

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Under the MPN Umbrella: Exploring Myelofibrosis'

Description:

Join us as we speak to Dr. Brady Stein, a clinical hematologist and researcher at the Northwestern University Feinberg School of Medicine in Chicago, IL. In this episode, Dr. Stein discusses the rare blood cancer, myelofibrosis (MF), which is a type of myeloproliferative neoplasms (MPNs). Hear about the unique characteristics of MF, how it develops, and the current and emerging treatments that give MF patients hope.

Transcript:

Elissa: Welcome to *The Bloodline with LLS*. I'm Elissa.

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

Elissa: Today we will be speaking to Dr. Brady Stein, a clinical hematologist and researcher at the Northwestern University Feinberg School of Medicine, where he serves as Associate Professor of Medicine, Associate Director of the Fellowship Program in Hematology and Oncology, and Disease Team Leader for the Myeloproliferative Neoplasms, or MPN, program.

His interests in research focus on improving treatments for MPNs and MPN thrombosis through clinical and translational investigation. He has led many MPN clinical trials, including six currently active trials as the primary investigator. He also serves as a panelist for the National Comprehensive Cancer Network (NCCN) MPN Guidelines and Associate Editor for *The New England Journal of Medicine*, *Journal Watch Hematology/Oncology*. Welcome, Dr. Stein.

Brady Stein, MD: Thank you very much for having me.

Elissa: So, let's get started with learning a little bit about you. How did you start in the field of medicine and study myeloproliferative neoplasms, also referred to as MPNs?

Dr. Stein: So that's a good way to start, a good question. Blood is in my blood, so my father's a hematologist.

Elissa: Okay.

Dr. Stein: So, it was almost as if I was destined to become a hematologist. I kind of learned early on about platelets and thrombosis and iron deficiency at a pretty young age. So, I was kind of introduced to the field early, and so I sort of knew throughout medical school and residency that I would go in that direction.

Specifically, MPNs, I became influenced by a mentor at Johns Hopkins, Dr. Alison Moliterno. I had worked with her on a case when I was an intern back in 2003 or so. And as my career matured a little bit and I made that decision to join the hematology fellowship program, I kind of knew all along that I'd want to work with her. We had good chemistry. I was inspired by what she did, and she's a really important MPN researcher at Johns Hopkins. So, she kind of really influenced my career very heavily early on when I was starting and still really today, we're good colleagues and great friends.

Elissa: Well, that's great. Now today's episode is on myelofibrosis or MF, which is under the umbrella of MPNs. Could you tell us what that is?

Dr. Stein: Yeah. So, myelofibrosis is one of the three, what we call, classical myeloproliferative neoplasms. So, under that umbrella of myeloproliferative neoplasms, there is a disease called essential thrombocythemia (ET), so that's typically characterized by an increase in the platelet count. There's also polycythemia vera (PV). It's most notably characterized by an increase in the hemoglobin, but there can be other blood count changes. And then myelofibrosis is also under that umbrella. It's

a little bit distinct from the others because it's typically characterized by often high white blood cell counts, often anemia, and often a very large spleen, together with significant scarring of the bone marrow. So, it does have some distinctions compared to the others.

Elissa: Oh, that's very interesting, particularly this scarring of the bone marrow. I mean how does that actually happen?

Dr. Stein: Well, that's a really good question about how it happens. It's kind of a very big question in the field in terms of looking at mechanisms for bone marrow scarring and how to address those mechanisms with drug therapy.

But a lot of it has to do with the environment in the bone marrow. There are increases in what we call cytokines, messengers of the immune system that are elaborated that probably contribute to the scarring process. And there's a lot of belief that what we call megakaryocytes, which are parents of platelets are also heavily responsible for the bone marrow fibrosis.

The bone marrow fibrosis or scarring is not a permanent situation, but right now the only way we can reverse it is with bone marrow transplants. Right now, the major goal for the field is to try to find drug therapies that can reverse fibrosis without having to do a bone marrow transplant.

Elissa: Now that scarring. Is that more just kind of a buildup inside of the bone marrow?

Dr. Stein: It is. So technically we call it fibrosis, but when we're talking with patients, the way to share what's happening is this is, essentially a scar forms after injury. So it's kind of a reflection of injury to the bone marrow.

