LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Achieving Long-term Remission with Chronic Lymphocytic Leukemia (CLL)'

Description:

Please join us as we speak to Dr. Matthew Davids of Dana-Farber Cancer Institute. In this episode, Dr. Davids discusses current treatments for chronic lymphocytic leukemia (CLL) and the exciting possibilities for the future using immunotherapies.

Dr. David shares how the goal of treatment is long term remission and quality of life. Since 2010, BTK Inhibitors, CAR T-cell therapy and other treatments have come on the market and have increased the possibilities for patients to live a long life with CLL.

Transcript:

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

Jesse: I'm Jesse.

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

Elissa: Today we will be speaking to Dr. Matthew Davids, an Attending Physician, Director of Clinical Research, and the Associate Director of the CLL Center at Dana-Farber Cancer Institute in Boston, Massachusetts. He is also an Associate Professor of Medicine at Harvard Medical School. Dr. Davids has an active translational research program on chronic lymphocytic leukemia, or CLL, and non-Hodgkin lymphoma. In this program, he leads clinical trials to evaluate novel therapeutic strategies in patients with CLL and other hematologic malignancies.

Welcome, Dr. Davids.

Matthew Davids, MD, MMSc: Thank you so much, Elissa. It's great to be with you today. I'll just start by noting that The LLS supported my very first grant, and I

continue to be funded through LLS today, so I'm very grateful to LLS and to be here today.

Elissa: That's wonderful! How exciting! Well let's get started by learning a little bit about you. How did you start in the field of medicine and studying leukemia?

Dr. Davids: I was one of the first doctors from my family, so not from a medical family, but I was fascinated initially by the science, underlying medicine and also the relationships that doctors have with patients. Oncology was really a natural fit for me because I felt like at the time when I was in medical school that the science was really at the cutting edge. It was actually the time when targeted therapies first came into the clinic. We'd been using chemotherapy for so many years and actually Gleevec, the very first targeted therapy in blood cancers, came into the clinic right when I was in medical school. So, that was very inspiring that perhaps we could develop these types of targeted therapies for other diseases.

And I got very interested in blood cancer specifically because as an oncologist you can make a huge difference for patients. You really are the primary person helping patients make decisions. I think that is very gratifying to be able to get to know my patients well and understand what their priorities and passions are and then to help make recommendations for what the best possible treatments are.

Jesse: Dr. Davids, since today's episode is focusing on chronic lymphocytic leukemia, also known as CLL, could you please tell our listeners what that is?

Dr. Davids: Sure. So chronic lymphocytic leukemia, three words. So, the first word chronic is because this is a chronic disease that patients often live with for many years. Lymphocytic means that it comes from a lymphocyte cell, which is a type of white blood cell that's normally there to help you fight off infections. But the leukemia part means that there's too many of these cells in the blood or in the lymph nodes or other organs.

And we don't actually understand a lot about what causes CLL, but we know that once it starts that these cells can gradually accumulate in the body over time, whether in the blood or in the bone marrow or in lymph nodes. And so that's sort of how the disease gets started. It's an interesting disease because it's one that we don't necessarily need to treat right away. In fact, most patients can go on a watch and wait or observation period often for several years. But eventually patients do typically need treatment and, as we'll discuss, there's a lot of exciting new treatments now for CLL.

Lizette: Sure. And that brings us along to really what are the common signs and symptoms of CLL and how do patients get diagnosed with CLL, especially since it's a chronic type of leukemia?

Dr. Davids: Most patients actually have no symptoms when they're first diagnosed. The most common presentation these days is a patient who's seen their primary care doctor for an annual visit. They get a routine blood count or they're having some other medical issue and they have a routine blood count in that context, and they're noted to have an elevated white blood cell count. And they might otherwise feel completely fine; but if that white blood cell count stays persistently high, then they should be evaluated for CLL.

And the test that we use to make the diagnosis is called flow cytometry, and that's a blood test that looks at a pattern of different proteins on the surface of the cells that can define the disease. That's the most common way that patients are told that they have CLL, and it's often hard to believe because they feel so well otherwise, and they're told that they have leukemia.

