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The Bloodline with Blood Cancer United Podcast

A Podcast for Patients and Caregivers

Episode: 'MRD Explained: What it Means for You and Your Care'

Description:

MRD (minimal/measurable residual disease) testing is changing the way doctors understand and monitor blood cancers. In this episode, we talk with Dr. John Burke of the Rocky Mountain Cancer Center about how MRD testing works, what the results mean to patients and their care teams, and how ongoing clinical research is helping shape more personalized and hopeful approaches to treatment.

Transcript:

Elissa: Welcome to *The Bloodline with Blood Cancer United*. I'm Elissa.

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

Elissa: Today, we are speaking to Dr. John Burke, a hematologist and medical oncologist at the Rocky Mountain Cancer Center in Colorado. He specializes in the treatment of lymphoid disorders, including lymphomas, chronic lymphocytic leukemia, or CLL, and multiple myeloma. Dr. Burke believes that the role of physicians is to educate patients about their diseases and their treatment options and to help patients select the best treatment for their situation. He also emphasizes to patients the importance of participating in clinical trials wherever possible, both to ensure that they are receiving the most up-to-date, cutting-edge treatments for their diseases and to help advance the field of oncology. Dr. Burke is very active in clinical research, helping to develop new therapies for lymphoid malignancies and has published numerous articles in peer-reviewed medical journals. Welcome, Dr. Burke.

John Burke, MD: Thanks for having me.

Elissa: Thank you for being here.

So, our episode today is on MRD, or minimal or measurable residual disease. Could you tell our listeners what that is and also why it's referred to as both minimal and measurable?

Dr. Burke: Sure. Yeah, I mean I think what it refers to is the ability to detect very small amounts of cancer in the body that, by more conventional ways of measuring cancer can't be detected. So, for example, historically, we could detect cancer by looking at a scan and seeing a mass or something like that; whereas with minimal residual disease testing, you can detect, even if a patient has a normal scan that doesn't show a mass, you can detect microscopic amounts of cancer cells in the body.

So, it's usually done by a test on the blood or on the bone marrow where you're looking for some manifestation of the disease. It can be DNA that's secreted by cancer cells into the blood that you're detecting, or it could be residual cells leftover in the blood. So, there are different tests that can be used and detect different things; but that's the basics of what it is referring to.

As to the name, I think, historically, it was first called minimal residual disease detection, but some people objected to that because there's not always residual disease; and so, some experts then sort of came along and said, "Well, we prefer the term 'measurable residual disease.'" By the time that happened, the acronym MRD had already sort of established itself. And so, you'll hear people just throw out MRD and sometimes they write "minimal" and sometimes they write "measurable," and it all sort of means the same thing.

Elissa: Yeah.

Dr. Burke: It doesn't really matter what you call it. It's just the ability to test for very small amounts of cancer in the body that otherwise could not be detected.

Elissa: Yeah, that's really making sense. I was diagnosed with acute myeloid leukemia (AML) in 2016; and I remember when the final biopsy came back saying that I had 0% leukemia cells, or leukemia blasts, left, he said but this is all we can detect. So, there might be a smaller amount of cells that the biopsy cannot detect, and so those might be lingering a little bit. So, that's why we need to keep monitoring for a while. So, is that what we're talking about?

Dr. Burke: That's exactly right. You know, the AML was a classic example. I remember, as I was learning oncology, in AML exactly, that a patient with new AML has somewhere on the order of a trillion cancer cells in their body. And that patient goes through induction therapy and a month later is in a complete remission, meaning we do a bone marrow biopsy, and we don't find any leukemia, and we've killed 99% of the trillion original cells. That still leaves the patient with a billion residual cells in their body; and you think they're in complete remission, but they've got a lot of cancer left behind that you still got to clean up. And the ability to detect that is what MRD tests are doing.

Elissa: That's good. So, what is the impact of MRD for patients? In other words, what does MRD tell a doctor and patient about their disease and/or their treatment?