And the way we see it is really the pathologist applying a stain to the bone marrow biopsy, and that highlights the degree of scar in the bone marrow. But the way I

would describe it is just what might happen after the bone marrow's been insulted or injured.

Elissa: One of the other things about myelofibrosis is an enlarged spleen. Could you talk a little bit about that and how that happens?

Dr. Stein: Absolutely. Another integral part about myelofibrosis and a great question. So roughly 85% of patients with myelofibrosis will have an enlarged spleen. So, an enlarged spleen could be the reason a patient becomes diagnosed. Perhaps it's something that the patient feels first. They have a symptom or during a routine physical examination the doctor feels an enlarged spleen or let's say the patient has imaging for another reason, and on that imaging test the spleen is found to be enlarged.

So, the spleen is a key part of myelofibrosis because most patients with the condition have an enlargement of the spleen. The reason it gets enlarged probably has to do with something about how bone marrow parents react to bone marrow injury. And so, what often happens, uniquely in myelofibrosis, is the bone marrow parents find kind of an unfriendly environment or a change in the bone marrow environment. And then they leave, and they set up shop in a new location, and so that location often first is the spleen.

So technically we call it extramedullary hematopoiesis. What it means is that essentially there is blood or production outside of the bone marrow, so the spleen becomes enlarged in part because it's almost like another factor that's producing blood.

Elissa: Now myelofibrosis is one of the MPNs, but it's also considered kind of a chronic leukemia. Why is that?

Dr. Stein: So, it's now considered a chronic leukemia or at least since the WHO (World Health Organization) reclassification around 2008. And that's mainly because

myelofibrosis in 90% of cases is characterized by one of three main driving mutations, and so most commonly JAK2. That's about 60% of patients. Next a mutation involving calreticulin, that's about 25% of patients. And then after that the more rare is called a mutation in MPL.

So, these are all blood mutations or bone marrow mutations that drive the disease. They give a unique advantage to blood or bone marrow cells. And essentially if there's some advantage that a blood or bone marrow cell has over a neighbor, that's technically considered a neoplastic condition. So that's why we now refer to these as chronic forms of blood cancers because blood and bone marrow cells have an advantage that they've gained.

Elissa: And it's also a pretty rare blood cancer, right? What is the incidence rate in the US and then around the world?

Dr. Stein: You're right, it's a rare condition. It's often a condition that many people have never really heard of, and that can be kind of isolating for patients when they describe it and their friends, family, and neighbors sort of say, "Well, I've never really heard of that."

So, yes, it's rare. The, the incidence is probably about 1 per 100,000 persons; and what that translates to in the United States is a prevalence of around 15,000 to 18,000 cases actively existing in the United States. So, yes, it's considered definitely a rare condition.

Edith: So, Dr. Stein, how does myelofibrosis develop? Can it evolve from other bone marrow disorders or cancers?

Dr. Stein: Absolutely. So, myelofibrosis can be primary, and what that means is that the patient had no preceding blood disease or blood condition before that. When they're first diagnosed, it's felt like the disease was relatively new in onset. So, we distinguish primary from other secondary forms of myelofibrosis that have evolved

from a preceding blood condition. So, it is confusing, but, for example, patients who start with ET or essential thrombocythemia, or PV, polycythemia vera, after long periods of time, they can develop bone marrow scarring. So, they can essentially transform over time. It usually takes 10 to 15 years or more.

Those patients can have a bone marrow that just looks just like primary myelofibrosis, but we call it secondary because they had a preceding myeloproliferative neoplasm that was a bit different before it became myelofibrosis. So that's kind of the confusing distinction between primary myelofibrosis or secondary myelofibrosis that would evolve from ET or PV.

Elissa: What are the signs and symptoms of myelofibrosis because it is, usually a slow growing disease. And sometimes the symptoms are delayed. And if they are delayed, besides the enlarged spleen, how does one end up getting diagnosed?

Dr. Stein: Yeah, so, it's a good question. It's important to kind of go over the symptoms. I mentioned earlier that sometimes the spleen is the tipoff, and I mentioned that the spleen can be the tipoff, either a patient noticing it, a doctor noticing it, or an incidental discovery on some imaging test.