There are a smaller number of patients who develop enlarged lymph glands that can be the presenting symptom or other more significant symptoms like unintentional weight loss or night sweats, but that's not very common in terms of the initial presentation.

Elissa: If they're having signs and symptoms already, is that generally a sign that the CLL may have been ongoing and it's just kind of started to progress now to the point where they would have these signs and symptoms?

Dr. Davids: Yeah, that's often the case. So, often when I'm meeting a patient like that who's newly diagnosed and is already having symptoms and has a significant burden of disease, I can look back sometimes and see even years before that they might've had a very subtly elevated white blood cell count that maybe was not investigated further. And it's possible that this has been developing over the course of several years.

I sometimes meet patients who haven't been staying up to date on their regular health visits with their primary physicians, and they may not have had a blood count in five or ten years, and so then you don't know if maybe there was something brewing for a while.

And then there's a very small subset of patients with CLL who have high-risk disease markers and they may have really just developed the disease a few months before, but it can begin to progress fairly quickly and they can develop symptoms even in that short time frame.

Lizette: And is this type of leukemia have a genetic predisposition?

Dr. Davids: So, yeah. One of the challenges with CLL is that we know that there is a genetic predisposition. That is very clear from statistics and epidemiology. If you're a patient with CLL and you have first degree relatives, typically we think of siblings or even children, their risk is about five- to seven-fold greater than the general population of someday developing CLL themselves.

One of the frustrating things for patients and for us, is that we don't know what the genes are that lead to the development of CLL. This is an area of investigation at our center. Dr. Jennifer Brown at our center has for years been studying families with CLL

and comparing them to CLL patients who have no family history to try to identify candidate genes. So, it would be great if someday we could actually have a genetic test that we could look for this risk of CLL. And although there's been some candidates, so far nothing that's really been clearly a genetic cause of CLL.

Jesse: Now what age group is most diagnosed with CLL? Is it true that it's more common with older patients versus younger?

Dr. Davids: It is much more common as patients age. So, the median age of diagnosis now is around 68, and it's a pretty wide bell curve there. So, pretty common to see CLL diagnosed in patients in their 50s through 80s, really. It's a lot less common to see CLL diagnosed in patients in their 30s and 40s, although we certainly do see it. I tend to see a fair number of those patients who get referred in to see me, but statistically it's much more common in elderly patients.

Jesse: And can children be diagnosed?

Dr. Davids: There's really no pediatric equivalent that I'm aware of for CLL, so we don't tend to think of it as CLL in people less than the age of 18. There's case reports of some patients diagnosed as late teens or in their 20s, but this would be exceedingly rare.

Elissa: Now speaking of younger patients, Dr. Davids, last year we interviewed your colleague, Dr. Caron Jacobson, about CAR T-cell therapy. In that episode, we had asked about an interview that you did with *CURE Magazine* in January of 2021 on The Future of CAR T for Younger Patients with CLL. In the article you said that, particularly for younger patients who had relapsed with prior treatments, there might be possibilities of using CAR T as an alternative to allogeneic stem cell transplant.

I would love to hear more about this. Has there been any progress made since that initial interview?

Dr. Davids: So there has been some incremental progress made with CAR T cells in CLL, although I would say it's been pretty slow and steady progress. Partly that's because we have patients in many cases, doing very well on the current treatments and so there aren't as many patients to accrue into the clinical trials of CAR T cells. And part of that is due to what we were discussing before that many CLL patients are older and have a lot of other medical issues and may not be able to endure the rigors of CAR T.

So, it's a relatively small group of younger, fitter CLL patients that we're talking about here. We have continuing data that are evolving with CAR T in CLL, which I think do look promising. But we don't yet have a CAR T product that's approved for CLL, so not as much progress as we hoped, but certainly we're headed in that direction

And we're hopeful that eventually we'll get a CAR T product approved in CLL because I continue to think it would be very useful for younger, fitter patients who have high-risk disease and have had relapse. We have seen some really impressive responses in patients like that with CAR T in the clinical trials.

