LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Clinical Trials in Lymphoma: An Evolution Not A Revolution'

Description:

Join us as we speak to Dr. Grzegorz (Greg) Nowakowski, a physician researcher and Professor of Medicine at the Mayo Clinic in Rochester, Minnesota, who also leads the Mayo Clinic Aggressive Lymphoma program. In this episode, Dr. Nowakowski discusses clinical trials for lymphoma patients, including recent advancements and how clinical trials work. He also discusses the benefits and common misconceptions of clinical trials. This episode is a must listen for patients of all cancers who want to know how they can get access to the latest advancements in treatment.

Transcript:

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

Edith: I'm Edith.

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

Elissa: Today we will be speaking to Dr. Greg Nowakowski. Dr. Nowakowski is a physician researcher at the Mayo Clinic in Rochester, Minnesota. He also serves as a Professor of Medicine, and he leads the Mayo Clinic Aggressive Lymphoma program. The goal of his research is to better understand the genetic and molecular causes of hematologic cancers in order to develop personalized therapies for the individual's cancer. He has led and is currently involved in many clinical trials for lymphoma. In addition, he serves or has served on many national and international bodies focused on improving therapy of lymphoma and other cancers, including on the federal Food & Drug Administration panel by advising the FDA on approval of new drugs in cancer.

Despite these roles, he is a busy clinician seeing and actively treating many patients with lymphoma, hence has a lot of experience talking to patients about clinical trials, which will be the primary discussion for today's episode.

Welcome, Dr. Nowakowski.

Grzegorz Nowakowski, MD: Hello, thank you for having me.

Elissa: So, let's start by getting to know a little bit about you. Why did you choose the field of medicine and the study of lymphoma?

Dr. Nowakowski: So, I was always interested in science, and initially I wanted to be a chemist or maybe a physicist. And then one of my mentors mentioned, "Hey, there's a lot to do in medicine, and there is this interface with both physics and chemistry, particular in molecular biology." I really got interested in medicine and that's why I selected medicine.

Now early in medical school, I really become interested in cancer and cancer therapy. This was at the time of molecular revolution and developments in our understanding of genetics of cancer and immunology of cancer really were ready to be moving into the clinic. So, I got very excited about being a part of this and really bridging this lab side and clinical side.

After completion of my training at Mayo Clinic, I was still debating if I wanted to be more in a lab or doing clinical studies and work more with patients in introducing new treatments. And at the time, and it's still the case today, there were just so many lab discoveries and so many new exciting treatments being really developed, waiting to be introduced to the clinic, so I decided that understanding the basic science and translational science behind it and try to move it to the clinic and how the best we can help patients with those new developments and treatments was something which I really would like to do. And that's what I'm doing right now. I would describe myself as a trialist.

And as my career evolves from initially being involved in directly in a lot of clinical trials, and I'm still very much hands on running a lot of clinical trials and having a busy clinical practice, as you mentioned, I'm also now interested in bigger picture in how we

can facilitate the patients' accrual to clinical trials, how we can overcome some of the barriers which people face every day in being on the trial or getting the best possible cancer care.

And for that reason, I serve a number of national committees which are trying to address those issues; a number of policy committees, including a service for FDA in the past reviewing some of the drug applications and making recommendations to FDA if some of those should or should not be approved for cancer therapy.

So, it's been in me for quite a long time, and I really enjoy what I'm doing; and it's very important that those new treatments can actually really make a difference in people's life every day.

Lizette: Yeah. It definitely sounds like you've been able to work in so many aspects of lymphoma treatment. I know we're talking about lymphomas today, and there's so many different types of lymphomas. Would you be able to go over a bit about what lymphoma is, and how the types can differ?

Dr. Nowakowski: Absolutely. It's a very complex field. In general, the lymphomas are divided into Hodgkin's and non-Hodgkin's lymphoma, so that's the first two big groups. The non-Hodgkin's lymphoma group is actually extremely diverse with many different diseases; but, in general, we would divide them into aggressive lymphomas – the ones which are growing or expanding rather quickly, and they usually require quite aggressive therapy early on – and then indolent or slowly-growing lymphomas, which tend to progress much slower, sometimes over years or decades, and approach to how we treat those varies quite a lot.

