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THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Treating Rare Disease with Compassion: Chronic Myelomonocytic Leukemia (CMML)'

Description:

While chronic myelomonocytic leukemia (CMML) is a rare disease, it is not rare to the patients and loved ones who are affected by it.

In this episode, Dr. Mrinal Patnaik of the Mayo Clinic in Rochester, MN, discusses the unique aspects of CMML and how it is classified and treated. Dr. Patnaik shares the latest treatment advances and discusses the importance of patients' quality of life.

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 Mrinal Patnaik, a physician scientist and Professor of Medicine at Mayo Clinic in Rochester, Minnesota. His research interests include understanding the development of blood cancers, such as chronic myelomonocytic leukemia, or CMML, myelodysplastic syndromes, or MDS, and acute leukemias.

Dr. Patnaik is the Principal Investigator on CMML trials and focuses much of his research on studying genetic changes in patients with CMML and developing novel therapeutic approaches to treat this disease. Welcome, Dr. Patnaik.

Mrinal S. Patnaik, M.B.B.S.: Thank you very much for having me.

Elissa: So, our episode today is on chronic myelomonocytic leukemia, or CMML. Could you share what that is?

Dr. Patnaik: Yeah. Chronic myelomonocytic leukemia is essentially a cancer of the blood and the bone marrow that is commonly encountered in individuals as they age. It is a rare disease and is an orphan entity, so there's not much known about it. But with dedicated research being done in this field, there's a lot more information that is available.

Now, chronic myelomonocytic leukemia typically starts off with patients having an increase in the special type of white blood cell called monocytes. Monocytes are white blood cells that play an important role in the body's defense against different organisms. It also has a role in tumor surveillance. But when they become cancerous, there is an abnormal, excessive production of B cells. And over time, this begins to harm the body and affect how the body functions. It leads to bone marrow dysfunction. Patients become quite symptomatic, and then this has an inherent tendency to progress to acute myeloid leukemia or acute myelomonocytic leukemia, which is often very difficult to treat.

Lizette: And we've also heard the term juvenile myelomonocytic leukemia, or JMML. Is that the same thing as CMML?

Dr. Patnaik: That's a great question. JMML, or juvenile myelomonocytic leukemia, is often considered a pediatric counterpart to myeloproliferative versions of CMML. However, they are not the same thing. JMML is exclusively seen in pediatric patients. Usually occurs within the first decade of life. More than 90% of patients with JMML have mutations in a genetic pathway called a RAS pathway. These children usually present with very high white blood cell counts with excessive monocytes in the blood. They tend to have enlarged spleens and livers, infiltration into organs; and in many cases, if this is not treated aggressively or patients are not transplanted, it can be fatal.

And so the genetic composition, the age of onset make these two entities different; but they share a lot of overlaps, which, especially on the adult side, we have now

begun to investigate how can we find treatment modalities that may be applicable to both, given that both entities are so rare; and it's hard to find research funding or even pharmaceutical companies interested in doing trials for patients with rare diseases. But as I have often said, rare diseases are not rare for the patients affected by them, and so it becomes almost an ethical obligation for us to make sure that they are not neglected.

Elissa: That would be wonderful to have a single medication or a treatment that would be applicable to both. And we'll get into some treatments a little bit later on.

Now, there are different subtypes of CMML, correct? Could you share what those are; and does that affect the prognosis?

Dr. Patnaik: Yeah, it does and this is a very important distinction. The most important classification of CMML actually is understanding whether this is a myelodysplastic subtype or a myeloproliferative subtype.

And this can be done quite easily by looking at the total white blood cell count. If it's greater than or equal to 13,000 consistently, then it's more likely myeloproliferative; whereas if it's less than 13,000, they're usually dysplastic similar subtypes.

This has a lot of biological basis and there's clinical implications. For example, in a very large study of over a thousand patients that we published in *Nature Communications* in 2021, we showed that the proliferative CMML subtype, the median survival is less than two years compared to the dysplastic subtype where the survival can be in the range of 36 to 40 months. Also, the proliferative subtype, the rates of leukemic transformation are higher than the dysplastic subtype.