Another tipoff can be a change in the blood count when the patient has a routine physical. So, a change in the blood count could be an increase in white blood cells, sometimes a decrease in white blood cells. Anemia can be a common way to present. Sometimes the platelet count can be very high. Sometimes the platelet count can be very low. It's more common to have a higher platelet count than a lower platelet count around the time of diagnosis.

And then if a doctor ordered a blood smear to kind of follow up on some of those blood count abnormalities, they could see some changes in the shapes and the contour of the blood cells; and they might see that some of the blood cells are less mature than we expect to see under the microscope.

The other way to present is symptoms. Some patients can present with unexpected weight loss. They could present with unexplained fevers or drenching night sweats where they have to change their sheets or their pajamas. They might have very unusual fatigue or very significant itching, especially after the shower. So that's kind of generally the way that patients present.

It's variable. I'd say probably more patients present with symptoms, but there certainly are some patients who have a completely incidental discovery.

Elissa: Now the itching itself stood out. We had a prior podcast with somebody with PV; and they said itching was kind of a major factor in that. So, if somebody has itching and maybe some other symptoms, how then is it distinguished between PV and myelofibrosis?

Dr. Stein: Yeah, very good question. So all of the myeloproliferative neoplasms can mimic one another, right? They can look very similar at presentation, and one can evolve to the next. So that's always been the challenge for patients and physicians.

But to be technical about it, the way to distinguish polycythemia vera from myelofibrosis is really the hemoglobin. All patients with polycythemia vera really should have a very high hemoglobin, above a World Health Organization threshold. So that should be kind of the key distinguishing feature between polycythemia vera and myelofibrosis.

Elissa: Oh, okay. And what are the current treatments now for myelofibrosis?

Dr. Stein: So, the treatments are kind of as follows. When I see a patient with myelofibrosis, I sort of think about treatments in two categories, and they're not mutually exclusive. But one is to sort of focus on risk-adapted therapies, that is to kind of get a sense for the risk of the disease. Is it in a very low-risk state, is it in a medium-risk state, or a high-risk state in terms of its progression?

And so, for a medium- or high-risk state for progression, we might consider something potentially curative like a stem cell transplant. So, we base that decision on risk. There's a lot of other factors that go into that decision, but the risk of the disease is what initiates the conversation about a potentially curative therapy. Of course, we have to look at eligibility in a lot of different ways, but the risk of the disease could prompt a hematologist to think about that therapy.

The other driver of treatment is the symptom profile. Right, and so there are some patients who have no symptoms. If a patient truly has no symptoms whatsoever, then watchful waiting is a consideration. I say that over time or I see over time more patients having symptoms than not. What I try to do is kind of group or prioritize those symptoms into one of three categories. Sometimes it's really the spleen that's driving all the symptoms; sometimes it's really the anemia that's driving the symptoms; and sometimes it's inflammation where a patient could have relentless fatigue, fevers, sweats, or weight loss and that could be the primary aspect of the symptom burden. So, I try to prioritize which of the symptoms are most pressing and then tailor the therapy based on that symptom profile.

So, when I make that priority, if I think that the spleen really is the problem, then probably the first class of medications to consider would be what we call a JAK inhibitor. And there are two approved JAK inhibitors. One is called ruxolitinib, and the other is called fedratinib. Those drugs are pretty effective at shrinking the spleen.

If anemia is really the main issue, I think about some of the medications that are out there to treat anemia; and it could be what we call an epo-stimulating agent. Patients may have heard of this as something called Procrit® or Aranesp®. I think about medications like steroids, androgens. The one we use often is called danazol. Drugs that also have been shown in earlier years to augment blood production, anemic myelofibrosis patients have responded to older drugs like thalidomide or lenalidomide.

If anemia really is the main issue for the myelofibrosis patient, I might think first about a clinical trial because that's really an area in myelofibrosis where some of these older drugs have not really offered us very durable or meaningful responses to improve anemia. So, I might think about clinical trials first, if that's an option for the patient. If it's really inflammation that's driving everything, I'll also probably look to the JAK inhibitor class of treatments.

Elissa: Okay, now are these generally oral pills? Are they going in for infusions? How does this all work?

Dr. Stein: The JAK inhibitors, ruxolitinib and fedratinib, are oral medications. In terms of anemia treatments, most of them are oral agents with the exception of epo-stimulating agents. Those are injections given under the skin. They're typically given in a clinic, but patients can do them at home.