In fact, if you look at the WHO (World Health Organization) classification of lymphoma, there are over 50 different subtypes. And if you look at site-specific lymphomas, there are even more. So, it's a very complex field with sometimes very specific therapies targeting lymphoma subtypes. Some of those could be quite rare. Some of those are more common.

Elissa: Now is that really the benefit of personalized medicine to target all those different types since they are so diverse?

Dr. Nowakowski: Yes, absolutely. And even with the initial classification between aggressive and indolent lymphoma, it is done based on molecular profiling and microscopy. So probably the most critical thing in a treatment of lymphoma is actually good pathological diagnosis. You really need to develop relation with the lymphoma pathologist, expert in lymphoma pathology, which can correctly categorize the lymphoma because there are just so many and there is some overlap between lymphomas.

And there are even some nonmalignant conditions, reactive changes which can sometimes mimic lymphomas. So you really have to be very careful to make sure that expert pathologists does review this pathology and does all the molecular workup needed to adequately classify lymphoma to best match therapy with a subtype of lymphoma.

In terms of the aggressive lymphomas, what's interesting about those lymphomas, although they progress quickly, we actually can cure significant proportion of those lymphomas. So early therapy with chemotherapy and chemo-immunotherapy can actually cure those lymphomas in significant proportion of patients.

On the flip side, most of the indolent or slowly-growing lymphomas are actually considered to be incurable. We can produce very long remissions in those lymphomas or some of them will never require treatment because they change so slowly. But with the currently available therapies, we don't really believe we can completely irradicate the seeds of those slowly-growing lymphomas, so we always have to follow patients for a very long time before we can say that the likelihood of this lymphoma coming back is very, very low.

So, there are very different approaches because in indolent lymphoma we tend to focus on minimizing toxicity and how to control it in years or decades ahead; in

aggressive lymphoma, really trying to do everything possible to get disease in remission and eradicate this lymphoma early on.

Edith: Thank you for that overview as it is important to know that there are different types of NHL. In today's episode, we would like to discuss clinical trials for lymphoma. How is clinical trial different from an already approved or standard treatment?

Dr. Nowakowski: That's a great question. And the way I define the clinical trial is the way for the patients to get access to new therapy. I think it's the best definition of the clinical trial which I can think about. It's really the way we can provide the benefit of this new therapy to patients.

Now because they had not been studied frequently, extensively when patients are being approached about the clinical trials, this is done in a setting of a clinical trial which is more controlled. So, the outcome of the patients are followed much more closely, the potential toxicities are followed much more closely, and there's quite much more regulation in terms of when you can enter clinical trial, when the assessment is being done, and how the patients are followed. So, there's frequently somewhat more time involved than standard therapy in this setting.

But I think the idea behind the clinical trial is not to experiment. As I frequently tell my patients, that's not the point of the clinical trial. The clinical trial is really to provide you an access to what we think is the better therapy, and we have to prove it's a better therapy than what we have, and that's why the clinical trial is being done.

Now clinical trials come in many different flavors and forms, and some of them are advanced clinical trials or Phase III clinical trials. In those trials, we have a standard treatment, which we used sometimes for years or decades, which has certain results; and then we'd like to improve those results.

So, there is a experimental arm in the protocol which usually uses this treatment with added new agents or sometimes some with different treatment and is trying really to

establish if any of those, any of this new treatment is better than the old treatment. In those studies, patients are typically randomized, which means you have no choice if you're going to get new treatment or the old one because we don't really know, truly we don't know if the new one is better than old. And you really need to do it in a controlled fashion where some patients randomly will assign to the old treatment and some too new to see if we can make a difference.

And some of the patients might be somewhat reluctant pursuing those trials because we say, "I really would like to get a new treatment" or "I really would like to be in a standard of therapy." And I usually tell them that exactly that, that we don't really know if this new treatment is necessarily better than standard therapy. That's why there is this random assignment.

And many times, those early studies are looking very promising, and we really have to prove it in this controlled way, and that's the only way to evaluate those treatments with each other, which can then lead to change of practice to everybody.

Then there are also earlier clinical trials, which are more focused on evaluating specific combination in a group of patients to produce results. And some of them are extremely promising and produce without any randomization, so without assigning to one treatment or another and results very early on which can then lead to the drug approval.