Elissa: Would you say that would be the best candidate for CAR T-cell therapy is those younger, fitter, maybe healthier patients?

Dr. Davids: Yeah. I don't mean to exclude older patients and we have a lot of patients who are older by numerical age but are still fit and active. I think patients in that age group can also be good candidates for CAR T. And we've seen this in other lymphomas where patients in their 70s can go through CAR T and tolerate it well, so I think that will be true for some CLL patients as well. But it will be a little bit more important to really select the patients who are best able to tolerate that type of approach.

Lizette: Sure. And speaking of CAR T-cell therapy, another article came out earlier this year in the *American Journal of Managed Care* that shared that a CLL patient was

now considered cured 10 years after CAR T-cell treatment. Now what are your thoughts on this because usually I don't really hear the word cure with CLL.

Dr. Davids: We hesitate to use the word cure in CLL because historically most of the treatments that we've had have not been able to cure the vast majority of patients.

Now that being said, we have patients who undergo allogeneic transplantation who go a decade or longer without any evidence of CLL coming back and so those patients probably are cured. I'll note also that we've had patients who received chemoimmunotherapy with a regimen called FCR, which is three different drugs all put together. And we have patients 15 years out from 6 months of treatment with FCR who are still in complete remission, some of those patients are also probably functionally cured. But these are probably the minority of CLL patients.

So, I think what's particularly exciting about this patient with the long response to the CAR T therapy is, number one, there's still no CLL detectable; but, number two, that there are still CAR T cells detectable in this patient 10 years later, speaking to the longevity of the treatment. And it suggests to me that even if CLL were lurking somewhere and we're trying to make a comeback, that this patient could potentially still be protected by virtue of having CAR T cells around still. And I think that really does raise the prospect of the curative potential of CAR T, at least for a subset of patients with CLL.

Lizette: And do you think that CAR T in the future when it is approved for CLL will have more patients than folks that are put into a stem cell transplantation process?

Dr. Davids: I guess the way I would see it playing out is that we would think about using CAR T-cell therapy first because, although it does have some risks and side effects, it is far less risky than allogeneic transplantation or donor stem cell transplant. I think that some patients will probably enjoy very long remissions after CAR T and will never need to move on to allotransplant. But for patients where the CLL does get worse after CART T, there will still be a role for donor stem cell transplant in that

population. At that point, you're probably talking about a pretty small population of patients.

Jesse: Dr. Davids, for those impacted by CLL, what are the most current treatments? I've been hearing about other therapies like monoclonal antibodies, BTK inhibitors. Are these newer therapies; and, if so, could you please explain them further?

Dr. Davids: So, I'll give you the short version because I could spend a few hours with this question. Historically we would use chemotherapy-based treatments for CLL and that would be effective at putting the disease into remission for some patients for a period of time. But then the CLL would come back, and it would be much harder to treat. It would not respond as well to chemotherapy.

So already at this point, 25 years ago or so, the first monoclonal antibody was coming into the clinic. That's rituximab, which a lot of people probably have heard of, which is a more targeted therapy that goes after the B cells, including CLL cells.

And so, big innovation when I was first starting to do CLL in the, the late 2000s was the combination of rituximab with chemotherapy. And that's what we call chemoimmunotherapy. And although that was more effective than chemotherapy alone, it still led to this issue of relapses and being unable to treat patients after relapse very effectively.

And so around 2010 or so is when this whole new wave of drugs start coming into clinical trials in the clinic starting with drugs targeting BTK, or Bruton tyrosine kinase, and the next drugs targeting PI3 kinase, drugs like idelalisib and duvelisib. And these are basically drugs that interrupt, what we call the survival pathways, in the CLL cells.

As I mentioned before, there aren't really characteristic mutations that define CLL like there are in some other diseases. So instead, what these drugs do is interrupt the pathways inside CLL cells that the cells rely on for their survival. CLL cells like to be in lymph nodes and bone marrow. They tend to be happier in those environments.