So right now, of the approved therapies for myelofibrosis, they're typically oral or injected. They're not infusions where patients would have to come into an infusion or treatment area and spend a couple hours there.

Elissa: Now I'm curious. Earlier on you mentioned some mutations, right? And like we know with other leukemias, mutations can determine, to some degree, prognosis, and also, the treatment. Could you tell us a little bit about that?

Dr. Stein: Definitely. So, I think a couple of important points about mutations. One, I think they help a lot with diagnosis. So, 90% of patients with myelofibrosis have one of those three mutations: JAK2, calreticulin, or MPL. So, it's helpful from a diagnostic perspective.

From a perspective of therapy, each of these mutations kind of has subtle nuances; but in the end, they activate what we call the JAK/STAT signaling pathway. So, it often comes up, patients will say, "Well I don't have a JAK2 mutation. Why would you

give me a JAK2 inhibitor?" It's because each of these mutations activates the pathway. Each of these mutations can confer sensitivity to JAK inhibitors.

So, for the most part, if we think about approved therapies, the mutation doesn't necessarily negate certain types of treatment. Okay, so JAK inhibitors can be used almost regardless of the mutation, and it's the same for any of the other medications that we discussed.

From a prognosis standpoint, I think there are some subtle differences. If we think about blood clotting, and that's something I didn't bring up earlier with myelofibrosis, but there are myelofibrosis patients that are at an increased risk for blood clotting. Patients with JAK2 could be at a higher risk for blood clotting compared to patients who have the others. And from a prognostic standpoint, it's generally thought that calreticulin mutations might associate more with indolence or perhaps longevity compared to JAK2 or MPL; so, there is some important prognostic information.

And the other thing that we think a lot about in this day and age is not just those mutations that we say are driving the disease. We call those drivers. There are other mutations that can either be present at diagnosis or be picked up along the way. I kind of call them hitchhikers. Like you never really want to pick up a hitchhiker, but over the course of the disease process, it can happen. And so, there's a number of mutations that are picked up through what we call next-generation sequencing tests, which can be done by blood or from the bone marrow that kind of give us a sense for prognosis beyond what we know is expected from whether a patient has JAK2, calreticulin, or MPL. So, there's a handful of those: IDH, EZH, ASXL1, P53, SRSF2, U2AF1. They're all kind of little codes that are not always intuitive to patients; but it's testing that we would get to further understand the patient's individual prognosis.

Elissa: You mentioned IDH. Now that's also in leukemias, correct?

Dr. Stein: Correct.

Elissa: Can they have leukemia and myelofibrosis at the same time? Is that something that's possible?

Dr. Stein: So, it's not usually the same time, but acute leukemia can evolve from myelofibrosis usually over time. And so, they don't necessarily exist together. It can be an evolution from one to the next.

Elissa: Oh, that's very interesting. Now we mentioned prognosis a little bit, so what is the life expectancy of somebody diagnosed with myelofibrosis?

Dr. Stein: So, the life expectancy is quite variable, right. There's a huge range. And that's because the disease is very heterogeneous. I mean within this rare disease, there's a lower-risk grouping, an intermediate-or medium-risk grouping, and a high-risk grouping, and the lifespan can vary from some patients in the lower-risk grouping can live 15 to 20 years. There are many patients who are in a lower-risk grouping who can live most of those years untreated.

In the medium-risk grouping, some patients can live five to ten years, and there can be patients who have very high-risk features where the disease could progress quickly in a matter of one to two years. And because the disease is aggressive, the physician might need to respond aggressively with treatment.

Elissa: We talked about current treatments. And I mentioned in the introduction that you are leading clinical trials. Could you tell us about some emerging therapies that you're excited about?

Dr. Stein: Yeah. I think that this is sort of an unprecedented era for clinical trials in myelofibrosis. It's very hard even for someone in the field to kind of keep up with all of the developments. So, the first class that's still under investigation or class of medications would be the JAK inhibitor class. So, we have two that are approved, but there are others that are emerging to try to improve upon the currently existing treatments. And so, some of the emerging ones would include a drug called

momelitinib or pacritinib and they're each unique because perhaps they are better utilized in anemic patients or patients with low platelet counts. So those are under investigation within the JAK inhibitor class.