And finally, there are very early trials, so-called Phase I studies, where the new compounds are being tested. And this field has changed quite a bit. In the past, it used to be more of exploration of different agents – will they work, how was the toxicity? Nowadays we've targeted therapy. They're really very targeted. They usually are quite matched to the tumor already when we are developing those trials with a high level of success. So those are the different types of flavors of clinical trials.

Elissa: Now you mentioned that when they are put into a trial, they're either given that standard treatment that's been around or they're given maybe a combination or

new treatment. Now that is different, right, than, for instance, our recent clinical trials with the COVID vaccine where you might be given a placebo. Could you tell us the difference in that with why they're not given a placebo with things like cancer?

Dr. Nowakowski: Yeah, thanks for mentioning this. That's a common misconception about the cancer clinical trials that the placebo is used, or I will just get a sugar pill and not necessarily benefit from being on the trial or I will not get the treatment because of this.

In cancer, we don't do that. So, typically, the active therapy is used in those studies. They're just different sometimes design or recipes for what we think is the best treatment option at the time. We're just trying to compare the new-generation treatment with the older-generation treatment in those studies.

Occasionally, in a cancer trials could be a placebo or sugar pill built in, but this is never given alone. If we have such a trial, it is usually given with the active therapy, on the top of active therapy.

For example, I was a principal investigator of recently completed trial which was looking at addition of the drug called lenalidomide to standard chemotherapy called R-CHOP in patients with diffuse large B-cell lymphoma. And in this study, half of the patients received lenalidomide, and half of the patients received placebo, sugar pill looking like lenalidomide. But everybody, regardless, still received standard chemotherapy with R-CHOP. So, the standard chemotherapy was unaffected by using a placebo.

And it is very important because it would be unethical and not right, withdrawing active treatment from anybody, and that's why we do not use placebo alone. If placebo is used, this would be only in the context of already ongoing active therapy on the top of it, if you would.

Elissa: Yeah, and that's definitely one of the misconceptions. And there are others. One is that the clinical trials are only used as a last resort treatment. So, would you tell us about when in the patient's treatment that they'd usually be placed into a clinical trial?

Dr. Nowakowski: I would say anytime during the treatment you can be on the clinical trial, and anytime during the treatment it's worth to be on a clinical trial because you have access to something new. So, some of the clinical trials are designed for frontline therapy of the disease which could be curable with standard treatment; but you would like to cure more patients with this therapy.

And the example of the trial which I just mentioned to you with lenalidomide was exactly designed this way. Everybody was getting R-CHOP, which cures approximately 50 to 60% of the patients; and we wanted to make it better. This way this pill was added on the top of standard therapy. And that's the example of the clinical trial which was for patients with newly diagnosed lymphoma which actually do have other treatment options, but the trial is designed to make this frontline treatment better and achieve better rate of cures.

There are some trials which are then designed for patients who are running out of standard therapy options as well. Those are usually later in the disease course and, unfortunately, some patients will relapse after frontline or even second- or third-line therapy; and those patients will be candidates for those trials.

But at any point during lymphoma treatment, patients should consider participation in clinical trials for this added benefit. The way the modern trials are designed, they are not taking away anything. They're trying to add on the top what we have to make it better.

Edith: I'm curious if the trial is good at the beginning of their treatment, are they often presented as an option?

Dr. Nowakowski: Yes. So, we typically, if the trial is available, we discuss it with the patient and we strongly encourage patients to participate in a trial if they're interested.

And I usually get this reaction from patient when I mention possibility of participation in a clinical trial, particularly if they have a standard therapy available. There is sort of reluctance in their face, and frequently they say, "Well, yeah, I will do it because I guess progress of science is important and I would like to help you and help medicine to develop." And I stop them right there, and I say, "This is not done to help the trial or progress of medicine. I mean it's great that you want to do it, but that's not why we are doing this trial. I'm proposing this trial for you because I want you to benefit from this therapy. This is the way you can get the access to state-of-the-art development in science, and this is done on the clinical trial."

So, this is really done for the benefit of the particular patient. Obviously, the progress happens, and we learn as a society as well and then medical field from that, but I always look at this from a perspective from the patient, and I want them to be selfish. I say, "What's in it for you because I want you to benefit from this trial. I want you to benefit from the access to this new drug." And sometimes it may be appropriate. Sometimes it may not, so we have this discussion. Sometimes there are some personal preferences as well. Sometimes, being on a trial could be quite involved, and people have to make a decision is it worth additional traveling or time investment in it. And people have very different preferences in what they want to do, but the understanding is they are doing it for themself.