One of the interesting effects of these drugs is that they move the CLL cells out of the bone marrow and out of the lymph nodes and into the blood. And it turns out CLL cells are not as happy in the blood if they can't go back to the lymph nodes or the bone marrow, so they tend to be relatively slow in terms of how they actually kill the cells. But by moving them out of the lymph nodes, the lymph nodes can shrink fairly quickly and then eventually these CLL cells will die off. So that was really an important innovation in terms of targeting that pathway.

The other key agent to know about is venetoclax which targets a completely different pathway in the CLL cells. It targets what's called the mitochondria, which you can think of as the powerhouse of the cell. It's like the factory that keeps the energy going in the cell. And so venetoclax very effectively can target this factory for energy and shut it down almost instantaneously. And so, it's very effective at killing CLL cells. That drug has also now been approved and is widely used in this disease.

So, we have many different tools at our disposal. We have newer versions of some of these drugs, like the BTK inhibitor drugs that are very effective but have fewer side effects than the earlier generation. There's a lot of options now for patients, but it also makes it confusing in terms of which ones to use first, what kind of combinations. A lot of the work we're doing now in clinical trials is trying to fine tune that.

That was the short answer, but I'm happy to expand on any of that as you like.

Jesse: Thank you so much. I was thinking to myself it gives us an excuse for a future episode to talk about that further.

Dr. Davids: Sure.

Jesse: Talking about treatments could you tell us a little bit more about emerging treatments. Is there anything on the horizon that you're really excited about and would love to share with our listeners?

Dr. Davids: So probably the nearest things on the horizon are, number one, combinations of BTK inhibitors and the BCL2 inhibitor venetoclax. We anticipate in the next few months we'll likely see the first labeled indication for a combination regimen of ibrutinib with venetoclax. And what's nice about that is that it's a time-limited regimen of about 15 months, and it's all oral medications so patients don't need infusions. That'll be nice to have that as an option for certain patients.

And the other area that I'm very excited about is a new class of BTK inhibitor drugs called noncovalent BTK inhibitors. Sort of a fancy way of saying it, it targets the BTK protein in a different way from the first generation of covalent inhibitors.

One of the drugs being develop there is called pirtobrutinib. And what we're finding is that pirtobrutinib can be very effective even for patients who have previously been on a different BTK inhibitor, like ibrutinib, and if the CLL's gotten worse, they can go on pirtobrutinib and do very well. And so, it'll be nice to have that eventually approved for CLL patients to have another option that can be very effective.

I would say as we look further out over the next few years, there's also some exciting new approaches in development; we've talked about CAR T already. One of the limitations though of CAR T cells is that it does take a while to manufacture them. So, you have to get the cells from the patient. You have to ship them off somewhere. They have to be engineered and grown up and then shipped back and reinfused.

Another technology that I'm excited about that's just getting into clinical trials in CLL, and it's called bispecific antibodies.

Elissa: Oh!

Dr. Davids: So, you mentioned before rituximab, which is sort of a monospecific antibody or a monoclonal antibody; it targets one protein on the CLL cells. But what the bispecific antibodies, as you could guess it does is it targets two different proteins. One of them is on the CLL cell, but the other protein targets on a different type of

white blood cell called a T lymphocyte. You may be familiar with T lymphocytes; it's an important part of your immune system normally there to help you fight off infections. But one of the things that T lymphocytes can also do is kill off tumor cells.

The bispecific antibody targets the CLL cell, and it targets the T cell, and it brings the two in close proximity to each other and it allows the T cell to more easily kill the CLL then. And that is a technology that we've just seen some early data for in other lymphomas, which looks very impressive, and it's what we'd call more of an off-the-shelf technology, meaning you don't have to go through that whole manufacturing process. You can just have the drug in the pharmacy and just give it to patients; yet it still has this potential for immune responses. We're hopeful that we'll see good responses with this approach in CLL as well, although we don't really have much data yet in CLL specifically.

Elissa: So, are you just starting clinical trials for bispecifics then?

Dr. Davids: Exactly. That's really just getting off the ground now, so it's really too early to say anything.

Elissa: Wow! That's just so exciting. There is so many different treatments, immunotherapies, CAR T-cell therapy. That is just so great.

