Episode: 'Exploring Hairy Cell Leukemia'

Description:

A diagnosis of cancer can cause significant emotional distress to a patient. A diagnosis of a rare leukemia can leave patients and caregivers feeling unsure and nervous about the future. In this episode, we speak to Dr. Caner Saygin of University of Chicago Medicine about hairy cell leukemia, a rare, but treatable cancer. Dr. Saygin delves into this disease, highlighting the need for an accurate diagnosis, as well as current and emerging treatments. Patients will be given hope for a good quality of life while managing this disease.

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. Caner Saygin, a hematologist/oncologist and Assistant Professor of Medicine at the University of Chicago Medicine in Chicago, Illinois. As a primary investigator on several clinical trials, his research interests focus on the development of leukemia and utilizing those unique pathways for therapeutic advancements. As an attending physician at the University of Chicago Comprehensive Cancer Center, Dr. Saygin runs a clinic focused on high-risk leukemias.

Welcome Dr. Saygin.

Caner Saygin, MD: Thank you very much. Thank you for having me.

Elissa: So, our episode today is on hairy cell leukemia. Could you explain to our listeners what that is?
**Dr. Saygin:** Sure. So, hairy cell leukemia is a type of blood cancer, and it's a cancer of the immune system. More specifically, it's a cancer of B cells, which are the cells that produce antibodies in our body. And when these cells proliferate abnormally under the control of mutations, DNA changes, they have this interesting shape with hairy projections. And initially, when these cells were observed under the microscope, they were named hairy cells due to these projections that they have on their surface. And since then, we call this disease hairy cell leukemia.

It's a chronic leukemia, meaning people can live with this disease for many years, and sometimes they may not need treatment right away; but it certainly has several implications for the individual's health. So, it's critical to diagnose this accurately because it's a rare disease, but also at the same time take necessary precautions and interventions so that people don't get in trouble due to hairy cell leukemia.

**Lizette:** Yeah, so you mentioned that it is rare, so it's more of an uncommon blood cancer. How do doctors find that it is hairy cell leukemia versus the other types of more common leukemias?

**Dr. Saygin:** So, the diagnosis of hairy cell leukemia can be achieved with flow cytometry, which is a blood test, and people will often need a bone marrow biopsy, as well. I can start by describing perhaps how people present and what might be some of the initial signs for this disease.

Most commonly, people will present with abnormal blood counts. And these abnormal blood counts are typically low white blood cell count, which are the infection-fighting cells. People may also be anemic with a low hemoglobin, and they might be thrombocytopenic with low platelet count. And, obviously, the initial presentation will be based on these low blood counts. When the white cell count is low, neutrophils are low, monocytes are low, people might present with infections. And sometimes these infections can be significant, life-threatening infections and other times if the platelets
are too low, there might be bleeding complications, or if hemoglobin is low, there might be anemia complications.

But typically, people come with these symptoms or also commonly they might present with more vague, symptoms such as fatigue. They are so fatigued; it’s getting worse that they cannot do their usual activities anymore. Like they don’t go out on weekends to meet with friends anymore, they don’t do the fun things that they used to do, or they need to take multiple naps during the day to refresh. And along with that, there might be weight loss, there might be night sweats, so those are some of the important symptoms to be aware of.

And some patients might have a big spleen, and this disease can cause very big spleens and that can cause abdominal discomfort and also it can cause early satiety because when spleen is too big, it will press on the stomach and people may feel like they are not able to finish their plates anymore. They can't eat as much because they get full very quickly.

Those are some of the symptoms that people will present with. The first test that any physician would do is a complete blood count, and they will notice something is abnormal with the blood counts. And then the next step for the accurate diagnosis of this disease would be doing tests on this bone marrow sample to reach the diagnosis.

Sometimes, I see that hairy cell leukemia can be confused with other B cell cancers, such as chronic lymphocytic leukemia, or CLL; but there are very specific markers for this disease that are expressed on these abnormal hairy cells and with an expert pathologist who is well informed and savvy with these markers, the diagnosis is not difficult. But oftentimes, when we get referrals, we want to review those slides and also repeat our own flow cytometry testing to make sure the diagnosis is correct and we are accurately distinguishing between hairy cell leukemia versus CLL or another B cell disorder.
**Elissa:** So, a lot of the leukemias have genetic mutations or chromosomal abnormalities. Is that the same for hairy cell leukemia?

