Episode: 'Living a Full Life: Exploring Myeloproliferative Neoplasms (MPNs)'

Description:

Myeloproliferative Neoplasms (MPNS) is an umbrella term that includes myelofibrosis (MF), essential thrombocythemia (ET) and polycythemia vera (PV). In this episode, Dr. Angela Fleischman of the Chao Comprehensive Cancer Center in Orange, CA, delves into these disorders in more detail. She shares how a patient’s quality of life can be improved with the latest advancements in treatment.

Transcript:

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

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

Elissa: Today we will be speaking to Dr. Angela Fleischman, a Hematologist/Oncologist and Associate Professor of Medicine at University of California Irvine Health Chao Family Comprehensive Cancer Center in Orange, California. At UCI Health, Dr. Fleischman developed an independent laboratory group focusing on myeloproliferative neoplasms or MPNs. Her overarching research goal is to identify what drives disease initiation in MPNs and ultimately transfer these scientific discoveries into therapies that benefit MPN patients.

Welcome, Dr. Fleischman.

Angela Fleischman, MD: Thank you very much for having me. Always love to talk about myeloproliferative neoplasms and always am happy to engage with The Leukemia & Lymphoma Society that provides so much support for our patients.
**Elissa:** Wonderful. Well we are so excited to have you today. Now, of course, our discussion today is on myeloproliferative neoplasms or MPNs. Could you explain what that is and the various types of MPNs that are under that umbrella?

**Dr. Fleischman:** Sure. The word myeloproliferative neoplasms basically mean somebody's making too many cells, either red blood cells, platelets, or white blood cells. And we now know the reason for that in myeloproliferative neoplasms in a blood stem cell, patients develop a mutation which makes them basically think that they're always getting the hormone that our bodies are normally getting to tell us to make more blood cells. But the mutation tricks the immature cells or the precursor cells to think they're getting the hormone telling them to make more blood.

There can be many consequences of a myeloproliferative neoplasm. First and foremost, would be some abnormal blood counts. However, some people with MPNs don't necessarily have to have abnormal blood counts. Many times, people can present with a blood clot. For example, in their legs or in their lungs or elsewhere in their body or a stroke or a heart attack. And then they're found to have some abnormal blood counts. Then they're further investigated and found to have a myeloproliferative neoplasm.

**Lizette:** And there's different types of myeloproliferative neoplasms, right? It's kind of like an umbrella term.

**Dr. Fleischman:** Correct. The word classic myeloproliferative neoplasms or an older word could have been Ph-negative myeloproliferative neoplasms are polycythemia vera, where people have characteristically too many red blood cells. However, in polycythemia vera, or PV for short, people can commonly also have high white count as well as high platelets.

Essential thrombocytopenia, or ET, basically the person has high platelets. ET patients don't commonly have high white count but sometimes they can. And then myelofibrosis (MF) which can either be primary myelofibrosis, meaning the person
didn't have a diagnosis of ET or PV beforehand or post-PV or post-ET myelofibrosis. And in myelofibrosis, patients can have low blood counts, in particular, low red blood cells and/or low platelets and they can have an enlarged spleen.

Now you cannot have more than one MPN technically, so you can't have ET and PV. Actually, part of the diagnosis of one of those is you cannot have another one, so you have one or the other. However, if you have ET or PV, then you can transit into myelofibrosis.

Elissa: I was just talking to a patient, who is a Bloodline listener and she was saying that she transited, I believe, from ET to myelofibrosis at some point.

Dr. Fleischman: Correct. That is part of the natural history of the disease. Some people with ET or PV will never get myelofibrosis. Some people will. Another aspect that really should be mentioned is all people with ET, PV, and myelofibrosis have an increased risk of developing an AML (acute myeloid leukemia), but the risk is greatest in patients with myelofibrosis for progression to AML.

Lizette: And what distinguishes MPNs from other blood cancers and, really, are they that common?