In terms of the non-JAK inhibitor class, that's where we have a kind of an unprecedented number of treatments targeting a lot of different non-JAK-STAT pathways that probably contribute to the disease process and, hopefully, can build upon the success of the JAK inhibitor, which is kind of the foundation. It's made important advances, the JAK inhibitor class, but what we're not seeing is kind of complete remissions. The JAK inhibitor class of therapy helps with symptoms and helps shrink the spleen, but it doesn't reverse the bone marrow scar and it doesn't put a patient into remission. So definitely there's room for improvement and that's why you're seeing an overwhelming number of novel strategies that can be offered.

We participate right now in multi-institutional trials, so we are a site among many for some of the trials and right now the trial that we've had more experience with is a class of medications called a BET inhibitor. The code name for the drug is CPI0610, and we've been kind of intrigued by that because it's a drug that can really help patients with anemia, and we haven't had a lot of success in that area. So, we're sort of intrigued by that and we're following that. That's in mature development along with some of the other novel JAK inhibitors that I've mentioned.

There are other drugs like navitoclax, there's drugs like luspatercept for anemia, and then there are many other kind of novel emerging experimental agents that are used across many different hematologic malignancies that are being tried in myelofibrosis as well. So, I kind of invite the listener to follow headlines, to listen to podcasts like this, to follow along patient blogs after the ASH (American Society of Hematology) meeting. That's our big meeting-

Dr. Stein: -for the year where we're going to learn about important advances for all of the non-JAK inhibitor therapies for the treatment of myelofibrosis. So, there's at least five to seven important clinical trials that are going to be presented.

Elissa: Absolutely, yeah. And joining clinical trials is so important, and that's why LLS has a Clinical Trial Support Center so we can help connect patients to trials like yours where they can get the latest treatment and, hopefully, reach that complete remission, which is really what we're wanting. So that's really exciting.

Edith: So, Dr. Stein, on our patient podcast home page, we have a quote that says, "After diagnosis comes hope." What would you say to myelofibrosis patients and their families to give them hope for the future?

Dr. Stein: Oh, yeah. That's a great statement. I think, obviously, there's a lot of stress and anxiety that goes along with a new diagnosis or having the diagnosis of a chronic illness that has a chance for progressing overtime. So, there's a lot of stress, anxiety, and worry that goes along with that. But I would say that now with the unprecedented number of clinical trials, with the expanding drug approvals, drugs in mature development, absolutely a patient has every reason to be very hopeful about the outlook. Things are only getting better, things are only moving forward, advances are being made, and our patients often ask, they say, "Well, this is such a rare disease why would anyone be interested in it?"

I can't tell you how many pharmaceutical companies and researchers there are that are interested in these diseases. One, because many of the people who lead the research programs are former hematologists that are just doing research in a different location, perhaps at a pharmaceutical company compared to when they used to be at a university, so it's the same motivation to help patients.

Also, things that are discovered in myelofibrosis, medications that help in myelofibrosis could be wide-ranging in their positive impacts for other diseases, so a lot of these pathways, for example, the JAK-STAT pathway, there's a lot of use of JAK inhibitors in

rheumatologic diseases, in dermatology conditions, autoimmune hair loss. There's graft-versus-host disease (GVHD) after stem cell transplant. There's a lot of different ways to use these medications. So, discoveries in myelofibrosis impact many other patients and discoveries in other areas can impact myelofibrosis patients, so every reason to be hopeful.

Elissa: I think we're seeing that a lot that cancer research is really affecting so many different cancers and other diseases and particularly in blood cancer research when we're going down deep into the blood that is really kind of the heart of everything.

So, thank you so much, Dr. Stein, for joining us today. We really appreciate you talking about a rare disease like myelofibrosis, and we hope that listeners will get educated about it, particularly if they have this disease and then, hopefully, really look at the clinical trials and see what new treatments are out there that will, hopefully, get them into that complete remission. So, again, we appreciate your time today and sharing all about this.

Dr. Stein: Thank you very much for having me.

Elissa: And thank you to everyone listening today. *The Bloodline with LLS* is one part of the mission of The Leukemia & Lymphoma Society to improve the quality of lives of patients and their families. To help us to continue to provide the 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.

We hope this podcast helped you today. Stay tuned for more information on the resources that LLS has for you or your loved ones who have been affected by cancer.



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