Elissa: So, there's been a lot of discussion lately about shared decision-making with patients and their doctors. So when a patient's coming in and there is the standard treatment, but there's also clinical trials that could be used for the frontline treatment, are you presenting them as, "Hey, here's a standard treatment that we use, but then there's these clinical trials going on that I feel like could really benefit you, and here's

all the options laid out on the table, and here's what each of them does"? Is that kind of usually how that's presented?

Dr. Nowakowski: That's exactly right. So, I usually present the standard treatment options, and we discuss that because I think it's very important to understand where the bar is and what are the expectations with the standard treatment to understand how the clinical trial would alter it and what are the perspectives of being on the trial.

So, we usually start with discussion of what are the expected outcomes with the standard treatment in the short term and the long term, what are the potential toxicities of this treatment and potential side effects, and then we discuss what trial is trying to add to this treatment or how is it different than standard therapy? And in two ways, one is a scientific way – why this new agent is so promising. I usually like to explain it a little bit better to patients, so they understand why we believe this is going to make a difference.

But they also need to understand what are the potential risks and being on the trial of potential additional side effects. And they also have to understand what are the additional requirements of being on the trial because sometimes there are additional visits which are needed or additional evaluations which you wouldn't have to do on a standard of care. So, there is some additional work on the side of the patient which needs to be done. Depending on the trial, it can be more involved. And we would like to fully understand those requirements before making this decision.

Now the most important thing though I tell the patient in this process is when it comes to discussing of the study consent. So, study consent is a document which outlines what the study is and what are the expected potential side effects of the medications and what are the potential expectations of the patients, when they need to show up. And it's a legal document which sometimes is quite lengthy. And we've been told in primary school and by our parents not to sign the document without careful reading, right.

Those documents are sometimes quite long. They could be 30 pages, and I can see in my patients' faces when I'm pulling this consent, "This is the consent which reviews the study." There's a little bit of hesitancy there. "My mom told me never sign the document without careful review. Maybe even having a lawyer and now you're putting this document in front of me."

And the good thing about the consenting for the study is that this is a consent, not a contract.

Elissa: Right.

Dr. Nowakowski: And I cannot emphasize it enough.

Elissa: They can withdraw at any time.

Dr. Nowakowski: Exactly. This is a consent, not a contract. This is not like a contract for your cell phone company that if you start using different provider, you have some financial penalty. There's no penalty for withdrawing anytime. That's what I always tell my patients. And I tell them that we can withdraw from the study for two reasons: one is if the patient feels for some reason that they changed their mind or the drug doesn't agree with them and patients don't want to do it or we decided that logistically it might be just too difficult to do. And I say, "That's fine. We can stop the study. We can consider other options."

And the other reason, it could be me. If I feel that you're not tolerating this study well for some reason or if there are some other issues which are really affecting potentially your outcome with this treatment, I'm not going to keep you on the study. I will recommend that you actually stop the study and go to different therapy option. So, for those two reasons, I always tell my patients, "We can always tell the study team we are done and no explanation is needed and no penalty for that. It's really a consent, not a contract."

But it does work both ways. I always tell people that just because they signed a consent, it doesn't mean the trial will happen. There's some clinic procedures required as well, so you need to be sometimes fit for the trial based on multiple parameters. And occasionally it may happen that despite initially thinking that patient will be a candidate for a trial and signing the consent, we may find out that there are some lab abnormalities or some other reasons why we don't think at the end it would be a good idea to enroll patient in the trial. And we will discuss it then and not necessarily pursue this option.

Elissa: So, you just went over some front-line clinical trials if they were just right at the beginning of their treatment. So are there situations as they were going along in their treatment and then maybe a new clinical trial comes up that you feel that they would be a good candidate for, are you presenting it to them at their next visit or how is that happening?

Dr. Nowakowski: Yes. So, if something else comes up in the meantime, we typically would present it and discuss this as an option. Again, there are different trials which fit different patient scenario; and in our lymphoma portfolio here at the Mayo Clinic, we always try to make sure that we have clinical trial for almost any situation a patient might be in if there is one available. Now occasionally, there may not be a trial available for a specific situation, but we really try to have a trial for almost any clinical situation in terms of early disease or later on and different subtypes of lymphoma, with the idea is that the best possible treatment is to be on this trial because it provides you access to benefits of research development in science.