Dr. Fleischman: So, the characteristic feature of a myeloproliferative neoplasm is almost all patients will have one of what we call MPN driver mutations. The most common is JAK2, in a specific location in JAK2 called JAK2 V617F. Over 97% of people with polycythemia vera have a JAK2 mutation. About 50% of people with ET have a JAK2 mutation. Then about 30/40% of people with myelofibrosis will have JAK2 mutation. And these are acquired mutations, not that they were born with them but with the caveat that we do now know that a lot of times people actually develop their mutation in utero before they were born. So, they live their entire life with these mutant cells in their body. And then a third most common mutation is called MPL.
For example, if you were diagnosed with PV and you don't have a JAK2 mutation, one should really question that diagnosis because, really, JAK2 is synonymous with PV. And if you don't have an MPN driver mutation then also one should really think hard whether somebody really has a myeloproliferative neoplasm. There can be other reasons why people can have high platelet count, high red count, and can have fibrosis in their marrow. Just because you have a high platelet count does not mean you have ET. There's many more common reasons why people have a high platelet count such as iron deficiency or inflammation. Also, there's a lot more common reasons why people would have a high red cell count like smoking or sleep apnea or if they're taking testosterone. And then myelofibrosis can be seen in lots of other autoimmune diseases without a myeloproliferative neoplasm.

And when you're talking about mutations, these mutations can be seen in other diseases, can be seen, sometimes in AMLs, sometimes in certain sub-types of myelodysplastic syndrome.

And then you asked how common is it? We say it's an uncommon disease, however, it's probably much more common than we really realize. For example, screening of the Danish population revealed that about 3% of the Danish population, if you screen with a very sensitive method, actually harbor JAK2 mutant cells.

**Elissa:** Oh!

**Dr. Fleischman:** Also screening of normal populations say, for example, 23andMe® customers who deny a history of MPN will pick up a JAK2 mutation in about 1 in 1,000 people. So, it's much more common in our population than we realize. Also, there is a phenomenon that's very common in normal human aging called clonal hematopoiesis of indeterminate potential. Over 20 to 30% of people over the age of 50 will have this. As we age, we get mutant cells in our blood; that's just inevitable. And the fifth most common one is JAK2. So, there's plenty of people out there that are walking around with these JAK2 mutant cells.
Elissa: Wow! I'd like to go back for a quick moment. You mentioned that some MPN patients, particularly with myelofibrosis, might transit to AML, or acute myeloid leukemia. How does that happen, and is that something that myelofibrosis patients should be particularly worried about happening?

Dr. Fleischman: To start with the worry, from my perspective, I don't think that it's worthwhile and/or productive to worry about something. And, unfortunately, there's no treatments that we can give at the present time that prevent progression of myelofibrosis to an AML. So, from my perspective, there's nothing you can do about it, why worry about it.

Elissa: Yeah.

Dr. Fleischman: Exactly how that happens, we're not entirely clear. We do know that particular mutations, that are termed high-risk mutations that people have in addition to their MPN driver mutation, like ASXL1, EZH2, or IDH1 or 2, sort of predict that this person may be more likely to progress to AML. So, if somebody does have one of those high-risk mutations or has high risk features, like they have blasts in their peripheral blood or they really have very heavy transfusion needs, then they should be really watched very carefully and, if eligible, potentially think about a bone marrow transplant before they progress to an acute leukemia.

Elissa: Okay. Now we have often heard from MPN patients that at diagnosis they're told they have a blood disorder; it isn't referred to as a blood cancer. Why is it so often referred to as a blood disorder versus a cancer?

Dr. Fleischman: Well, it was a disorder previously. So, if somebody was diagnosed, say prior to 2013, the MPNs used to be called MPDs, myeloproliferative disorders. And so, yes, they would have been diagnosed with a disorder, not a cancer. It was classified as a benign disease previously because when the mutations were identified in these diseases, then it got into the category of a quote, "cancer" because the definition of cancer is you have mutant cells and those cells grow. Then that changed the
nomenclature from MPD, myeloproliferative disorder, to MPN, myeloproliferative neoplasm. And now that we're realizing that normal people can have these mutant cells in their blood, I think that that distinction is now really blurring.