**Dr. Saygin:** Absolutely. And, glad you asked that. There is actually a very pathognomonic mutation. It's not very specific for hairy cell, but about 99% of classic hairy cell leukemia patients would have that particular genetic abnormality. It’s a mutation in a gene called BRAF and that mutation, BRAF V600E, is seen in almost all cases of classic hairy cell leukemia. Diagnostically it's very valuable and, also, it is valuable therapeutically because we have some drugs that can target this abnormal protein.

In addition to this, we also do additional genetic studies too. We do cytogenetics as well, looking at the chromosomes of these hairy cells because since it's a cancer, there might be abnormalities in addition to the BRAF mutation.

And the other important piece, actually, is the germline testing looking for inherited mutations. We really need to distinguish inherited mutations from mutations that are acquired later in life when this disease happens. And BRAF mutation, the one that I mentioned that's present on almost all classical hairy cell leukemias, is an acquired mutation; people are not born with it. But, we also know that hairy cell leukemia has a strong hereditary component, much like CLL. We can see that these people might have individuals in their family who also have a blood cancer. It can be another relative with hairy cell leukemia. It can be relatives with CLL. And in those individuals, we also do what we call germline testing, which is looking for inherited mutations, as this is important to understand their disease. It also provides some clarity as to why this individual developed hairy cell leukemia and also has implications for other family members, obviously.

**Elissa:** So, could it be inherited then?

**Dr. Saygin:** In some cases, we actually have families of hairy cell leukemia, multiple family members with hairy cell or CLLs, and some of them will have inherited
mutations. So, yes, we see this in a hereditary manner too. We cannot always identify a mutation when we do that inherited gene testing. Even though this family history is very strong, we might not end up with an inherited mutation that we can identify with skin biopsy and germline testing.

And in those cases, we do research. We then broaden the testing to whole exome, whole genome sequencing to see if we can discover perhaps a new mutation associated with this disease. Because right now, in terms of finding, identifying an inherited mutation confidently, that will be perhaps less than 10% of the cases. But we have many more patients who have strong family histories that are yet to be discovered in terms of what might be running in that family.

**Lizette:** Wow! I know that Elissa's going to get into the treatments for hairy cell leukemia. How do many people do with the treatment?

**Dr. Saygin:** Yeah. So hairy cell leukemia is actually a disease that we can successfully treat. That's really important. We need to get the diagnosis right – it's very critical – and it's critical because this is a very treatable disease. There are, obviously, complications associated with the disease itself and complications associated with treatment, which I guess we'll get more into pretty soon; but it's a very treatable disease and people can live many, many years with this chronic leukemia. And they can be in remission for many, many years. We have treatments that we use upfront at initial diagnosis. There are also several backup options treatments we can use later on if they ever relapse. So, treatments in general, are quite successful.

**Elissa:** So, what are the current treatments for hairy cell leukemia?

**Dr. Saygin:** The most typically, for a newly diagnosed hairy cell leukemia patient, the first decision to make, is whether they need treatment. Because for some people, the abnormalities might be subtle. First of all, the individual might be completely asymptomatic, and they might see their primary care doctor and just get a routine
CBC, and they might notice something is slightly off and then further investigation might reveal hairy cell leukemia.

But there are some patients who don't need the treatment right away, much like some cases with CLL which I think is a cousin disease for hairy cell leukemia. So, we treat hairy cell leukemia if the patient is symptomatic, all the symptoms I mentioned earlier such as fatigue, weight loss, early satiety, loss of appetite, big spleen, symptoms from big spleen, or symptoms from big lymph nodes.

Also, blood count abnormalities. If they have low hemoglobin, low platelets, if they have low white count neutrophils, infection-fighting cells, then those are indications for treatment. But for some people, it might just be a mild CBC abnormality without any symptoms, so they can be observed with active surveillance. And we would intervene when they develop symptoms or more abnormalities in their blood counts.