The process of informing patients of ongoing trials later on depends a little bit where they are with their treatment. So if somebody is already receiving standard therapy and responding well to that, there is really no point to enter the clinical trial at the time; and it's not even allowed because the treatment was actually started.

But there might be some trials which use additional maintenance treatment later on, or there could be some trials which are using additional monitoring; and based on that, this monitoring, able to assign patient to additional treatment later on. And if such a trial is available, we can discuss it even if they're already receiving therapy.

Lizette: And with so many types of lymphoma too, and you said that some types of lymphoma are rare, there's still clinical trials for rare forms of lymphoma, correct?

Dr. Nowakowski: Absolutely. There are clinical trials for rare types of lymphoma. And, in general, some of the rarer subtypes we put in a little bit of a larger pocket. So, for example, some of the slowly-growing lymphomas, which are rare, are frequently incorporated in the clinical trials of slowly-growing lymphomas which are more common, and that's a common practice because the treatment results and the treatment modalities, treatment types which we use for those lymphomas are very similar. So, it makes lot of sense to incorporate those rarer subtypes.

And sometimes, even in the very rare types of lymphoma, you may actually have very specific treatment design for it. Now, as an example, Waldenström's macroglobulinemia, or lymphoplasmacytic lymphoma, it's not a very common subtype of lymphoma, but we had made a lot of progress in understanding biology and the drivers behind this type of lymphoma. And there's a huge interest in developing therapies specifically for this lymphoma, just because we understand the science behind it so well. And for that reason, there are actually a number of trials which focus specifically on this rarer subtype of lymphoma.

Elissa: It's really good to know that there are just so many different clinical trials out there for the rare types or for the common types, at different points throughout their treatment. For our listeners who don't know, LLS has a Clinical Trial Support Center where an Oncology Nurse Navigator can search for trials around the country, including at the Mayo Clinic, and help to find those that the patient might be qualified for to

participate in. And so, we'll share a link at the end of the episode to find out more information about our trial center to try to get on some trials.

Dr. Nowakowski: Thanks for sharing it because it's extremely important. It could be very confusing because of multiple lymphoma subtypes and multiple hematological malignancy subtypes to clearly understand what's available. And there are a number of databases on the Internet which are trying to help, including some of the government-run sites, clinicaltrials.gov. But it's not the perfect system; and if somebody's not in a medical field, it could be very difficult to navigate through different clinical trials, looking for information out there.

So having this resource at LLS, and with the Clinical Trial Navigator and Nurse Navigator, it's a great way of matching the potential interested patient with what clinical trials that are available. And also, what clinical trials are available in proximity because not everybody has resources or time to travel to the tertiary centers; and it's very important that some of those trials which are available closer to your door, are considered.

Elissa: I would assume it would also be hard, if they're going to a community cancer clinic versus an academic institution for oncologists who see all different types of cancers to be able to know what every single trial is going on all around the country and what might benefit their patients.

Dr. Nowakowski: Yes, absolutely. And again, there's some access to the databases and some information; but having this Navigator system, which you have, it's extremely helpful for oncology practices as well.

I'll also mention another initiative which LLS has which is the IMPACT program which you're now working with a number of tertiary centers, including us, and the local practices, community practices in how to deliver this care on a clinical trial closer to patients, particularly in rural areas or underserved areas. This is something which is very close to my heart and what we are trying to do here.

Because I always see the opportunity of extending the benefit of this trial to folks who cannot necessarily fully commit to travel; and there's really no reason why we couldn't do it. There's some regulatory red tape. There are some other barriers; but, if people really align with this mission, we can do it. We can help; and we can spread the accessibility to clinical trials closer to patients.

Now sometimes when I talk about what drives me about doing the clinical trials are the patient stories; and I have here a picture on my desk of the patient of mine who had refractory Hodgkin's lymphoma. And he arrives after transplant, and at that time when this happened, the survival of these patients, and he was in his 20s, was measured in months – 3 to 6 months was average survival. In fact, he came here because he ran out of options, and they told him to consider hospice.