And in that paper, we very elaborately show that there is a lot of genetic transcriptomic and biological basis for which this classification, in my opinion, is the most important classification we can use to help patients better understand the tempo of their disease and their overall outlook.

Lizette: Sure. It is kind of interesting that the World Health Organization does consider CMML an MPN as well as an MDS. I haven't seen that before. Is this one of the only diagnoses that has that type of distinction?

Dr. Patnaik: Actually, it is not. There are a few disorders that come under this category, what is called as the MDS/MPN overlap neoplasms. And the reason that was given is because they share features of MDS and features of myeloproliferative neoplasms.

The most common is chronic myelomonocytic leukemia. But there are other entities, such as atypical chronic myeloid leukemia, which is also called as MDS/MPN with neutrophilia. There is MDS/MPN with ring sideroblasts (RS) and thrombocytosis, and then MDS/MPN not otherwise specified. So, these entities come under this overlap category; and until recently, even juvenile myelomonocytic leukemia was considered an overlap neoplasm. But in 2022, the WHO (World Health Organization) and the ICC (International Consensus Classification), there were two classification systems, both have moved it out into either myeloproliferative neoplasms or in pediatric neoplasms arising in germline situations.

Lizette: And are there chromosomal abnormalities or genetic mutations in CMML like we see in some other leukemias?

Dr. Patnaik: Yes, absolutely. There are two levels of genetic analysis that we do in CMML. The first one is cytogenetics, where we do chromosome and FISH (Fluorescence In Situ Hybridization) studies on bone marrow specimens. Cytogenetic abnormalities are seen in up to 30%, so a third of patients will have some kind of chromosomal abnormalities. Most commonly, the abnormality that we see is an extra copy of chromosome 8, or Trisomy 8. There are other chromosomal abnormalities, but none of them are specific to CMML. They can be seen in a variety of myeloid neoplasms and bone marrow failure states.

There are two risk stratification systems based on chromosomes, the Spanish Risk Stratification System and then the Mayo Clinic French Risk Stratification System, which can help understand how aggressive or not these chromosome abnormalities are.

But what really is ubiquitous in these patients are somatic gene mutations, which we detect on a test called next-generation sequencing, or NGS. This test is very important. I know that there are some insurance companies that give push-back, but I cannot emphasize how important it is to move towards a universal coverage for sequencing and diagnosis. Mutations that define the landscape in CMML largely occur around a set of 8 or 9 genes. The most common is a gene called TET2, followed by ASXL1. SRSF2 is the third-most common, and then the others are signaling mutations such as in the RAS pathway, occasionally JAK2, SETBP1, RUNX1, and others.

Now, important to remember that none of these mutations are specific to a diagnosis of CMML. They can be seen in various other myeloid neoplasms and even non-myeloid states. So, a diagnosis of CMML has to be made clinically based on morphology with sequencing and cytogenetic data as adjunct, but not on its own.

Lizette: And the next-generation sequencing, is this something that would measure minimal or measurable residual disease (MRD) for this particular diagnosis?

Dr. Patnaik: No. The type of next-generation sequencing that is available for frontline use is not an MRD assay. This usually, depending on the lab, detects somatic variance between 2 to 5% or higher variant allele fraction.

The role of measurable residual disease in CMML is undefined. Like in acute myeloid leukemia and acute lymphoblastic leukemia, where there are clear paradigms, I think there's still a lot of work needed to be done in this space to see if it's even relevant or not.

Elissa: Now, you mentioned a little bit earlier that CMML can turn into acute myeloid leukemia, or AML. Are there similar genetic mutations or chromosomal abnormalities as AML?

Dr. Patnaik: Yeah, so this is a great question. The AML that arises from an underlying CMML is usually monocytic in nature and does not share the same genetic landscape or chromosomal landscape that de novo AML does. So, de novo AML mutations in MPN1, FLT3are common subtypes, such as core binding factor leukemia because of the inversion 16 or translocation 8;21, are common. These are very infrequent in CMML that transform to AML.

These patients typically have the same genetic structure that the baseline CMML does, and we had published this in our *Nature Communications* paper. Usually, it is because of acquisition of RAS pathway mutations or increments in existing RAS pathway mutations or complex somatic copy number changes in chromosomes.