So, after that initial evaluation, let's say the person needs treatment, then the standard of care first-line treatment would be a purine nucleoside analog. What this is, is essentially a chemotherapy drug, and there are two different treatments that one can offer. One of them is called cladribine and the other one is called pentostatin. These are both intravenous drugs, and the difference is how they are administered. Cladribine is given intravenously for five days in a row. Our practice is usually give daily infusions. It can also be given as a continuous infusion, but most people would do IV daily for just five days.

And then for pentostatin, that would be given every two weeks. And the nice thing about cladribine is you give it just once for most cases. You give it five days in a row and then you're done with cladribine. With pentostatin, you need to keep getting it every two weeks until successful response is achieved or until blood counts are starting to get abnormal, patient is not tolerating well anymore, etc. So, for most centers, including ourselves, we prefer cladribine because patients prefer that too. You get five doses and that you're done with cladribine.
In most cases, we add a second drug and that is an antibody targeting CD20, which is a protein on the surface of these hairy cells, and it's called rituximab. So, there are two different approaches for this. So, everyone gets the cladribine, starts with that, day 1 to day 5 and rituximab, this intravenous targeted therapy, can be added either six to eight weeks after cladribine is done or it can be given concurrently.

There was actually a randomized study few years ago done by NCI (National Cancer Institute). They compared rituximab plus cladribine concurrently; both drugs starting on day 1 versus rituximab starting late. The bottom line is responses were quite good and the toxicities were manageable when two are given together. So, I personally give them together. I start rituximab on day 1 with cladribine, but some of my colleagues would add the rituximab on weeks six to eight after people recover from cladribine effects. I think both options are fine.

The bottom line is, when cladribine and rituximab are given for first-line treatment, 80% of people will achieve very deep MRD (minimal/measurable residual disease) negative remissions. And the good news is, especially on the trial, those responses can be durable for up to eight years now that they reported. So, it's pretty effective therapy.

**Elissa:** I'm really glad that you mentioned MRD, that is minimal or measurable residual disease. Could you explain a little bit to our listeners what that is in case they don't know?

**Dr. Saygin:** Absolutely. Thank you for asking that. So, we give this treatment and then we would, obviously, want to assess how the patient is responding. We would do a follow-up bone marrow exam typically a month after the cladribine is done, and you will already see signs of improvement like people's blood counts will recover, they will feel better. So, we already will have a sense that they are responding to this treatment based on the improvements in blood counts. But we want to confirm that, so we do a bone marrow biopsy. If there are no hairy cells, that's great. That's a
morphologic remission, right. To the human eye to the pathologist, there is no hairy cell anymore. But that's not enough, and we want additional tests to see if there is any residual disease. The disease that cannot be seen by human eye but can be measured with technology is called measurable residual disease or MRD. And that's a very important assessment for all leukemias now and even beyond leukemias. For solid tumors, there are even now MRD methods.

There are different methods to assess MRD. What I quoted here was flow cytometry-based MRD, which means, the sample bone marrow or blood sample is run through this flow cytometry machine. Again, looking at those hairy cell specific cell surface markers and see if we can detect any hairy cell with this sophisticated flow cytometry-based MRD assay.

It will typically have a sensitivity of $10^{-4}$ 0.01%, meaning it can detect an abnormal cell at that depth 0.01% sensitivity. Human eye is 1% sensitivity, so this improves it by two log. And that's the assay that was used in most clinical trials. And if the patient achieves flow MRD negativity on top of that morphologic remission, then that's a great predictor that this disease will not come back for many years just as I said.

Now technology is continuing to advance, and we have emerging newer MRD methods too. I must say they are mostly investigational. I use some of them in my clinical practice and I think in the future we'll have those used more routinely. And the one that I want to highlight is next generation sequencing-based MRD.