And so he wanted to try. And there're a couple of clinical trials which we tried over the years. He had some response to the first one, brentuximab vedotin. And then subsequently on another trial and was one of the first patients which entered PD-1 antibody trials, nivolumab at the time, in relapsed-refractory Hodgkin's lymphoma in the world.

And nobody knew that this antibody would work so well as it did, but it resulted in a complete remission; and since then, he got married, and he has two kids. And fortunately, his lymphoma stays in remission.

Elissa: That's so wonderful.

Dr. Nowakowski: And this just shows the power of those new agents. And the only way to access this drug at the time was through this clinical trial. So, if not clinical trial, I would not have this picture on my desk of him with his kids. And this is what really drives me every day for the discoveries and moving the bar in clinical trials and trying to provide access to clinical trials and benefits from clinical trials to as many patients as we can.

Lizette: Wow, you're absolutely right. We're right there with you trying to work on decreasing those barriers for patients to be able to get into clinical trials a little bit easier. Of course, with personal preferences, it's very important to really talk to a patient about what they can and cannot do to be a part of a clinical trial.

And thank you so much, and your institution, for really trying to minimize those barriers for our patients because with our Clinical Trial Support Center, we are really trying hard to get patients into clinical trials but really facilitating the whole process for them to actually get into the trial. Because as you mentioned, it's not the easiest process; but it really is something that has saved people's lives.

Dr. Nowakowski: Absolutely. It's particularly the new generation of the compounds and drugs which we have, and immunotherapy, this is changing people's lives every day. You know, the CAR T cells were later in the clinical trials as well. Now they're approved, but people who are able to access those CAR T cells early for the clinical trials are the folks who were able to benefit from those therapies early on. And that's the whole idea of the clinical trial is providing you access to state-of-the-art therapy early on.

Lizette: There's definitely that benefit. I know that we talked a lot about different misconceptions that people have. Is there other misconceptions that people, sitting down with you, they have mentioned? I know we've gone over placebo, that clinical trials are not a last option for treatment. Are there any other concerns that people have spoken to you about in regards to clinical trials?

Dr. Nowakowski: I think we already outlined it partially, but I would like to, again, rephrase it because I think it's very important. The major misconception is the clinical trial is done to advance science of medicine and medical field and develop these new treatments for the benefit of the society. And this is how many people think. You know, it's almost like an exclamation. Yes, I would like to contribute to the progress of

society, and that's true. We learn a lot, and it causes progress in medical science and society and discovery of those new treatments are then are becoming standard.

But the major reason why we are doing it and why I'm considering the clinical trial for my patients is the benefit to a particular patient. It's the benefit to you directly being on the trial and having this access to new treatment.

The other misconception, we talk a little bit about it, that consent that you can actually withdraw from the study at any point if the treating physician or you as the patient do not feel you would benefit from the treatment, or the treatment doesn't agree for some reason. So it's not a contract. It's a consent. And that's always very important to keep in mind.

And finally, with some of the trials, although it is difficult to come because sometimes you need to come to the tertiary center or somewhere farther for multiple times. Nowadays we're able to sometimes bill some small token just to help with the travel and accommodations. It's something which patients with less resources are sometimes shy even to mention. But you should always ask because, number one, the institution or the trial could have some small help in those logistics. And it is true also about LLS as well and other organizations that there is some support for the patients having difficult financial situation.

And in addition, there is also some social barriers as well. Some people cannot have caregivers or family members which are able to support them. So, there's the patient support groups. So, we have a network to help you dealing with the trial.

Elissa: Yeah, we all know that cancer is really expensive; and there are all these financial issues. So, with the trial, are the out-of-pocket expenses different for a patient on a trial versus the standard treatment?

Dr. Nowakowski: Great question. So, on the clinical trial, we typically divide everything in two groups. One is associated with care no matter what. So, seeing

your physician or maybe having a CAT scan later on to see how you're responding to treatment, that's something which you do getting standard therapy or not. And that's typically a standard of care, and that's typically billed to insurance company as normally it would be.

Now whatever is the intervention in the study, in terms of the new experimental treatment, and some additional assessment which are maybe needed because of this experimental treatment, that's actually paid for on this study. So, this is at no cost to you. This cost is buried by the people who develop the drug.