Dr. Burke: Yeah, it depends a little bit on the situation. But just to apply this across all the diseases, it's basically, you do a test and it could be either a binary result like, yes or no, there is cancer left in the body. Or it can be a quantitative result where it'll give you information about, well, how much cancer is in the body? How many out of say a million cells are cancerous cells; and how many are not? So, you can get qualitative and quantitative information about whether someone has residual cancer left in their

body and how much. And so, you can imagine it can be used in a variety of different circumstances. One is just for prognostic information. So, for example, at the end of a treatment, you can do an MRD test. And if it's positive, that might tell you that the patient is likely to relapse. Whereas if it's negative, maybe that patient is more likely to be cured.

Alternatively, in diseases where we think most everyone relapses, regardless of the MRD test results, a positive test may indicate that that patient's likely to have a shorter time to relapse. An MRD-negative patient is likely to have a longer time to relapse. So, that's how it could be used in patients with diseases that may not be curable. And you can also imagine scenarios where, in theory, it could be used to change treatment.

So, for example, if you do a test and it's positive, maybe the treatment isn't working as well as you would like. And therefore, you need to switch treatment modalities. Maybe add a different drug. So that's another way it can be used.

A fourth way it could be used would be to stop treatment. So, let's say, we're treating disease that requires long-term, so-called maintenance therapy, disease like multiple myeloma or something like that where patients stay on treatment for a long time. You could say, well, what if a patient is MRD-negative? They have a couple of tests that show we can't find any residual cancer cells in their body. Maybe that person can go ahead and stop that treatment and not have to go through additional years of therapy if they're going to do well without it.

And then a fifth way it could be used is to sort of really determine the duration of somebody's treatment. So, for example, we can say in some trials, "Well, we're going to do this treatment until that MRD becomes negative a couple times in a row. But if they don't get that undetectable MRD status or MRD-negative status, we're going to

keep the treatment going." So, it can be used to sort of help people understand their prognosis but also, in theory, we ought to be able to use it to tailor treatment to the individual and how they're responding to treatment. So that's kind of the idea and some of the ways it could be used even more in the future.

Elissa: Okay.

Holly: Dr. Burke, could you tell us which type of blood cancers MRD is currently used with?

Dr. Burke: Yeah, I would say in chronic lymphocytic leukemia (CLL), it's fairly common. It's certainly available to be used there. Multiple myeloma, it can be used. Acute lymphoblastic leukemia, or ALL, it can be used. Acute myeloid leukemia, yes, although my understanding, and I don't treat that disease hardly at all anymore, but it's trickier in that disease.

Non-Hodgkin lymphoma, I would say it's probably not used as commonly, although there are techniques for that; and there may be some new MRD tests available in the fairly near future where it can be used. I mean, I probably named most of the blood cancers, most of the big ones where certainly it can be used in. But that said, its role is still, even though it's been around for years, somewhat debatable and used by more doctors than others and not entirely standardized across all physicians in the nation or in the world. It's used differently by different people.

Elissa: Now, I'm sure some patients listening for blood cancers that you may not have mentioned or for me, for AML that it's not really used for, could you tell us why it wouldn't be used for certain blood cancers?

Dr. Burke: Yeah, first of all, there has to be a test that's able to detect the cancer cells. And that can differ. For example, in leukemia, say ALL or CLL, where there are a lot of

circulating cancer cells and circulating DNA from cancer cells, that's an area where one can use the blood as a source of testing. In contrast to cancer like multiple myeloma where there's not as many circulating cells and not as much circulating DNA perhaps, then the bone marrow biopsy needs to be done to detect MRD; and so that makes it a little bit logistically more challenging for the MRD test to be done. Not impossible, but just a little bit more challenging. And in addition to that, there's just different ways of detecting the cells and different ways of detecting the DNA. So those are some issues that come up.

But then the other issue is, well, what is the clinical utility? The knock against MRD testing that comes up all the time is that you can use it to understand the patient's disease status and how much disease burden they might have left, but that doesn't really change anything you're going to do. So, that really has been the reason, I think, that many physicians don't do that much, if any, MRD testing in their patients is that it's just really not always clear what to do with the information and that you should change something with that patient's treatment based on the results of an MRD test; and it costs a fair amount of money. So, that's the biggest barrier, I would say, to routine use of MRD testing in many of these diseases.