So hairy cell is very unique. In the beginning, I told you it's a B cell disorder. And B cells are antibody-producing cells, and there is a very specific rearrangement in the immunoglobulin gene that would be a fingerprint for different cells. We can identify the fingerprint V(D)J sequence of the hairy cells at diagnosis and then track it all along treatment. And this V(D)J-based NGS (Next-Generation Sequencing) MRD can reach a sensitivity of $10^{-6}$, meaning one abnormal cell in a million.
Flow [cytometry] is two logs better than human eye and NGS MRD seems like two logs better than flow. So, I have been using that but it's not what the trials were based on. In other words, flow MRD negativity is sufficient predictor of long-term good response. But if we add the NGS MRD on top of that and if it is negative, I think it gives a lot more confidence to us. And more data will emerge on that.

**Elissa:** Now if they are MRD negative, does that mean they can stop treatment?

**Dr. Saygin:** Oh yes. This treatment is very limited. So cladribine I already said five days. Rituximab is typically given for eight doses. And what we would do is we would do weekly rituximab for eight doses. Sometimes, it can be cut to six depending on how the patient is doing or tolerating and especially if they're MRD negative, right. But, yeah, it's very limited therapy. It's not ongoing therapy. That's the beauty. It's very frontloaded. Cladribine has some side effects, but it's a limited therapy and at the end of the therapy, patient stops and, hopefully, enjoys many years of remission.

**Lizette:** Sure. And I know that you mentioned that this is more of a chronic blood cancer. So, for chronic blood cancers, the goal or treatment is often to manage side effects and improve quality of life for the patient. Is that the same case with hairy cell leukemia? Usually, we hear the word cure with the aggressive forms of leukemia.

**Dr. Saygin:** Yes, very true. Quality of life is an important piece here. That's why for some patients, if they are asymptomatic, if their blood counts are satisfactory, we delay treatment. We don't treat it upfront because, just as you said, it's a chronic leukemia and, you only want to treat them when their quality of life is essentially disturbed by the disease. And also for long term, we obviously, want to preserve that quality of life as well.

One of the other important pieces here is hairy cell leukemia usually causes trouble due to the immunosuppression, and both the disease and the treatment can be immunosuppressive. Since it’s immune system's cancer, it disrupts the immune system and all the treatments we give will also disrupt the immune system. Decades ago, we
did not have the antibiotic prophylaxis that we have today so people would often die from infections. Not really from hairy cell itself, but from the infectious complications of that.

During this treatment when people's blood counts are low, we put them on prophylactic antibiotics to prevent viral infections, to prevent another unique infection, pneumocystis infection; and sometimes they might need an antibiotic and antifungal too if their neutrophils are very low. So, we need to support them through this. And if they have any infections at initial diagnosis, that can also be the case, that needs to be adequately treated before some of these treatments are considered. Those are other important angles to long-term management as well.

**Elissa:** Now, what are some of the emerging therapies? Is there anything recent or on the horizon that you're excited about?

**Dr. Saygin:** Sure. I already mentioned that the first-line treatment is quite effective for vast majority of patients, and they can enjoy many years of remission, right. But if this disease recurs because it's a chronic leukemia, cure is a big word for this disease.

**Elissa:** Yeah.

**Dr. Saygin:** And even if they achieve MRD negativity, particularly with these very sensitive assays, that's great. But right now, it's hard to tell if someone is cured because this disease may come back 10 years later. So, if that happens, then one can consider treatment with the same agent especially if it was like many years that this disease was controlled. Then we can do the cladribine again. Sometimes you can switch. If you did cladribine upfront, you can switch to pentostatin, etc., but there are also new therapies, just as you alluded to.

And so, there are lots of data with different new therapies. Not all of them are officially FDA approved yet, but we have the data, so they are emerging therapies and most of them are FDA approved for other indications, particularly CLL.
One of the drugs that can be used is ibrutinib, which is a BTK inhibitor. And it's, obviously, very successfully used in CLL. Now there are newer BTK inhibitors for CLL like acalabrutinib-zanubrutinib. And since this is also a B cell cancer, those BTK inhibitors can be effective for hairy cell leukemia. Perhaps it can also be combined with CD20 antibodies like rituximab.