So, I always tell my patients during the consenting process because the consent has that small paragraph about the finances of the clinical trials as well as that we are going to get this drug for free for you. And we will see if this drug is approved in the future it's given to you for free. But if it gets approved and somebody will, in the future, make a profit, neither me or you will get any payment for it either. So it's one of the development parts of the clinical trial that cost is buried by the sponsor, and sometimes it's quite substantial running those large trials. But the standard of care procedure is usually paid by insurance.

Elissa: You brought up earlier that LLS does have some financial assistance. We have travel assistance to help patients to maybe drive a little bit further from a rural area into a major hospital. But we also have copay assistance that might help with out-of-pocket expenses for scans, lab tests, or treatment-related supportive medication. So, for antinausea medication and pain medication, things like that that may not be part of the standard drug. So again, we'll have a listing in the show notes for our listeners so you can find out all about the financial assistance that may help if you are in a trial.

And now that we've discussed the basics of clinical trials, are there some new emerging therapies that you would be able to tell our listeners about? What on the horizon is there that is getting you excited?

Dr. Nowakowski: So, this is an absolute revolution in lymphoma therapy and actually hematological malignancies altogether. You can think about different periods in the histories, which are transformational, right? We had renaissance, we have enlightenment, and right now in medicine and in cancer therapy we're in a period of time where work over decades, understanding molecular biology, understanding immunology, understanding the underpinning of cancer is really changing the way we treat it.

So, the treatments are different. Rather than us, this was developed in the past. There was a drug screening, and sometimes they were somewhat blindly tested in different tumor types. This doesn't happen often now. Most of the treatments now are specifically targeted. They are designed with specific targets and sometimes tumor in mind. So, the whole engineering of this, it has changed quite a lot.

And just regarding specifically lymphoma, we have a number of trials in both aggressive and slowly growing lymphomas and Hodgkin's lymphoma as well incorporating those immune therapies and targeted therapies into the standard therapy using them alone later on.

There are a number of studies, for example, in frontline therapy of diffuse large B-cell lymphoma, which are using the standard chemotherapy called R-CHOP or alterations of R-CHOP and adding new agents on top of it. In the past, we used to add one agent at a time, and the bar was difficult to move. But now there are actually doublets or even triplets on the top of this treatment. It's really trying to improve the outcomes, and they are designed specific to cure more patients up front with this disease.

In a second-line therapy, we just had an announcement that some of the trials done in large cell lymphoma for patients with relapse of lymphoma, the first relapse, are now showing that new treatment with CAR T-cell therapies are better than what we had done in the past, which was high-dose chemotherapy and transplant. We haven't seen the results. The study is publicly released, but they're already announced as a positive

study, so we're really looking forward to it; and it's a great example how the trial and early access of patients to this new treatment is now changing the whole field. And this is about to become a standard treatment. But the field is always moving forward, and people are already building on it and trying to add additional agents to make those CAR T-cells and several approaches even better.

And in patients beyond second or third relapse, there are also a lot of exciting developments of the so-called CAR T cells in a vial which are bispecific antibodies which can engage immune cells and the tumor cells directly and have your own immune recognize your cancer cells and destroy them. And in contrast to CAR T cells which are more difficult to produce and time involved, to actually be able just from the vials. They're basically small protein fragments or antibodies which are bringing the effector cells, the immune cells closer, tumor proximity so, the immune system can see the tumor cells and say, "Oh, wow, this is a bad cell. We better get rid of it."

Elissa: Wow.

Dr. Nowakowski: Yeah, that's really cool. And immunotherapy also has some new agents directed towards what I'm calling a cancer fake ID. So, the cancer cell is trying sometimes to show this fake ID to immune cells and say, "Hey, I'm actually a good cell." But now we have like a UV light like at the airport where you can actually check this fake ID and say, "Ah, this really looks fake." And then immune system can eradicate the cancer cells, the so-called "do not eat me" inhibitors and many other compounds in this area.

There are a lot of small molecules which target specific pathways in the cancer, which are also very promising and working quite well. I think the biggest difference between the previous generation of trials and what we see now is direct clinical benefit.

So, in the past when somebody was designing the trial, it was understanding that the chance of success was actually quite low – sometimes within 5 to 10% in early trials of

the drugs which actually showed significant activity to advance later on to their treatment.