Holly: So, while we're on the topic of MRD testing, what are the different tests for MRD? You mentioned earlier a sample taken as part of a biopsy, or is it just as simple as a normal blood test?

Dr. Burke: It can be on the blood in some diseases but not in others. And then the exact tool used to detect the residual cancer cells can differ. There's various ways of doing that. For example, the technique called flow cytometry has been used in some of these diseases where it measures proteins on the surface of the cell; and you can use that sensitive way of doing flow cytometry to find cancer cells in the blood or in the bone marrow. So, that's kind of an older way of doing this.

A more modern technique includes using next-generation sequencing strategies where it identifies DNA segments that are unique to cancer cells and can be used to find cancer cells by measuring DNA. So, you're not measuring proteins on the surface of the cells, you're measuring, in fact, DNA sequences that are unique to cancer cells. So, that's another technique that's probably more commonly used.

Now, there is a newer technique that is emerging as potentially useful in lymphomas that is looking for, not only single DNA sequences related to cancer cells, but combinations of DNA abnormalities in the same sequence of DNA. So, these combinations, the technique called PhasED-Seq (Phased Variant Enrichment and Detection Sequencing) can be used to sort of screen out the noise, so to speak, and increase the sensitivity and specificity of detecting cancer cells, as opposed to just normal DNA variants that are in the blood. So there's a number of different technologies that have been and can be used to detect minimal residual disease.

Holly: And with testing for MRD, is this something that you are openly discussing with the patient that you will be testing for MRD?

Dr. Burke: Yeah, personally I do; and I think probably every physician has a different style. Being a physician that treats mostly CLL, lymphoma, and myeloma, where I am using it currently in my CLL patients is largely as a prognostic tool after the patient has finished a fixed duration of therapy, say one or two years of treatment. And I do have that sit down with the patient and say, "We have the option of doing this test for MRD, and what we know about the results is that a negative test correlates with a longer time to your cancer coming back whereas a positive test suggests a shorter time to when your cancer's likely to come back. So, it gives us that prognostic information. That said, it's not real clear that we should do anything different at this time, based on the results of this test. That is even if the test is positive, we may opt

not to continue therapy and just to leave you off therapy, wait until the cancer comes back, and then restart therapy at that time."

So, that's kind of the gist of the conversation that I have with patients with CLL; and I have some patients who say, "Yeah, I'd like to have that done, and if my insurance doesn't cover it, I'm willing to pay this or that dollar amount to get that information." Others say, "Um, nah, no thanks. I don't think I really want to know that information. Just follow me like you would otherwise, and we'll just treat me when it comes back."

So, that's how I have that conversation with CLL patients. I am sure that it's different in different doctors' offices. I am sure that some physicians never bring up the option of MRD testing with their patients with CLL, and I am sure that other physicians do an MRD test at every follow-up visit every few months. And I know that because I've talked to doctors who do different things. And so it's not standardized; and it's not something that sort of everyone agrees upon what needs to be done. And that's just CLL.

We could talk about ALL and AML. I will tell you, in multiple myeloma, I've always been one where I've been a slow adopter, I would say, in my multiple myeloma patients. I've just never quite known what to do with the information. And it's harder to get the information because you have to do bone marrow biopsies to sort of follow MRD in multiple myeloma. And a lot of people don't like undergoing bone marrow biopsies for that reason.

Now in multiple myeloma, I would say there's some emerging data that gives us some ideas about how it might be useful. One can debate whether you really should be using MRD to adjust your therapies for myeloma patients, but there's several ways in which MRD could be used in multiple myeloma now as well. So, and again, it's a little bit different for every disease. In ALL previously, there was a drug that was approved for

patients who had a positive MRD test, that's blinatumomab. Now, blinatumomab is sort of approved for everyone with ALL; and so, whether you really need that MRD to decide to give somebody blinatumomab is not entirely clear.