In terms of whether it's called a disorder or a neoplasm, you know, there are some pros and cons. One can think of some benefits. For example, access to support systems. When this disease was moved from a category of a disorder to a neoplasm because previously MPD patients, unfortunately, did not have access to support for medications through grant foundations that support cancer patients, so there are some real positives for that patient population to be categorized as a cancer. From my perspective, there actually might be also some negatives. This is currently technically considered a quote, "cancer," however, it has a lot of aspects of more of a chronic inflammatory disorder. So I think it may be doing patients sometimes a disservice to say, "Oh I have cancer," and addressing their disease like a cancer where they maybe should be thinking about addressing it more like a chronic inflammatory disorder and really focusing on their general health rather than putting themselves in a quote, "cancer" category.

**Elissa:** Right. Yeah, that makes a lot of sense. Now a lot of patients might get diagnosed through their community oncologist or a general oncologist or maybe even their primary doctor. Is it important for them to find an oncologist who specializes in MPNs?

**Dr. Fleischman:** As an oncologist who specializes MPNs, I think it depends on the patient whether or not they think it's right for them to go to a specialist. To be honest, our treatments of myeloproliferative neoplasms, many people are just on a baby aspirin or even younger people could now maybe not even be on a baby aspirin if they don't have a JAK2 mutation. So, I think that the reason to go to a specialist is to gather more information for yourself about your disease and not necessarily expecting that there's going to be a change in your therapy, but it's for your own personal benefit to learn more about the disease. There are specific situations, for example, if
you have myelofibrosis and you may have some high-risk features that may warrant closer monitoring, yes, in that case, going to a specialist will change your care. I'm not saying these people don't need to go to a specialist, but I think the role of the specialist is to educate the patient about their disease rather than the expectation that they're going to be getting some different therapy than they would from their general oncologist.

Elissa: Right. And if they're in a rural area, they're not near a specialist, it might be something where you would be able to consult with their oncologist to educate the patient, but still have them being seen by their community oncologist?

Dr. Fleischman: Correct, yes. That's a usual scenario in all blood cancers or probably all cancers. You have your specialist in a metropolitan area and then the person has their home oncologist nearer to their house.

Lizette: Right. And what are the common signs and symptoms of MPNs and are there different signs and symptoms depending on the type of MPN somebody has?

Dr. Fleischman: Yes, there are. Probably characteristically for polycythemia vera, people will notice, severe itching, in particular after hot showers. Maybe their family members will say, "Oh my gosh, your skin looks really red or your eyes look really bloodshot." Those can be signs that somebody has high red blood cells.

People can also, from high platelets, get more headaches. I know headaches are very common, but-

Lizette: Right.

Dr. Fleischman: -can get a lot of headaches. Can also have some numbness and tingling in their hands or burning and really red hands and feet. Those can be symptoms of a high platelet count. People can have large spleens which can cause them some abdominal pain and maybe they feel that their abdomen is growing. In
myelofibrosis, people can have night sweats, fever, and weight loss. And in
myelofibrosis, in particular, people can have some severe fatigue.

**Lizette:** Now, some of these signs and symptoms I feel that you can find in other
diseases, a lot of the other blood cancers. So, is it really the type of abnormalities you
find to actually be able to diagnose MPNs?

**Dr. Fleischman:** Correct, yes. Many of these symptoms are really very vague and
can be seen in other blood cancers, as well as just other general conditions. People
with MPN really do have a characteristic look to their blood counts, so if somebody's
complaining of these symptoms yet their blood counts look totally normal, it would be
really unlikely that they would have an MPN. But now that we have these genetic tests
reducing in cost and becoming much more widely available, that's the cincher to say
whether somebody has an MPN or not. But I would say that if somebody is
complaining about some vague symptoms and their CBC is totally normal, it probably is
not appropriate to test them for a myeloproliferative neoplasm.

Also, in some cases, if somebody shows up with a blood clot and they don't know why,
testing, for example, JAK2 can sometimes be on a list of things of what's called a
hypercoagulable workup. Basically, somebody shows up with a clot, you want to know
why, you order a whole panel of tests that could tell you why they've clotted. And
JAK2 can be sometimes on that list of a hypercoagulable panel.

**Elissa:** So what are the current treatments available for the various types of MPNs?

**Dr. Fleischman:** In MPNs, just to be clear in terms of our treatment goals for this
disease, and this probably dates back to when it was characterized as disorder, is that
the stated goals are to reduce somebody's risk of blood clots.