But that being said, only about 50% of patients in our cohort that transform from CMML to AML had a genetic basis for explaining why this evolution occurred.

Elissa: Okay.

Dr. Patnaik: It goes on to show you that there are many other factors, including epigenetic factors or changes in noncoding regions that may be playing an important role; and so this yet remains to be elucidated.

Elissa: Oh, that's very interesting.

Now, what is the incidence rate of CMML? You mentioned earlier that it's a rare disease.

Dr. Patnaik: Yeah. It's highly underreported and underdiagnosed. And so, if you go back and look at literature, people estimate that 4 cases per 100,000 population, but I think it's more than that. I think a lot of cases of CMML are, unfortunately, diagnosed

as MDS or they're just put into MDS or MPN. And that's where CMML has suffered over decades. People have seen it as a rare disease, infrequent, and they're just trying to lump it when there's clear biological reason not to do that.

In my opinion, this hasn't been proven yet, CMML probably has the same incidence as myeloproliferative neoplasms; but the prevalence is lower because, unlike patients with MPN who live longer, CMML patients, because of their transformation to AML and usually high mortality associated with AML, don't live that long. So it seems like the pool of patients is shorter, but the prevalence may be the same as MPN, especially myelofibrosis.

Lizette: Okay, and what are the common signs and symptoms for CMML?

Dr. Patnaik: Yeah, the signs and symptoms, I like to approach it depending on whether they're myelodysplastic or myeloproliferative. Myeloproliferative CMML patients can be very symptomatic. They can have drenching night sweats, fatigue, weight loss. They usually have progressive splenomegaly, which leads to early satiety. They don't feel like eating. They can have fullness in the left upper quadrant. They can have pain related to splenic infarctions. They can develop hyperleukocytosis with increased uric acid levels that can cause gout or urate kidney stones; and eventually, there can be involvement of the skin. There can be coexisting skin lesions from related conditions.

Whereas the myelodysplastic, they tend to be more anemic and thrombocytopenic, so they have anemia-related symptoms such as fatigue, exertional dyspnea, they can become transfusion dependent soon and needing either red blood cell or platelet transfusions. And because of low and abnormal platelets, bruising or mucocutaneous bleeding can predominate. So, this is kind of the spectrum of symptoms that patients can manifest with.

Lizette: Sure. And a lot of those are common to a lot of different disorders or even other blood cancers.

Dr. Patnaik: Correct.

Lizette: I know that you alluded to this earlier, but how is CMML really diagnosed?

Dr. Patnaik: A lot of what I have spoken is nonspecific, correct? So, you can have this in not just heme (hematology) malignancies, it could be from cancer in general. But, when you start coming in with these symptoms and your blood test starts showing that your monocyte counts are raised and they're sustained. So, for more than three months, they're increased at least in general, above a thousand. But, now the recent criteria are saying that even above 500, without reactive causes. So, monocytosis, most often, is not cancer. You know, viral infections, autoimmunity, drugs. All of them can cause monocytosis.

So, if you see a high monocyte count, 90% of the time, it's not going to be cancer. Very important message to get across to the viewership. But, if it's sustained, you rule out other causes, then the suspicion for CMML is high. And that's what then should lead to testing, such as flow cytometry, bone marrow, sequencing, and all of that put together. Once it satisfies what we call the diagnostic criteria that organizations, such as the World Health Organization, have put forward, then we can make an established diagnosis of CMML.

Elissa: Now, let's discuss the current treatments, but first we know some patients are put on active monitoring, also known as watch and wait.

Dr. Patnaik: Yes.

Elissa: Why would some patients go with that treatment route versus medication right away?

Dr. Patnaik: I'll say two things. One is, at least in my practice, the paradigm that I love to follow is that we should not make the cure of disease more grievous than the endurance of the same. And number two is, wait and watch for a physician most often translates into wait and worry for the patients. You have to balance these two things.

Now, because we don't have a curative therapy for CMML, that is why there are several patients that are asked to wait until their disease progresses to the point where treatments are needed. If we had a cure, we would have not done this.