Now, particularly in lymphoma, because those agents are designed with such a precision and really in novel ways, their success rate is actually much higher. It's 30%, 50% or even higher. Some of the new combinations are going almost way than 50% in a relapsed-refractory setting, which was previously unheard of. And they're actually much better tolerated too than chemotherapy agents, which we had previously. They had a different scope of side effects, but they're actually much better tolerated typically than classical chemotherapy in this setting. So really a huge progress in all lines of therapy of aggressive lymphoma.

The same is true about low grade lymphomas. We now have new antibodies, new oral therapies which are being incorporated into the treatments at various stages of therapy. And in Hodgkin's, we already mentioned earlier my patient who benefitted from nivolumab, now those PD-1 inhibitors pembrolizumab and nivolumab and others are now moving to frontline therapy as well. So, they are trying to partially improve or maybe even displace chemotherapy over time so we can cure more patients just with using their own immune system rather than typical chemotherapy.

So in any subtype of lymphoma, you have those novel agents, coming. And they are well designed and really changing the way we treat our patients with lymphoid cancers.

Elissa: It's such the neat thing about targeted therapy that you can really just find these particular molecules or proteins on certain cancers and really help that versus a one-size-fits-all approach.

Dr. Nowakowski: Absolutely, and here hats off to people who did this work over many, many years and decades. So, it looks like a revolution now; but it was really an evolution. It took a long time to develop those maps of human genome, to understand the signaling pathway in cancers, to understand some of those targets.

It takes countless individuals, thousands of people working tirelessly in the lab and investigators trying to develop those treatments and move them as quickly to patients as possible.

One other area which I'm really interested in right now because we have so many interesting treatments, is do we even need to necessarily complete all the large trials of all those agents, or can we move them even faster to the clinic because we really have acquired experience with the previous treatment? So rather than designing some of the studies which I mentioned that you randomized people to, standard treatment or new treatment, can we bypass it? Then basically compare it with our historical experience and move the field forward faster? And I think there are some niches that, truly some findings which are so revolutionary that you probably don't need randomized study.

One of my, one of my colleagues always jokes that there was no randomized study of parachuting, right? And it's true. Nobody had ever had time for; no need to crash anything or not because some things just make sense. And if we see some of those compounds right now being so active, we have to use what we know already to facilitate their development so they can get to the clinic faster.

Edith: This all sounds really exciting. So, doctor, on our patient podcast homepage, we have quote that says, "After diagnosis comes hope." What would you say to lymphoma patients and their families to give them hope for the future?

Dr. Nowakowski: This is an unprecedented time in terms of the development of new therapies, specifically lymphoma. Even before this revolution, we already had quite active treatments for many lymphoma subtypes. So, comparison with some of the other cancers, we are doing actually quite well but not as good as we would hope for.

Now with these new agents and new treatments, the outcomes keep improving fairly rapidly. So, I completely agree with this statement. There's definitely hope, and this

hope is actually within reach. It's not something we're talking about coming years ahead of development. It's here and it's here in the form of the clinical trials. Because you can get access to those new developments in the science and those state-of-the-art therapies through being on the clinical trials. And all of us involved in this and working with the patients are really excited about possibility of patients benefitting from it.

We only have to make sure that this hope of better outcomes are available to everybody. And I really appreciate what LLS is doing in terms of your patient support, both logistically, finding the trials and navigating through this process and, and sometimes the financial, logistical support as well because we would like to extend this excitement and benefit to everybody.

Elissa: Well, thank you so much, Dr. Nowakowski. This was such an exciting discussion about all the things on the horizon with lymphoma therapies and the benefits of being on a trial and really combatted a lot of the misconceptions for our patients. So, I really hope that a lot of our patients listening will ask their doctor at their next visit about what clinical trials might be available to them that they will qualify for.

So, thank you, again, for sharing your expertise about this subject. We really appreciate it.

Dr. Nowakowski: Thank you again for inviting me. It's been a pleasure to discuss it and thank you for all what you're doing for progress in lymphoma research.

Elissa: Also, a special thank you to the Mayo Clinic for supporting this episode. And thank you to everyone listening today. *The Bloodline with LLS* is one part of the mission of The Leukemia & Lymphoma Society to improve the quality of lives of patients and their families.

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We would also like to know about you and how we can serve you better. The survey is completely anonymous, and no identifying information will be taken.

We hope this podcast helped you today. Stay tuned for more information on the resources that LLS has for you or your loved ones who have been affected by cancer.

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