I think that's an important point because when somebody thinks they have a cancer,
they think that their treatment is focusing on basically getting rid of the cancer cells.
But in a myeloproliferative neoplasm, where many people can live a totally normal
lifespan, it's sort of a different goal of care, so we try to reduce the risk of blood clots. Almost all MPN patients are on aspirin. Many PV patients who are under the age of 60 and have not had a blood clot in the past can be managed on a baby aspirin and what's called phlebotomy, basically donation of blood, to keep their hematocrit, one of the blood parameters, below 45%.

Many people with ET are managed with aspirin alone. And then we get into the word cytoreductive therapy, basically meaning something that brings down your blood counts. The most common medication that all MPN patients take as a cytoreductive therapy is called hydroxyurea, and this brings down all of somebody's blood counts – white count, hemoglobin, hematocrit, and platelets. And it's been shown, people on hydroxyurea with an MPN have fewer blood clots than with people without hydroxyurea. So, if you're on hydroxyurea, the purpose is to reduce your blood counts and to reduce your risk of thrombosis. It's not necessarily getting to the root of the disease.

A second drug can be anagrelide, which is usually only given in essential thrombocythemia or ET because that only reduces the platelet count and also reduce risk of blood clots.

One interesting drug, interferon alpha, which can be in many different formulations; Pegasys®, which is pegylated interferon alpha; or Ropeginterferon, which is a very long-acting interferon alpha, can be used in ET and PV to reduce blood counts, reduce risk of blood clots. And, interestingly, that's the only drug that we currently have that, in some people, can reduce or get rid of the JAK2 mutant cells, so I'd like to emphasize that, that that has the potential of what we say "A disease-modifying agent." People can be on JAK inhibitors or the one JAK inhibitor that's available currently for PV is called ruxolitinib or Jakafi®. That's very good for improving symptoms in patients with PV, in particular the itching. It also can normalize blood counts.
Important to note with the Jakafi or ruxolitinib in PV, the studies were not created for the purpose of testing whether it reduces blood clots, so we don’t necessarily know the impact of ruxolitinib or Jakafi on blood clots in PV, which is an important point to make.

In myelofibrosis, people with myelofibrosis have a variety of issues. So, from my perspective, you address the issue that you would like that the person needs to have addressed. Because in myelofibrosis, some people have high counts, some people can have low counts and need transfusions. Some people, their primary issue is symptoms. Some people, their primary issue is a large spleen. So, we do have now three JAK inhibitors, potentially a fourth one coming on the market in the near future. The JAK inhibitors reduce spleen size and improve symptoms. That’s clear. How they change the natural history of the disease is unclear.

I will not go into a large discussion about different treatments with myelofibrosis but the purpose of treatment in myelofibrosis is a little different than PV and ET. The treatments that we have available at the present time address symptom management and spleen reduction. And potentially with a new JAK inhibitor coming on the market may address the anemia.

**Lizette:** Wow! So there are new things coming out of studies right now then for the MPNs.

**Dr. Fleischman:** Correct. There are new drugs coming on the market. I think that we’ve really progressed quite a bit in the past 10 years. Until very recently, we only had one option for a JAK inhibitor. Now we have three and potentially a fourth one. Each JAK inhibitor is a little bit different in terms of the side effect profile and the impact. So, now we’re able to tailor a JAK inhibitor to the specific myelofibrosis patient.

Many of the trials incorporate what we say a JAK inhibitor add-on therapy, basically adding something onto what’s a JAK inhibitor backbone. There are other novel drugs
coming through the pipeline. But I also want to emphasize that at the present time, the only curative option for myelofibrosis is a bone marrow transplant.

The timing for a bone marrow transplant in myelofibrosis, honestly, I think is one of the most difficult decisions because many times, you want to balance the risks of the bone marrow transplant, which really have real risks of death and bad consequences against their likelihood of having real problems from their myelofibrosis. Because you don't want to give somebody a worse disease with a transplant like graft-verse-host disease (GVHD) or even lead to their death earlier than they would've progressed on their own naturally from myelofibrosis. So, really, it's reserved for those people in whom you know that if you do not do a transplant, they're going to have a very bad outcome pretty quickly, and so it's worth the significant risk of having a transplant. Whereas many myelofibrosis patients, the risks of the transplant outweigh the risks of their actual disease.