Elissa: Right.

Dr. Patnaik: We do not have a cure. Whatever treatments exist are clearly suboptimal. They all have side effects. They can make things worse. They can reduce quality of life and increase morbidity and mortality. And hence, in life, like any other decision which is a risk/benefit balance, until there are indications to treat, we do not treat patients.

Now, there are certain issues that we are looking at very carefully. The higher the monocyte count goes in the blood and the longer it's present, we have started noticing that monocytes produce a chemical called lysozyme; and this lysozyme can cause kidney damage. And so, we are now weighing into the caveats of how much of a high white blood cell count is actually okay physiologically; and should we be cutting back? This concept is called permissive leukocytosis, and myself with other investigators, we are trying to define what would be limits of saying, "Okay, we're safely waiting and watching versus maybe we need to do something."

Lizette: Right. And the other current treatments, do the different subtypes, like you're mentioning, if one is the MDS versus the MPN, are the treatments different?

Dr. Patnaik: The US FDA (Food and Drug Administration) has approved three agents for CMML management. These are all called hypomethylating agents or DNA methyltransferase inhibitors. They're drugs like azacitidine, decitabine, and now there's an oral formulation of decitabine combined with azacitidine deaminase inhibitor called cedazuridine.

Now, these drugs were largely approved in Phase III trials that were done for MDS. And they included a handful of patients with CMML, all of whom had dysplastic CMML.

So, there's no good data prospectively done to show that these drugs are actually effective in prolonging overall survival in CMML patients.

And the French, led by Raphael Itzykson, just published a very important CMML study in *JCO (Journal of Clinical Oncology)*. This trial is called the DACOTA study. And what they did is they took monoproliferative CMML patients, and they randomized them to receive either decitabine, which is a hypomethylating agent, or hydroxyurea, which is a very old, nonspecific drug that just reduces blood counts.

And they powered the study for event-free survival and found that on conclusion of the study, there was no difference in event-free survival between decitabine or hydroxyurea. And although they were not powered for overall survival, they could not show any survival advantage at all.

So, while decitabine did delay AML progression in patients or had higher complete response rates, this was offset by a higher mortality to decitabine. Patients were dying because of complications related to the drug, and so, at the end it evened out and showed no difference.

In our experience, there are subsets of CMML patients that do well on drugs like decitabine. These are usually dysplastic CMML patients, and we are published in 2019 in a journal called *Leukemia*, where we showed those who have the TET2 mutation without the ASXL1 mutation have the best responses. So, we use a very precision medicine-guided approach in treating our patients with CMML. We do not believe in the paradigm that one size fits all. We approach every individual uniquely, and we make sure that we balance quality of life with quantity of life and make their journey with CMML dignified, compassionate, and respectful.

Elissa: So, with the ones that are more closely related to MPNs, we know that with MPNs, a lot of times they're really just trying to help with the side effects and the symptoms of the disease itself. Is that similar to CMML treatment, that we're really trying to deal with the symptoms?

Dr. Patnaik: Unfortunately, because we don't have any disease-modifying drug yet, that is the truth. So, we use hydroxyurea to control the count, reduce the spleen size. There are trials being done using JAK inhibitors, so drugs like ruxolitinib, which are approved for myeloproliferative neoplasms. Not yet for CMML, but the trial data looks encouraging.

But at Mayo Clinic, for example, we are constantly developing new clinical trials for these patients. So, right now we have a very interesting trial, MC210807 which uses an oral PLK1 inhibitor for patients with proliferative CMML who don't tolerate hydroxyurea or decitabine. We hope that trials like this would be innovative and disease-modifying as we move forward.

Elissa: That's great. So, since CMML is a chronic disease, what can you do to manage the side effects and improve quality of life for the patient?

Dr. Patnaik: I think quality of life is paramount. It's not just merely existing, but it's living with some kind of quality that patients can subscribe to. We work hard to try and improve symptoms. For example, if they have drenching night sweats or they have spleen-related symptoms, how can we manage that? If they have anemia as a dominant problem, could we give certain agents that improve their hemoglobin level? If they have pruritis or if they have deep bone pains, how can we work to ameliorate that?

