzyme monitoring; and again, we watch for cytopenias in those patients too. But these are some of the common scope of side effects would be the cytopenias; and then each of these JAK inhibitors have some uniqueness in terms of their toxicity profile, which again can help determine what's the right JAK inhibitor for an individual patient as well.

Lizette: And I know that this is the exciting part, but let's discuss the future of myelofibrosis treatment. There seems like there's been some great advances recently, so what emerging therapies are you particularly excited about for myelofibrosis?

Dr. Jain: So, that's a long topic. Maybe I'll talk about what's most exciting to me.

Elissa: Yes.

Dr. Jain: Okay. So, one of the things that we're hearing more and more about is interferons in MPNs and where their role stands. So, as you know, ropeginterferon is FDA approved for polycythemia vera. We have now Phase III data comparing it to anagrelide after hydroxyurea in ET and also some of the patients in EXCEED-ET trial

who got ropeginterferons upfront, but that was not a comparative trial, so, emerging data in early MPNs.

But as I was mentioning earlier, there is more and more consideration in terms of what may be the role of interferons in myelofibrosis, whether it's in combination with JAK inhibitors or whether it's by themselves. So, that is something where we'll see more and more data, or at least I hope we will see more and more data emerge because this is one of the strategies where we have seen more reliably a reduction in the JAK2 variant allele fraction over time with treatment.

Now, a couple of products that are in the more advanced trial phase, so in Phase III trials, one of them is selinexor, which is an export inhibitor, and we should hear about a readout on their large first-line randomized trial in the coming couple of weeks. There is the BOREAS trial which uses navtemadlin, which is an MDM2 inhibitor. This MDM2 inhibits TP53, so when you inhibit MDM2, you release that pressure off of TP53. Right, two negatives make a positive. So, navtemadlin is being studied in people who have a suboptimal response to ruxolitinib, as an add-on to ruxolitinib. So, that trial is getting closer to finishing enrollment.

The other products that have looked at Phase I and Phase II are products like LSD1 inhibitors, so bomedemstat has had data in combination with ruxolitinib that looks interesting and will be worthwhile seeing how that data matures and what the future of that pathway looks like.

One of the most exciting things at ASH (American Society of Hematology Annual Meeting and Exposition) has been the mutant CALR-directed strategies. So, finally, we're in a phase where we're able to target not just the JAK/STAT pathway, which is what most of the JAK inhibitors do, but also directly suppress upstream where the exact mutation lies. Right, so, again, coming to the personalized treatments or more individualized treatments, the mutant CALR antibody is where we heard about in ET, as well as with myelofibrosis. So, right now, these are Phase I data, so, we'll see how the data matures and how additional studies may be done.

J&J (Johnson & Johnson) and Janssen has a mutant CALR BiTE (bispecific antibody T-cell engager), so that's now targeting or using patients' own T cells without engineering them. No modification happening but bringing them just closer to the mutant CALR for cell killing.

The company that makes ruxolitinib and also makes a mutant CALR antibody, Incyte, also has another T-cell redirecting antibody against mutant CALR. And I'll say the mutant CALR space has certainly garnered a lot of interest for this reason because it's personalized therapies. It seems like the target is functioning pretty well in terms of using these strategies to inhibit the target with some meaningful results, including reduction in the CALR mutational allele burden. But, again, all of these data that I'm talking about are early. We need to see how they mature. We need to see how they eventually pan out.

There are a couple of drugswhich, unfortunately, did not move forward, like pelabresib, which is currently being explored in another Phase III trial; and the one that is not being pursued anymore include navitoclax and parsaclisib, but those potentially had some disease activity, as well. But there are several other concepts that are being explored, including blocking the TPO receptor, including using CD123-directed strategies and including interleukin-inhibiting strategies like canakinumab, and NLRP inhibitors, which are again very, very early to determine if they would have a role in preventing progression or slowing progression, at least.

And then imetelstat is another trial that is of interest, which in the earlier phase of the study showed some indication that it may improve overall survival. But that's something that we're all looking forward to see how that pans out in a larger study. So, that's a telomerase inhibitor.

But there's certainly a lot of activity in the clinical trial space in myelofibrosis. It's a good problem to have. It's good to be able to offer options that may make more sense for one patient versus another. So, whether it's clinical trials or standard of care therapies, I think we definitely need more to offer to our patients.

Elissa: Yeah, that sounds like quite a lot. Now, you did mention BiTE, and that is bispecific antibodies, correct?

Dr. Jain: Yes. Thank you for clarifying. Yes, that does mean a T-cell engager, which means that it brings the host or the patient T cells on one end and the mutant cell on the other end, sort of close to each other. So, it brings into action patient's own T cells.

Elissa: Very exciting.

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 myelofibrosis?

Dr. Jain: I think the last two decades in the myelofibrosis space have truly been a testament to hope. As I was alluding to earlier, as I was talking about JAK inhibitors, there was a time when we had no JAK inhibitors, which wasn't too long ago if you think about it. The first JAK inhibitor was approved in 2012, and then there was another phase of about half a decade or more than half a decade when we only had the one JAK inhibitor.

And now in the span of the last four, five years we've had approval of three additional, commercial availability of three additional JAK inhibitors and a pipeline that is pretty solid, I would say, in terms of potential for benefitting patients. Even the drugs that did not eventually achieve FDA approval, for a variety of reasons, we have all seen patients, maybe not a majority, but we've all seen patients who benefitted from those drugs and clinical trials.

So, I will say that the fact that we are deeper into the understanding of biology of MPNs and a lot of strong work that's coming from our friends and colleagues and investigators around the globe has enabled the field to really develop drugs, develop treatments that can potentially treat this better in the future. And that is where I think there is a lot to be hopeful for.

Elissa: Yes, absolutely; and that is what we love to see, the continued research, again. And that couldn't happen without patients joining clinical trials. So, I hope that patients listening will go and take a look at our link for the Clinical Trial Support Center and maybe get connected with a clinical trial that's just right for them.

But thank you, so much, Dr. Jain, for joining us today and for this wonderful discussion all about myelofibrosis. I do think that this is going to give patients and their loved ones listening a lot of hope with all these drugs that are out right now and then the future, and the possibilities in the future. So, thank you so much. We really appreciate you being here with us today.

Dr. Jain: Well, thank you for having me; and, yes, I could not agree more that hope is what I would like to leave everyone with because it's there. There are options. We probably just need to help you find what's the right fit for every single person.

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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In addition to the Lounge, we could use your feedback to help us continue to provide engaging content for all people affected by cancer. We would like to ask you to complete a brief survey that can be found in the show notes or at TheBloodline.org. This is your opportunity to provide feedback and suggested topics that will help so many people.

We would also like to know about you and how we can serve you better. The survey is completely anonymous, and no identifying information will be taken. However, if you would like to contact Blood Cancer United staff, please email, TheBloodline@BloodCancerUnited.org. We hope this podcast helped you today. Stay tuned for more information on the resources that Blood Cancer United has for you or your loved ones who have been affected by cancer.

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Have you or a loved one been affected by a blood cancer? Blood Cancer United has many resources available to you – financial support, peer-to-peer connection, nutritional support, and more. We encourage patients and caregivers to contact our Information Specialists at 1-800-955-4572 or go to BloodCancerUnited.org/PatientSupport. You can find more information on myelofibrosis at BloodCancerUnited.org/MPN. These links and more will be found in the show notes or at TheBloodline.org. Thank you again for listening. Be sure to subscriber to *The Bloodline* so you don't miss an episode. We look forward to having you join us next time.