Elissa: So, you mentioned earlier about when you do the testing. Now, for chronic cancers like myeloma or CLL or maybe slow-growing lymphoma, would you do this multiple times, or are we really just doing this once after one or two years?

Dr. Burke: Yeah, let's take CLL first. The spectrum, as I said, ranges from never doing it at all to doing it multiple times when you're following patients to see how they're doing with treatment and how they're doing off of treatment and is their disease coming back. And if so, how fast?

So, my practice is mostly to check it one time at the end of fixed-duration treatment to give them that prognostic information. I usually don't check it much beyond that, although I do have patients who ask me for it; and we do check it sort of serially to kind of monitor their relapse. In myeloma, there are some data published this year from a trial called the MIDAS trial that used MRD responses after initial induction therapy and then tested for those who had a good MRD response, say undetectable to a certain level, whether the conventional therapy of autologous stem cell transplant, was better than the different strategy of just continuing their induction.

And as it turned out, continuing their induction therapy turned out to be just as effective at making that MRD become even more undetectable than the transplant. And so, one possible scenario emerging, I would say, not standard yet, but emerging in the future might be to use MRD testing after induction. And for those who've achieved a very good deep response or mostly undetectable disease, to skip the high-dose chemotherapy and autologous stem cell transplant, which might be nice for patients if

they don't have to go through that. So, that's one way that it appears to be emerging in multiple myeloma.

Another way is to shorten the duration of maintenance therapy, that is there have been some studies that show that patients who achieve undetectable MRD that is sustained for, say at least a year or two, do well if they come off of their maintenance therapy, whether that's lenalidomide pill or daratumumab injections. And so that might be a reasonable thing to do is check MRD serially in multiple myeloma patients who are on maintenance therapy to use that as an indication to stop treatment.

Now, I will say that those trials have not compared outcomes, stopping treatment with not stopping treatment, so we don't have a clear scientific study that says that stopping is better than not stopping. It's just that we know patients who get sustained undetectable MRD do pretty well if they stop therapy, and that might be good enough.

In non-Hodgkin lymphoma, what's coming, what we think, probably the first test to be used in non-Hodgkin lymphoma is a test that at the end of their chemo, which will predict their likelihood of being cured. That is if they're-

Elissa: Oh!

Dr. Burke: -undetectable MRD, it's probably better than the PET scan at saying, "This patient is likely to be cured or not to be cured." And then the question becomes, "Well, if they're not undetectable, what do you do about it?" And there's some trials ongoing to sort of try to answer that question. Can we take people who are not undetectable and, therefore, not likely cured of their aggressive lymphoma and do something about that to cure them before it's too late. So, that's an ongoing area of research in non-Hodgkin lymphoma.

Elissa: Is there a particular type of non-Hodgkin lymphoma or multiple types that you're looking at that with?

Dr. Burke: Well, the one I'm referring to is diffuse large B-cell lymphoma.

Elissa: Okay.

Dr. Burke: Yeah, because those patients, you need to cure them.

Elissa: Yeah.

Dr. Burke: So, in that scenario, you need to get to an undetectable MRD state.

Holly: So, why is it beneficial for patients to get tested for MRD? There's, obviously, lots of benefits I'm sure you could tell us about, but also equally, are there any disadvantages to testing?

Dr. Burke: Yeah, I think the advantage and the disadvantages, I would say, the key advantages would be patients do like the knowledge. They like to know, not all of them, as I said, but many of them like to know what the status of their disease is and what's their prognosis, so that could help them sleep better at night. It could help them plan their lives, that sort of thing. That's one advantage of it.

Another, as I said, is these emerging trials where we're trying to figure out what to do about it. Can we do something for those patients who are MRD-positive to give them a better chance of cure than they would have if you just waited until their cancer came back in its full state that makes the patient real sick. Can you prevent the patient from having to go through all that and treat them when you have a better chance of curing them, that is when the disease burden is less?

And then, finally, the ability to reduce therapy is advantage. That is, if somebody's MRD-negative for a while and you can back off the therapy, that's great for the

patient because then they don't have to get exposed to the drug and the side effects and the cost of therapies that maybe they don't need. Maybe they're not going to benefit that much from those.