And in CMML, about 30% of patients have autoimmune manifestations. They often end up with rheumatologists without any good answer. Using disease-modifying agents, that may epigenetically reduce the degree of inflammation has also been an approach that we have tried. So, yes, our focus, till we find that elusive disease-modifying agent or group of agents, is on quality of life.

Now, I must remind you that there are subsets of younger patients with CMML who are fit. We know they have high-risk disease, so getting them to see a bone marrow transplanter and looking at allogeneic stem cell transplant is an important part.

However, since the median age at which these patients are diagnosed is 73 to 74, a lot of them are older. They have comorbidities and are not very good transplant candidates. I would say the bulk of patients are not transplant candidates to start with.

Elissa: Could transplant be curative for the younger population?

Dr. Patnaik: Yes. I have been doing this for 15 years now. I have long-term patients who are now more than a decade out after allogeneic stem cell transplant from CMML who have no relapse or recurrence of disease. So, it is like it is in other diseases like AML, aplastic anemia, MDS. The problem is, it's by no means a perfect modality. It still has high mortality and morbidity, especially with graft-versus-host disease (GVHD).

But there are a lot of encouraging changes in transplant. The post-transplant cyclophosphamide reduces rates of GVHD. The use of haploidentical donors. Drugs such as abatacept for mismatched transplants. So, there is optimism that we may be able to transplant a larger number of patients with time.

Elissa: That's wonderful.

Lizette: Yeah. And I know that you've mentioned clinical trials. Any emerging treatments in clinical trials that you are excited about at this time?

Dr. Patnaik: Yeah, I'm always excited.

Elissa: That's good.

Dr. Patnaik: Well, it's important to be optimistic. We ourselves are looking at three compounds. So one is the PLK1 inhibitor that's already open at Mayo Clinic, MC210807. They're very close to opening a bromodomain p300 epigenetic inhibitor. This is BRD4 p300 in collaboration with a company called Epigenetics. And this drug,

we believe, will have a lot of activity against ASXL1-mutant CMML, which is such a high-risk CMML with patients doing very poorly.

We're also in collaborations looking at a cytokine receptor called CCR2 to see if that could be a therapeutic target. We have a very nice collaboration with other colleagues at Moffitt Cancer Center, at Gustave Roussy in France, who are looking at inhibiting JAK/STAT pathway. We're looking at splicing modulation. The target call is CLK. CLK1, DLK1, so there is a lot coming out. And I also want to thank The Leukemia & Lymphoma Society for a very exciting RFA (Requests for Applications) opportunity specifically dedicated to CMML, which has really galvanized a lot of us working in the field of CMML to organize ourselves, organize trials, organize a central core and really change how we approach this disease.

I think the disservice that this disease has been subjected to by being combined with MDS and MPN needs to end.

Elissa: Yes. Well, thank you so much, Dr. Patnaik, for joining us today. I think this was a wonderful discussion on CMML. And like you said, it's a rare disease; but it does matter so much to the patients and, of course, their loved ones as well. So, we really appreciate you coming on today and sharing all about the exciting treatments potentially on the way and where we can progress with CMML.

Dr. Patnaik: I have one last comment. I really want to express my heartfelt gratitude to all the patients with CMML. When I started the CMML program at Mayo Clinic 15 years ago, we barely had 50 patients that had come and been evaluated here. Today, our institutional biobank is up to 750; and this is all because of patients traveling from all across, not just North America, but the globe, coming to seek expertise. But at the same time, the benevolence and altruism of saying that, okay, you can have my bone marrow sample. You can have my blood sample for studies. This has defined why we are today doing a podcast dedicated on CMML, when for several years, this entity was either lumped into MDS or MPN. So, every single patient

that has traveled, come to us, come to see me, in particular, I want to tell them that I am very grateful and will always remain grateful.

Elissa: It's so wonderful, and we really do love that you brought up clinical trials and then brought that up as well. It is so important for patients to participate in clinical trials, for themselves, and then for others, and really progressing that research. We'll have information on clinical trials in the show notes, but, again, thank you so much, Dr. Patnaik, for joining us today.

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