**Lizette:** And I know that you mentioned that MPNs are chronic diseases, so that's long-term treatments that could come with a lot of side effects. How do you manage the side effects to make sure that your patients have a better quality of life?

**Dr. Fleischman:** That's actually a very good point because one of the main goals of our treatments in myelofibrosis is to improve symptoms, so it makes absolutely no sense to give somebody a treatment that is going to make their quality of life worse because that's totally defeating the purpose. But there can be tradeoffs. For example, a JAK inhibitor is really making somebody's fatigue get better and shrinks their spleen, but all medications have some, side effects. That's just a fact of life. Some worse than others. With JAK inhibitors, there's the concern that they are immunosuppressant so can make somebody a little more susceptible to infections; can increase one's risk of skin cancers; and a significant side effect, from my perspective, is the weight gain associated with it because it increases hunger. Those things are significant and should really play a role in when somebody's deciding whether starting a medication is right
for them and are the benefits that they're deriving from the medication worth the side effects.

In PV and ET, there's a whole another set of side effects with interferon such as flu-like symptoms or can exacerbate anxiety or depression or autoimmune diseases. I think it's really important for the patient to know about all of the potential side effects and decide whether the benefits of the drug are worth the side effects. Hydroxyurea also has issues with skin cancer risk.

Every medication has its pros and cons and because in this disease our goal is to make the quality of life better, it's really up to the patient whether they think that the benefits of the drug outweigh the risks.

**Elissa:** Now, you mentioned earlier about some new treatments and emergent treatments and add-ons. Is there anything else on the horizon or in clinical trials that you're really excited about?

**Dr. Fleischman:** There are always new drugs coming out. I think one thing that we're sort of missing the mark on is focusing on disease modification. Unfortunately, there needs to be an outcome for the clinical trial that can be measured in an appropriate amount of time. And so for myelofibrosis, those markers have been spleen reduction and symptom score, which are very important. But in terms of things like lifespan or that are actually changing the disease, those things are a lot more hard to incorporate into the outcomes for clinical trials, so are really not necessarily being captured in clinical trials. There is one clinical trial with imetelstat which actually, I think, has a very forward-thinking outcome in terms of survival. But, I think we're, unfortunately, not capturing the really important outcomes in clinical trials for myelofibrosis and other MPNs just because it's such a chronic disease-

**Elissa:** Yeah.
Dr. Fleischman: -that it would really be almost impossible to try to capture those really important outcomes in clinical trials without huge and very, very long clinical trials.

Elissa: Yeah. We'd almost need one of those studies that take place over 20, 30 years that they've done, right?

Dr. Fleischman: Yeah, exactly.

Elissa: Yeah.

Dr. Fleischman: Yeah.

Elissa: Yeah. Well, thank you. Now on our patient podcast home page, we have a quote that says, "After diagnosis comes hope." What would you say to patients and caregivers to give them hope after a diagnosis of an MPN?

Dr. Fleischman: I would say that, with a diagnosis of an MPN, I would put a positive spin on it. It's a chronic disorder, and I've had a lot of patients tell me that it has actually been the best thing that's happened to them because it's been a wakeup call for them-

Elissa: Oh.

Dr. Fleischman: -to say that now I know I have this chronic disorder or chronic cancer, and I know I need to focus on my health. I'm going to lose weight, I'm going to eat healthy, I'm going to exercise because I know I have this underlying condition that it's even that much more important for me to be as healthy as I can and to do all that I can do to keep my body, and my mind, healthy. So I would say take it as a wakeup call that your health is really important and that you're in charge of your health.

Elissa: Yeah. That's good to know. Well thank you so much, Dr. Fleischman, for joining us today, and sharing all about MPNs. And I think it is just so hopeful to hear
that doctors are trying to provide the best quality of life for patients that they can, and it is something that they can go on and live a normal life for the most part so that is wonderful news. So thank you, again, so much for joining us today.

**Dr. Fleischman:** Well thank you. Yes, I do not see any reason why an MPN person cannot live a full, exuberant, totally normal life.

**Elissa:** We love to hear it.

**Lizette:** Yes. Great.

**Elissa:** Thank you.

**Dr. Fleischman:** Thank you.

**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.

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