I think disadvantages include there are some costs to doing these tests. It's probably relatively small compared to the cost of the drugs. But, for example, a CLL patient who's coming in for their regular surveillance. Let's say they've finished therapy, and they're coming in for every three-month office visits. And at those office visits they see a doctor, get the blood counts drawn. Seeing the doctor costs 100 bucks, and getting the blood count drawn costs 100 bucks. So, say it's a $200 visit. If you get an MRD test for every one of those, you just turned a $200 visit into a $2,200 visit, and that adds up. So cost is an issue.

And I would say the biggest kind of barrier to use of MRD, as I said before, is it's a little unclear in most cases how the results of the tests are going to change your management. Are you really going to act on that, that test? And in medicine, a lot of times, we say, "Well, look, if you're not going to do anything with the results, don't do the test in the first place." And so, while it might be nice for patients to know what their MRD status is, if it's not going to change management, maybe that doesn't justify spending the money or doing the test.

So that's kind of the back and forth that docs have about MRD tests. And I do think it's why you see such a wide spectrum of use from doctors who send it all the time, to doctors who never send it at all, to others who do something in the middle. So, I think that's why there's not universal agreement on how to use the test.

Holly: And for those who do opt into getting MRD testing, how quickly are they getting their results back?

Dr. Burke: I would say typically the initial test to identify like the DNA takes about two weeks; and then the test to do the tracking where you say yes or no, you're in remission or not, or you're undetectable MRD or not, is only about a week. So, it's pretty fast.

Holly: Oh.

Elissa: And then you mentioned the cost. Is this something that's covered by insurance?

Dr. Burke: I find that it usually is, yeah. Most of my patients are not getting large bills for the test or anything like that. So, I find that, large majority of the time, it is being covered by insurance. Now, it may be that I'm using it more within the sort of typical realm where it is going to get covered; and you can imagine other scenarios where you might have a harder time getting it covered. But in my hands, it usually is getting covered.

Elissa: That is good to know.

Now, let's move onto the future of MRD testing. Are there any clinical trials that you're particularly excited about?

Dr. Burke: Yeah. So, we're participating in one that I kind of alluded to in diffuse large B-cell lymphoma called the ALPHA3 trial, which is kind of a two-part trial for patients with diffuse large B-cell lymphoma, or DLBCL. And what's happening in ALPHA3 is that patients with DLBCL go through their initial chemoimmunotherapy treatment that's trying to cure them and get them in remission. And then at the end of that treatment, they get a PET/CT scan. And that scan will tell us if they are in remission or not. Historically what we've done, is just stop there. If you're in remission, you're good, and we'll just monitor you for recurrence.

And we know that even in people who have a great PET scan that shows a complete remission, a number of them, maybe 30% or so, will eventually relapse and have to fight that battle again. So, the PET scan is far from perfect at predicting who is and who isn't going to relapse.

And what we're doing in ALPHA3 is we're doing an MRD test after that PET scan, and we know that some of those patients will test negative. In fact, most will test negative, meaning we don't find any residual cancer. And we know that those patients have an excellent prognosis with probably a less than 10% chance of recurrence. So, it adds to that PET scan.

On the other hand, we know that some of those patients will test positive, maybe 75-80% will test positive. And of those patients, even though their PET scans look fine, don't have a good prognosis. Those patients have a very high likelihood of recurrence in the near future. So, that's Part 1 of the trial.

And then Part 2 of the trials is taking that MRD-positive test and trying a treatment that is designed to try to cure that patient. So, patients who are MRD-positive will be randomly assigned to undergo very close surveillance, which is kind of the normal thing to do or get a treatment delivered to them. And that treatment is what's called a cellular therapy, specifically a product called Cema-cel, which is called an allogeneic CAR T-cell therapy-

Elissa: Oh.

Dr. Burke: -which is sort of off the shelf, and they get a CAR T-cell delivered to them. And so that's the design of the ALPHA3 trial. It's testing whether Cema-cel, administered early when the patients are in remission, but MRD-positive, -

Elissa: Okay.