Similarly, venetoclax BCL2 inhibitor used for CLL can be used for hairy cell leukemia. There is data on that too. But one treatment that's more specific for hairy cell leukemia would be targeting that BRAF mutation. In the beginning, we talked about the fact that vast majority, almost all of these hairy cell leukemia cases will have a active BRAF mutation. And what BRAF is essentially a growth-promoting signaling pathway. It just maintains the growth of these cells. And there are drugs that target BRAF that can be quite effective for hairy cell leukemia. We don't use them upfront, but they can be used for recurrent disease and there is enough data.

Now, a lot of these drugs were first developed for melanoma because half of the melanoma cases will have a BRAF mutation. It's the exact same variant V600E and interestingly, it happens in hairy cell leukemia too. So vemurafenib is one of the earliest BRAF inhibitors that can be used in hairy cell leukemia, there is data.

The things I'm telling now some of them will be off label. There is data but not an official FDA label on them. Dabrafenib-trametinib is another drug that targets BRAF. So dabrafenib targets BRAF and trametinib targets MEK. So, BRAF and MEK go together in that signaling pathway. And then, finally, there is encorafenib-binimetinib, also BRAF MEK inhibitor. So, all three of these drugs were essentially borrowed from melanoma, and they are effective in hairy cell leukemia.

The BTK inhibitors, BCL2 inhibitors, and these BRAF MEK inhibitors are very exciting new therapies for hairy cell.

**Elissa:** Now you had mentioned that cure is kind of a big word, right, but does it always come back?
**Dr. Saygin:** You know, not necessarily. We certainly have patients who have been in remission for a decade or longer. And the thing is traditionally this is a disease of more older individuals so they usually, not die from hairy cell leukemia, so we don’t have like 20-, 30-year follow-up on everyone. And I do believe, for some patients, this disease might actually be cured with this combination approach, cladribine and rituximab. It’s just we don’t have that 20-, 30-year data yet on those people to confidently say that they are cured. But I do believe there is a fraction that we are curing because I have patients who are in remission for more than a decade.

**Elissa:** Wow. That is just really great. Now for 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 families to give them hope after a diagnosis of hairy cell leukemia?

**Dr. Saygin:** I think this is a disease that I can confidently give hope because it's a very treatable disease. The key thing is that they need to see an expert. It's a rare disease and not every oncologist, especially in the community setting, might have the world's experience in this disease. Due to its rarity, it's always nice to get a second opinion from a higher volume center, but the treatments, cladribine, rituximab, even the other new therapies I mentioned, they can be administered anywhere. But the key is to get the diagnosis right and then make a treatment plan and it's a very treatable disease. One just needs to be comfortable with its management and the complications that might happen.

**Elissa:** You mentioned needing to see a specialist. So, if we're looking at more rural patients or patients who may not live near a research hospital or a major cancer center, are they still then able to get that treatment? You say treatment could be administered anywhere? Could they still get that treatment but then have their community oncologist work with a specialist?
**Dr. Saygin:** Absolutely. That's what we do a lot too. I mean we have people in rural parts of Illinois or Iowa or Indiana or neighboring states too. The treatments are often available in even remote oncology offices. Cladribine is a very old drug. Rituximab also is often very available.

The key is a good pathologist to make sure the diagnosis is right. So, one of the best things that can be done during your second opinion in a high-volume center is to get that bone marrow slides reviewed and agree with the diagnosis. And the BRAF mutation testing can also be sent out. So, even if that's just a one-time visit to confirm the diagnosis and then make that treatment plan, the high-volume center, tertiary center can work with the local oncologists that they have to make sure the treatment is implemented correctly with the correct diagnosis. I have several patients that I see, from time to time but their main management is through their local oncologist.

**Elissa:** That's great. Well thank you so much, Dr. Saygin, for joining us today and telling us all about hairy cell leukemia. And I think you did really provide patients hope, particularly newly diagnosed patients that don't know how this is going to go that there is so much hope for a long life, a good quality of life. And so, really, we appreciate you joining us today.

**Dr. Saygin:** Absolutely. My pleasure and thank you for the opportunity to talk about this rare but very treatable disease.

**Elissa:** And thank you to everyone listening today with a special thank you to the University of Chicago Medicine for their support of this episode.

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