Dr. Davids: Yeah. It's been very exciting to be involved with this over the last decade plus because when I started focusing on CLL, which was around 2009, as I mentioned, really all we had was chemotherapy and then the rituximab. And to see all these drugs come into clinic and even, in the early days of clinical trials to really benefit some patients who really didn't have other treatment options. And now to see how far they've moved and become the preferred therapies where we don't really need to use chemotherapy-based approaches very much at all these days in CLL, it's actually pretty rare. It's been a while since I prescribed CLL patients with chemotherapy, which is a pretty remarkable change in career.

Elissa: That's great. Especially moving away from chemotherapy. I'm sure all the patients listening are cheering-

Dr. Davids: Yes.

Elissa: -right now to move away from chemotherapy.

Dr. Davids: Yeah.

Elissa: That's just so exciting. If you look back just 10 years and where we were with cancer research in general for blood cancers for CLL, things have changed so much. What do you see 10 years from now where we could be at with CLL?

Dr. Davids: Yeah. We have most of the tools that we need now in CLL. In addition to developing some of those exciting new technologies it's also being very careful to study the existing therapies now to try to figure out, are there certain patients who might do better with like a continuous BTK inhibitor strategy like ibrutinib or acalabrutinib or zanubrutinib. Or are there patients who might benefit more from doing a combination approach with two or even three of these drugs for a short period of time and then getting off all therapy, going into remission and waiting until the disease comes back.

So, there's a study going on in Europe right now called CLL17 which is looking at that question. We're about to launch a study here in the US, a large Phase III trial called MAJIC, which is comparing two different venetoclax-based regimens in the initial treatment for CLL, either venetoclax with the BTK inhibitor acalabrutinib or venetoclax with obinutuzumab.

One of the exciting aspects we think of the MAJIC study is that the therapy duration is guided by a test called MRD. So MRD if you haven't heard of it stands for minimal residual disease. MRD is a way to look for any molecular traces of CLL in the blood or the bone marrow. So, we can take a blood sample. We might look under the

microscope and not see any cells visually, but there might still be cells there that we can detect with MRD.

The idea in the MAJIC study and several other studies that are looking at this approach is to use the MRD test to guide the length of therapy; meaning that all patients we think probably will need about a year of this therapy. But if a patient does not have any detectable MRD at the end of that year, they've had a great response and maybe we can spare them a second year of therapy, side effects and eventually cost.

Other patients at the end of the year might still have detectable MRD, and so we still have some work to do there and maybe they need a second year of therapy to really eradicate that and then, hopefully, have a very long remission.

I think this is really also the beginnings of trying to individualize therapy for patients with CLL. Right now, most of our regimens are either one year or two years for every patient. But every patient is different, and if we can try to really tailor the therapy duration for individual patients, then we can really both minimize toxicity and maximize the benefit of that treatment.

Elissa: Yeah. Because really what we're looking for, right, is, not only long-term remission but also quality of life. We want them to have a good quality of life as they're in remission until they progress in their disease again.

Dr. Davids: That's exactly right and that's why as soon as we can safely stop the treatment and know that we'll still have a great response, we want to do that to reduce the risks of side effects. But we also don't want to undertreat patients where they haven't gotten enough therapy and then the CLL comes back quickly because that's probably not going to be good for their quality of life either. So that's a lot of the work that we're doing now in these clinical trials is really trying to figure out can we use MRD to effectively individualize therapy? And does that make a difference compared to the standard approach of just using one or two years for each patient?

Elissa: Now, Dr. Davids, I feel like I would be remiss if I did not bring up COVID for CLL patients since a lot of CLL patients are on rituximab which can decrease the response to the vaccine. Where are we at as far as CLL patients now and where we're at with COVID?

Dr. Davids: It's been really tough time for patients with CLL over the last two and a half years with the pandemic. Not to minimize the effects of the pandemic on other people and other blood cancer patients, but this pandemic has hit patients with CLL particularly hard. Not just because they receive rituximab, but actually because of the immune dysfunction that's inherent in the disease itself. In other words, we know that patients with CLL historically have been at much higher risks of infection of all types – viruses, bacteria, other types of infections, and that really came to the fore with COVID.