Dr. Burke: -achieves better outcomes than the more conventional strategy of just waiting for that relapse to occur and then delivering a solid treatment like an autologous CAR T-cell therapy. So that's the design of that trial that is trying to take MRD testing and do something about it,

Elissa: Yeah.

Dr. Burke: -so that the results of an MRD test will change management of those patients.

Elissa: Okay, so you see MRD testing as an endpoint then of that trial?

Dr. Burke: Yeah, it is. Well, it's an endpoint and it's a screening. So, the trial is really doing two things.

Elissa: Yeah.

Dr. Burke: It's testing how good is this MRD test, to be used as a decision-making tool for doctors and patients; and it's testing the allogeneic CAR T-cell product itself.

Elissa: Okay. So, with all of these clinical trials done on MRD, do you see potentially at some point in the future there becoming more of a general consensus, set protocols for use of MRD, in the different blood cancers?

Dr. Burke: Absolutely, yes. I think that will be a big part of clinical research moving forward is finding exactly what you just said. Finding definitive roles for MRD testing to have it affect treatment decisions; and all the ways we've talked about shortening treatment to allow patients not to get treatment when they don't need it anymore, changing treatment to allow patients to switch treatments early when their current treatment is not working very well. That's a great potential tool. Another potential tool for future use is eliminating follow-up CAT scans to monitor patients with cancer

that's gone into remission. Right now, if somebody has lymphoma, they finish their treatment. We follow them with CAT scans for a couple years. Well, that exposes patients to some radiation.

Elissa: Yeah.

Dr. Burke: That's not good for them either. And if we could do that with a blood test, why not? That would be safer for everyone. So, there's countless ways that MRD could be used and it's a really useful tool in many blood cancers; and we'll continue to learn more about it in the future. That is for sure.

Elissa: That is great. Good to hear.

So, our final question today, on our patient podcast home page, we have a quote that says, "After diagnosis comes hope." With all that we have discussed today on the benefits of MRD testing and how it might guide decision-making, what would you say to patients and their loved ones to give them hope after a diagnosis of a blood cancer?

Dr. Burke: You know, I'm always optimistic when I see new patients with blood cancers. I don't mean to understate the seriousness of these things because they are extremely serious, but we do so well with the treatment of so many of these cancers; and absolutely there's always hope. There's never been a patient who walked in my door for the first time where I said, "There's nothing I can do for you." There's stuff we can do to help people and get them in remission. And yeah, we like to cure everyone and we're not there yet, so we could always do better; and that's why we encourage patients to go on trials and encourage our colleagues and other physicians to offer that option to patients.

So, we have work to do. We have improvement to make in how we treat cancer. But, I'll tell you this story. Twenty five years ago when I was starting my training, the average

survival for patients with multiple myeloma, getting what was at the time the current standard treatment, which was chemo and a stem cell transplant, was about three years. And now with modern therapy, I heard an expert estimate the other day that the average first remission of a myeloma patient who received modern therapy is probably going to be about 12 years. We don't know that exactly yet because we don't have 12 years of follow-up on that trial. But, that's a big difference in, in my two- or three-decade career for the average survival to go from 3 years to well over 12 years. And who knows what it really is because all these new treatments are becoming available, and patients are doing so well.

So, we don't cure everyone like we'd like and, and more progress needs to be made, but we have made tremendous progress. And so, we're always optimistic that we're really going to be able to help people when they walk in the doors.

Elissa: We love to see optimism here, and you're right, there has been so much research that has been done, particularly in the last even ten years that has just been groundbreaking. And we love sharing it with our patients and, again, giving them hope and hope to their loved ones as well.

And so, thank you, Dr. Burke, so much for joining us today and telling us all about MRD. We hope the patients and caregivers listening will take this back to their doctor and talk about it and see if it's right for them and if they're getting the MRD testing and what that means. And so again, we really appreciate you joining us today.

Dr. Burke: Thanks so much for having me on.

Elissa: And thank you to everyone listening today. *The Bloodline* with Blood Cancer United is one part of our mission to improve the quality of lives of patients and their families.

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