I think there's a number of studies now that really confirm this that even comparing patients with CLL to other patients with lymphoma who have all received rituximab, the effects on the immune system and the inability to fight COVID were unique to patients with CLL who are really the most vulnerable of all of our patients perhaps outside of the stem cell patients who are on immunosuppressive drugs. But patients on conventional therapy, our CLL patients have been at the most risk.

And it was pretty dark days early on. Unfortunately, we lost patients. Patients get very sick and debilitated from COVID. I think it was just such a remarkable story how the vaccines came so quickly and there was a lot of doubt early on about how beneficial they were for patients with CLL. Certainly, we find that the ability to make antibodies to these vaccines is less with patients who have CLL compared to certainly the general population but even to other blood cancer patients.

But I would say, a glimmer of hope in the last few months, in particular, is that, despite the fact that patients may not always mount great antibody responses, I think the effects of the vaccine have been very clear in terms of benefiting patients with CLL.

We still see a lot of infections in our patients, but the outcomes have been so much dramatically better. We don't tend to lose patients anymore. They don't even tend to wind up in the hospital very much these days. that speaks to the power of the vaccines, not just in creating antibodies but also harnessing other aspects of the immune system.

If you have CLL, you should ask your oncologist or your primary physician about Evusheld®. Evusheld is a cocktail of two monoclonal antibodies against COVID, and it could be a very helpful adjunct to take in addition to the vaccines to provide addition protection. And if you've already had Evusheld, the FDA is actually now recommending if you're immune suppressed, which you are if you have CLL, that you get it every six months.

Lizette: Wow!

Dr. Davids: And then the second thing is that if you are diagnosed with COVID-19 infection, we do have treatments now for COVID-19, which I think have also been quite helpful and probably the best known is Paxlovid®. And so, treatments like that and, and other antibody infusions are most effective if they're used within the first five days or so of knowing that you're infected. So, it's important if you test positive for COVID and you're having symptoms to contact your oncologist or primary care physician and try to get access to these treatments because they really do reduce the risk of severe infection and hospitalization, etc.

Elissa: Right. That's so good that there is some help out there for CLL patients as we're still continuing to live through this pandemic. That they have things like Evusheld and Paxlovid to get them through and maybe even a T cell response if they're not developing the antibodies.

So, our last question for you, Dr. Davids, on our patient podcast homepage we have a quote that says, "After diagnosis comes hope." What would you say to CLL patients and their families to give them hope for the future?

Dr. Davids: So, what I tell my CLL patients now when I meet them for the first time in a consultation is that, regardless of what their markers are, what their age is, my goal as their oncologist is to try to help them lead what would otherwise be their normal lifespan and that lifespan will not be shortened by CLL.

For older patients now, that is a very achievable goal with the therapies we already have. If you're already in your 70s and you're diagnosed with CLL, it's very likely we'll be able to induce remissions of 15, 20 years and you'll live toa ripe old age.

I think we still have a challenge ahead of us for our young patients who are diagnosed with CLL, particularly if they're very young like in their 30s and 40s. We don't know yet what happens with the new drugs, 30 or 40 years from now. So, with those types of longtime horizons, that's where I think the research is really crucial. CAR T cells, bispecific antibodies, noncovalent BTK inhibitors, all these things on the horizon are going to be needed for our young patients to try to get them a normal lifespan as well.

But I think that's the hope, that's the goal for all our patients with CLL. We're not quite there yet for everyone, but with all the continued research that we're doing, I do think that we'll get there.

Elissa: That's great. Well thank you so much, Dr. Davids, for joining us today and telling us all about CLL and where we're at and where we're going in the next several years with all these really exciting treatments. We really appreciate you joining us today.

Dr. Davids: It's my pleasure. Thank you 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 continue to provide the engaging content for all people affected by cancer, we would like to ask you to complete a brief survey that could be found in the Show Notes or at TheBloodline.org. This is your opportunity to

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